5.03 ERTUGLIFLOZIN, Tablet containing 5 mg ertugliflozin, Tablet containing 15 mg ertugliflozin, Steglatro®; ERTUGLIFLOZIN with METFORMIN, Tablet containing 2.5 mg ertugliflozin with 500 mg metformin hydrochloride, Tablet containing 2.5 mg ertugliflozin with 1 g metformin hydrochloride, Tablet containing 7.5 mg ertugliflozin with 500 mg metformin hydrochloride, Tablet containing 7.5 mg ertugliflozin with 1 g metformin hydrochloride, Segluromet®,
Merck Sharp & Dohme (Australia) Pty Ltd.

1 Purpose of Application

1.1 The submission requested an Authority Required (Streamlined) listing for ertugliflozin for dual oral therapy with metformin or a sulfonylurea, and ertugliflozin with metformin fixed dose combination (FDC), for the treatment of type 2 diabetes in patients inadequately controlled with metformin or a sulfonylurea. Ertugliflozin has not been previously considered by the PBAC.

1.2 The submission requested listing for ertugliflozin on a cost-minimisation basis to the two comparators, dapagliflozin and empagliflozin; the requested listing for ertugliflozin with metformin FDC is on a cost-minimisation basis to the individual components.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with type 2 diabetes who are inadequately controlled on metformin or a sulfonylurea.
Intervention	Ertugliflozin in dual oral therapy with metformin; including the FDC of ertugliflozin with metformin. No evidence of efficacy and safety for ertugliflozin with a sulfonylurea was presented in the submission.
Comparator	Dapagliflozin and empagliflozin (other SGLT2 inhibitors), in dual therapy with metformin or a sulfonylurea. For the ertugliflozin with metformin FDC, the main comparator is concurrent treatment with individual components at corresponding doses.
Outcomes	Mean change from baseline in HbA1c, fasting plasma glucose, and body weight, proportion of HbA1c responders (<7%), safety, hypoglycaemic events. Bioequivalence outcomes were also presented for the ertugliflozin with metformin FDC.
Clinical claim	In patients with type 2 diabetes who are inadequately controlled on metformin or a sulfonylurea, dual oral therapy with ertugliflozin and metformin is as effective at controlling glycaemic levels and reducing body weight compared to dual oral therapy with dapagliflozin or empagliflozin and metformin; and is as safe in terms of adverse events and hypoglycaemia. The FDC of ertugliflozin and metformin is bioequivalent to the individual components taken concurrently.

Abbreviations: FDC, fixed dose combination; HbA1c, glycosylated haemoglobin; SGLT2, sodium glucose co-transporter 2; TGA, Therapeutic Goods Administration.
Source: Table 1.1-1, p2 of the submission.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ERTUGLIFLOZIN				
Oral tablet, 5 mg	28	5	$58.27	Steglatro ®
Oral tablet, 15 mg	28	5	$58.27	Merck Sharp & Dohme

Category/Program:	General Schedule
PBS indication:	Diabetes mellitus type 2
Treatment phase:	N/A
Restriction:	Streamlined Authority
Clinical criteria:	The treatment must be in combination with metformin; OR The treatment must be in combination with a sulfonylurea, AND Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with either metformin or a sulfonylurea; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period despite treatment with either metformin or a sulfonylurea.
Prescriber criteria:	Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. Note: This drug is not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ERTUGLIFLOZIN WITH METFORMIN				
Oral tablet, 2.5 mg/500 mg	56	5	$59.78	Segluromet ®
Oral tablet, 2.5 mg/1000 mg	56	5	$61.18	Merck Sharp & Dohme
Oral tablet, 7.5 mg/500 mg	56	5	$59.78	
Oral tablet, 7.5 mg/1000 mg	56	5	$61.18	

Category/Program:	General Schedule
PBS indication:	Diabetes mellitus type 2
Treatment phase:	Initial or Continuing
Restriction:	Streamlined Authority
Clinical criteria:	Initial: Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with metformin; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period despite treatment with metformin. Continuing: Patient must have previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and ertugliflozin.
Prescriber criteria:	Note: This fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1. Note: A patient whose diabetes was previously demonstrated unable to be controlled with metformin does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.

2.1 No special pricing arrangement was proposed.

2.2 The proposed restrictions are consistent with existing dual therapy PBS listings for empagliflozin and dapagliflozin and their associated fixed dose combinations.

2.3 The PBAC noted that the proposed ertugliflozin (dual therapy only) listing is more restrictive than the PBS listings for the comparators, which also allow use in triple oral therapy and in combination with insulin. The proposed restriction does not exclude the use of the ertugliflozin with metformin FDC in combination with a sulfonylurea, which the PBAC considered could cause confusion amongst prescribers and lead to potential leakage outside the proposed restriction.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Clinical Evaluation Report and Delegate's Overview were available. The PBAC noted that the TGA Delegate's Overview was supportive

for the 5 mg dose strength of ertugliflozin (corresponding to 2.5 mg ertugliflozin with 500 mg/1 g metformin FDC tablets) only.

3.2 The requested TGA indications for ertugliflozin and ertugliflozin with metformin FDC are presented below:

- Ertugliflozin: as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as monotherapy when metformin is considered inappropriate due to intolerance or in combination with other anti-hyperglycaemic agents.
- Ertugliflozin with metformin FDC: as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and metformin is appropriate.

Previous PBAC consideration

3.3 Ertugliflozin had not previously been considered by the PBAC.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Type 2 diabetes is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, insufficient insulin secretion or both. Diet and exercise are the first steps in managing the disease, followed by initiation of drug therapy with metformin or a sulfonylurea if metformin is contraindicated or not tolerated. When metformin or sulfonylurea monotherapy is inadequate in controlling blood glucose, treatment options include dual therapy with metformin and a sulfonylurea, or the addition of insulin, glucagon like peptide 1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP4) inhibitors, thiazolidinediones (TZDs), or sodium glucose co-transporter 2 (SGLT2) inhibitors.

4.2 The submission positioned ertugliflozin as an alternative to other SGLT2 inhibitors, dapagliflozin and empagliflozin, for dual oral therapy with concurrent metformin or a sulfonylurea to treat type 2 diabetes mellitus in patients with inadequate glycaemic control, defined by glycosylated haemoglobin levels (HbA1c) >7.0%, despite treatment with metformin or a sulfonylurea.

5 Comparator

5.1 The submission nominated dapagliflozin and empagliflozin as the comparators for ertugliflozin, as they are pharmacological analogues and have similar dual therapy PBS listings as the requested ertugliflozin restriction. The submission nominated the individual components given at corresponding doses for the ertugliflozin with metformin FDC. These were considered appropriate. Other fixed dose combinations of empagliflozin or dapagliflozin with metformin could also be relevant comparators for the ertugliflozin with metformin FDC.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on an indirect comparison of ertugliflozin and pooled data for dapagliflozin and empagliflozin, with placebo as common reference, at different time points:

- 12/16 weeks: ertugliflozin 5 mg (trial P016, n=104) vs pooled dapagliflozin 10 mg (trial CT-003, p=198), empagliflozin 10 mg (trial 1245.10, n=142 and trial 1276.10, n=321), and empagliflozin 25 mg (trial 1245.10, n=141 and trial 1276.10, n=321).
- 24/26 weeks: ertugliflozin 5 mg (trial P007, n=416) vs pooled dapagliflozin 10 mg (CT-012, n=179, CT-014, n=266 and Yang 2016, n=288), empagliflozin 10 mg (trial 1245.23, n=424) and empagliflozin 25 mg (trial 1245.23, n=420).

6.4 Supplementary indirect comparisons using trials with a DPP4 inhibitor or a sulfonylurea as common reference were presented in support of the primary analysis.

6.5 The submission also presented data from four trials assessing the bioequivalence of ertugliflozin with metformin FDC with corresponding doses of individual components as follows:

- Ertugliflozin/metformin 7.5 mg/1 g FDC vs ertugliflozin 7.5 mg and metformin 1 g (Study P027, n=16 and Study P047, n=16); and
- Ertugliflozin/metformin 2.5 mg/500 mg FDC vs ertugliflozin 2.5 mg and metformin 500 mg (Study P050, n=16 and fasted and fed assessment of metformin component only for Study P052, n=16).

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ertugliflozin trials		
P002	A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Ertugliflozin (MK-8835/PF-04971729) Compared With the Addition of Glimepiride in Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin NCT01999218	November 2016
P005	A Phase III, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of the Combination of Ertugliflozin (MK-8835/PF-04971729) with Sitagliptin Compared with Ertugliflozin Alone and Sitagliptin Alone, in the Treatment of Subjects with T2DM With Inadequate Glycemic Control on Metformin Monotherapy NCT02099110	March 2017
P007	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 78-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin in Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Metformin Monotherapy NCT02033889	November 2016
P016	A 12-Week, Phase 2, Randomized, Double-Blinded, Placebo-Controlled, Dose-Ranging, Parallel Group Study to Evaluate the Safety, Tolerability, and Efficacy of Once Daily PF-04971729 and Sitagliptin on Glycemic Control and Body Weight in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin. NCT01059825 Amin NB, Wang X, Jain SM, Lee DS, Nucci G & Rusnak JM. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin.	January 2012 Diabetes Obes Metab 2015, 17(6): 591-8. 10.1111/dom.12460
Dapagliflozin trials		
CT-014	Bailey CJ, Gross JL, Pieters A, Bastien A & List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. NCT00528879	The Lancet 2010, 375(9733): 2223-2233. 10.1016/S0140-6736(10)60407-2
CT-003	Schumm-Draeger PM, Burgess L, Korányi L, Hruba V, Hamer-Maansson JE & de Bruin TWA. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: A 16-week randomized, placebo-controlled clinical trial. NCT01217892	Diabetes Obes Metab 2015, 17(1): 42-51. 10.1111/dom.12387
CT-012	Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, Sjöström CD, Sugg J & Parikh S. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. NCT00855166	Diabetes Obes Metab 2014, 16(2): 159-169. 10.1111/dom.12189
CT-004	Nauck MA, Del Prato S, Meier JJ, Durán GS, Rohwedder K, Elze M & Parikh. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: A randomized, 52-week, double-blind, active-controlled noninferiority trial. NCT00660907	Diabetes Care 2011, 34(9): 2015-2022. 10.2337/dc11-0606
Rosenstock 2015	Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B & Iqbal N. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: A Randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. NCT01606007	Diabetes Care 2015, 38(3): 376-383. 10.2337/dc14-1142
Yang 2016	Yang W, Han P, Min KW, Wang B, Mansfield T, T'Joen C, Iqbal N, Johnsson E & Ptaszynska A. Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: A randomized controlled trial. NCT01095666	Journal of Diabetes 2016, 8(6): 796-808. 10.1111/1753-0407.12357

Trial ID	Protocol title/ Publication title	Publication citation
Empagliflozin trials		
1245.10	Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T & Woerle HJ. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. NCT00749190	Diabetes Obes Metab 2013, 15(12): 1154-1160. 10.1111/dom.12185
1245.24	Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ & Broedl UC. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. NCT00881530	Diabetes Care 2013, 36(12): 4015-4021. 10.2337/dc13-0663
1245.23	Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC & Woerle HJ. Empagliflozin as add-on to metformin in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. NCT01159600	Diabetes Care 2014, 37(6): 1650-1659. 10.2337/dc13-2105
1245.31	Merker L, Häring HU, Christiansen AV, Roux F, Salsali A, Kim G, Meinicke T, Woerle HJ & Broedl UC. Empagliflozin as add-on to metformin in people with Type 2 diabetes. NCT01289990	Diabetic Medicine 2015, 32(12): 1555-1567. 10.1111/dme.12814
1245.28	Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ & Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: A 104-week randomised, active-controlled, double-blind, phase 3 trial. NCT01167881	The Lancet Diabetes and Endocrinology 2014, 2(9): 691-700. 10.1016/S2213-8587(14)70120-2
1275.1	DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ & Broedl UC. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. NCT01422876	Diabetes Care 2015, 38(3): 384-393. 10.2337/dc14-2364
1276.10	Ross S, Thamer C, Cescutti J, Meinicke T, Woerle HJ & Broedl UC. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: A 16-week, randomized, placebo-controlled trial. NCT01649297	Diabetes Obes Metab 2015, 17(7): 699-702. 10.1111/dom.12469
Ertugliflozin bioequivalence studies		
P050	A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 2.5 mg/Metformin 500 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Ertugliflozin and US-Sourced Metformin) in Healthy Subjects	May 2016
P052	A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of Metformin in Ertugliflozin 2.5 mg/Metformin 500 mg Fixed Dose Combination Tablet Versus Canadian-Sourced Glucophage Co–Administered With Ertugliflozin in Healthy Subjects in the Fasted and Fed States	January 2017
P027	A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 7.5 mg/Metformin 1000 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Ertugliflozin and US-Sourced Metformin) in Healthy Subjects	February 2016
P047	A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 7.5 mg/Metformin 1000 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Ertugliflozin and EU-Sourced Metformin) in Healthy Subjects	June 2016

Note: abstracts of studies with full publications are not included
Source: Table 2-8, pp30-39; Table 1-1, p2 Attachment 1 of the submission.

6.7 The key features of the included trials are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Primary indirect comparison: placebo + metformin common reference					
Ertugliflozin + metformin					
P007	621	MC, R, DB, PC 26 weeks	Low	T2D with HbA1c 7.0-10.5% on metformin monotherapy	Change from baseline in HbA1c at week 26
P016	328	R, DB, PC/AC dose finding phase 2 trial 12 weeks	Low	T2D with HbA1c 7-11% on metformin monotherapy, or 6.5-9.5% on metformin plus oral diabetes medicine	Change from baseline in HbA1c at week 12
Dapagliflozin + metformin					
CT-003	400	R, DB, PC 16 weeks	Low	T2D with HbA1c 6.7-10.5% on metformin	Change from baseline in HbA1c at week 16
CT-012	182	R, DB, PG, PC 24 weeks	Low	T2D with HbA1c 6.5-8.5% on metformin	Total body weight change from baseline at week 24.
CT-014	546	MC, R, DB, PG, PC 24 weeks	Low	T2D with HbA1c 7-10% on metformin	Change from baseline in HbA1c at 24 weeks
Yang 2016	444	R, DB, PG, PC 24 weeks	Low	Asian patients with T2D with HbA1c 7.5-10.5%.	Change from baseline in HbA1c at week 24.
Empagliflozin + metformin					
1245.10	495	R, DB, PC, dose ranging, 12 weeks	Low	T2D with HbA1c 7-10% on metformin monotherapy	Change from baseline in HbA1c at week 12
1276.10	983	R, DB, PG, PC 16 weeks	Low	T2D with HbA1c 7-10%	Change from baseline in HbA1c at week 16
1245.23	638	R, DB, PC 24 weeks	Low	T2D with HbA1c 7-10% on metformin	Change from baseline in HbA1c at week 24
1245.31[a]	638	R, DB, PC, extension 76 weeks	Low	Patients with T2D who completed 24 weeks treatment in Trial 1245.23	Change from baseline in HbA1c, fasting plasm glucose, body weight, blood pressure and use of rescue therapy at week 76
Supplementary indirect comparison: DPP4 inhibitor + metformin common reference					
Ertugliflozin + metformin					
P005	1233	R, DB, PG, factorial study, 52 weeks	Low	T2D with HbA1c 7.5-11% on metformin monotherapy	Change from baseline in HbA1c at weeks 26 and 52
P016	328	R, DB, PC/AC dose finding phase 2 trial 12 weeks	Low	T2D with HbA1c 7-11% on metformin monotherapy, or 6.5-9.5% on metformin plus oral diabetes medicine	Change from baseline in HbA1c at week 12
Dapagliflozin + metformin					
Rosenstock 2015	534	MC, R, DB, AC, PG 24 weeks	Low	T2D with HbA1c 8.0-12.0% on metformin	Adjusted mean change from baseline in HbA1c after 24 weeks
Empagliflozin + metformin					
1245.10	495	R, DB, PC, dose ranging, 12 weeks	Low	T2D with HbA1c 7-10% on metformin monotherapy	Change from baseline in HbA1c at week 12
1275.1	686	R, DB, PG, AC 52 weeks	Low	T2D with HbA1c 7-10.5% on metformin	Change from baseline in HbA1c at week 24
1245.24[a]	659	R, MC, OL, AC extension, 90 weeks	Unclear	T2D, successfully completed one of two 12-week trials	Safety of long-term treatment with empagliflozin, including adverse events and hypoglycaemia.
Supplementary indirect comparison: sulfonylurea + metformin common reference					
Ertugliflozin + metformin					
P002	1326	MC, R, DB, AC 52 weeks	Low	T2D with HbA1c 7-9% on metformin	Change from baseline in HbA1c at week 52

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Dapagliflozin + metformin					
CT-004	816	MC, R, DB, PG, AC 52 weeks	Low	T2D with HbA1c 6.5-10% on metformin	Absolute change in HbA1c from baseline to week 52
Empagliflozin + metformin					
1245.28	1549	R, DB, AC 104 weeks	Low	T2D with HbA1c 7-10% on metformin	Change from baseline in HbA1c at week 52 and 104
Ertugliflozin with metformin FDC bioequivalence studies					
P050	16	R, OL, crossover Single dose	Low	Healthy subjects	Bioequivalence
P052	16	R, OL, crossover Single dose	Low	Healthy subjects	Bioequivalence
P027	16	R, OL, crossover Single dose	Low	Healthy subjects	Bioequivalence
P047	16	R, OL, crossover Single dose	Low	Healthy subjects	Bioequivalence

[a] Included in sensitivity analyses only

Abbreviations: AC, active controlled; DB, double blind; MC, multi-centre; OL, open label; PG, parallel group; R, randomised; T2D, type 2 diabetes

Source: Attachment 4 of the submission, relevant trial publications

6.8 The submission supplied details of trial characteristics for the ertugliflozin trials and only the dapagliflozin / empagliflozin trials that contributed to the primary indirect analysis using placebo + metformin as common reference. The submission argued that the dapagliflozin and empagliflozin trials with either DPP4 inhibitor + metformin or sulfonylurea + metformin as common references have been previously evaluated by the PBAC and that therefore a formal critique and summary of the direct results was not presented. These trials were included in the supplementary indirect comparisons, and it was therefore inappropriate to exclude details of the trial characteristics from the submission. Information regarding these trials was compiled during the evaluation.

Comparative effectiveness

6.9 Tables 4 to 6 present the results of the key efficacy outcome, change from baseline in HbA1c, from the included ertugliflozin trials at available time points.

Table 4: Results of change from baseline in HbA1c in placebo-controlled ertugliflozin trials

Trial ID	Ertugliflozin + metformin Hba1c, mean (SD)				Placebo + metformin Hba1c, mean (SD)				LS Mean difference (95% CI)
	N	Baseline	Endpoint	Change	N	Baseline	Endpoint	Change	
P016, 12 weeks									
ERTU 5 mg	53	7.88 (0.13)	NR	[redacted]	51	8.08 (0.14)	NR	[redacted]	[redacted]
P007, 26 weeks									
ERTU 5 mg	207	8.06 (0.89)	7.29 (0.82)	-0.73 (0.88)	209	8.17 (0.90)	7.84 (1.06)	-0.03 (0.92)	-0.70 (-0.87, -0.53)
ERTU 15 mg	205	8.13 (0.93)	7.20 (0.75)	-0.91 (0.91)	209	8.17 (0.90)	7.84 (1.06)	-0.03 (0.92)	-0.88 (-1.05, -0.71)

[a] 95% confidence interval for LS mean difference in Trial P016 was calculated during the submission using Review Manager 5.3 (the Clinical Trial Report included 80% confidence intervals only)

Source: Table 2-17, pp105-106 of the submission, relevant trial reports and publications

CI, confidence interval; ERTU, ertugliflozin; HbA1c, glycosylated haemoglobin; LS, least squares; NR, not reported; SD, standard deviation.

6.10 Results of the placebo-controlled ertugliflozin trials showed statistically significantly greater reductions from baseline in HbA1c compared to placebo at 12 weeks for ertugliflozin 5 mg and at 26 weeks for ertugliflozin 5 mg and 15 mg dose strengths.

6.11 Results for change from baseline in fasting plasma glucose (FPG) levels and proportions of HbA1c responders (HbA1c <7%) were also statistically significantly in favour of ertugliflozin compared to placebo.

6.12 The PBAC considered that, overall, the results of the placebo-controlled ertugliflozin trials suggested a statistically significant difference in HbA1c, FPG and body weight outcomes in favour of ertugliflozin.

Table 5: Results of change from baseline in HbA1c in ertugliflozin trials with sitagliptin arm

Trial ID	Ertugliflozin + metformin Hba1c %, mean (SD)				Sitagliptin + metformin Hba1c %, mean (SD)				LS Mean difference (95% CI) [a]
	N	Baseline	Endpoint	Change	N	Baseline	Endpoint	Change	
P016, 12 weeks									
ERTU 5 mg	55	7.88 (0.13)	NR	[redacted]	55	8.24 (0.15)	NR	[redacted]	[redacted]
P005, 26 weeks									
ERTU 5 mg	250	8.57 (1.05)	7.41 (0.93)	-1.08 (0.98)	247	8.50 (1.03)	7.34 (1.10)	-1.06 (1.04)	0.03 (-0.14, 0.20)
ERTU 15 mg	248	8.57 (1.01)	7.41 (1.04)	-1.11 (0.95)	247	8.50 (1.03)	7.34 (1.10)	-1.06 (1.04)	-0.03 (-0.20, 0.14)
P005, 52 weeks									
ERTU 5 mg	250	8.57 (1.05)	7.23 (0.80)	-1.14 (1.01)	247	8.50 (1.03)	7.13 (0.90)	-1.09 (0.96)	-0.14 (-0.34, 0.06)
ERTU 15 mg	248	8.57 (1.01)	7.16 (0.85)	-1.15 (0.96)	247	8.50 (1.03)	7.13 (0.90)	-1.09 (0.96)	-0.11 (-0.31, 0.09)

[a] Treatment differences for ertugliflozin vs sitagliptin were not performed in Trial P005 or Trial P016, these were calculated post hoc in the submission using Review Manager 5.3

Source: Table 2-17, pp105-106 of the submission, relevant trial reports and publications

CI, confidence interval; ERTU, ertugliflozin; HbA1c, glycosylated haemoglobin; LS, least squares; NR, not reported; SD, standard deviation.

6.13 The included trials were not designed to compare the ertugliflozin and sitagliptin treatment arms, so the difference between treatment groups was calculated *post hoc* in the submission. Results for ertugliflozin 5 mg showed no statistically significant difference in change from baseline in HbA1c compared to sitagliptin 100 mg at 12, 26 and 52 weeks, nor for ertugliflozin 15 mg compared to sitagliptin 100 mg at 26 and 52 weeks. Results of the comparisons between ertugliflozin and sitagliptin were within the non-inferiority margin specified in the submission (the upper bound of the 95% confidence interval was less than 0.4%). This non-inferiority margin has previously been accepted by the PBAC.

6.14 There were no statistically significant differences between ertugliflozin and sitagliptin treatment arms in proportion of HbA1c responders. There was a statistically significant difference in mean change from baseline in fasting plasma glucose in favour of ertugliflozin after 26 and 52 weeks of treatment, but no difference at 12 weeks.

6.15 The PBAC noted there was a statistically significant difference between ertugliflozin and sitagliptin treatment arms in FPG and body weight in favour of ertugliflozin, but considered that these trials were not designed to compare the ertugliflozin and sitagliptin treatment arms, and results must therefore be interpreted with caution.

Table 6: Results of change from baseline in HbA1c in sulfonylurea-controlled ertugliflozin trial

Trial ID	Ertugliflozin + metformin Hba1c %, mean (SD)				Glimepiride + metformin Hba1c %, mean (SD)				LS Mean difference (95% CI) [a]
	N	Baseline	Endpoint	Change	N	Baseline	Endpoint	Change	
P002, 52 weeks									
ERTU 5 mg	448	7.81 (0.60)	7.13 (0.88)	-0.56 (0.97)	437	7.8 (0.6)	6.97 (0.93)	-0.74 (0.96)	0.18 (0.06, 0.30)
ERTU 15 mg	440	7.80 (0.60)	7.09 (0.81)	-0.64 (0.96)	437	7.8 (0.6)	6.97 (0.93)	-0.74 (0.96)	0.10 (-0.02, 0.22)

[a] Treatment differences for ertugliflozin vs sitagliptin were not performed in Trial P005 or Trial P016, these were calculated post hoc in the submission using Review Manager 5.3

Abbreviations: CI, confidence interval; ERTU, ertugliflozin; HbA1c, glycosylated haemoglobin; LS, least squares; SD, standard deviation.

Source: Table 2-17, pp105-106 of the submission, relevant trial reports and publications

6.16 Results of a comparison between ertugliflozin and glimepiride showed no statistically significant difference in change from baseline to week 52 in HbA1c for ertugliflozin 15 mg, but a statistically significant difference in favour of glimepiride for the comparison with ertugliflozin 5 mg. The comparison of ertugliflozin 15mg and glimepiride were within the non-inferiority margin specified in the submission (the upper bound of the 95% confidence interval was less than 0.4%), but glimepiride therapy demonstrated a statistically significantly superior reduction in HbA1c compared to ertugliflozin 5 mg. The submission suggested that the relatively lower baseline HbA1c for patients in trial P002 may have contributed to the lesser treatment effect in this trial compared to the other ertugliflozin trials. Further, dosing of glimepiride in trial P002 exceeded the maximum TGA-recommended dose of 4 mg/day, which the submission suggested could result in an overestimation of the HbA1c reduction from baseline in the glimepiride group.

6.17 A statistically significantly greater proportion of glimepiride treated patients were treatment responders at 52 weeks compared with ertugliflozin treated patients. The submission noted that the administration of glimepiride at doses above the recommended maximum of 4 mg/day, and lower baseline HbA1c levels in this trial, may have contributed to this outcome.

6.18 In contrast, there was a statistically significant difference in change from baseline for FPG in favour of ertugliflozin 15 mg when compared with glimepiride after 52 weeks of treatment, but not for the 5 mg dose.

6.19 The PBAC noted that the glimepiride-controlled ertugliflozin trial suggested a statistically superior reduction in HbA1c in favour of glimepiride compared with ertugliflozin 5 mg, and no statistically significant difference between glimepiride compared with ertugliflozin 15 mg. However the PBAC considered the greater than maximum recommended doses of glimepiride administered in this trial may have influenced the outcome of this comparison.

6.20 In all trials, ertugliflozin treatment was associated with a consistent reduction in total body weight. These results were consistent with the known effects of SGLT2 inhibitors.

6.21 Table 7 presents a summary of the primary and supplementary indirect comparisons of ertugliflozin, dapagliflozin and empagliflozin in change from baseline in HbA1c, with placebo, DPP4 inhibitors or a sulfonylurea as common reference.

Table 7: Summary results of the indirect comparison of change in HbA1c from baseline with ertugliflozin, dapagliflozin and empagliflozin

Change in HbA1c from baseline (mean difference 95% CI, negative results favour ertugliflozin)			
Comparison	**Placebo reference**	**DPP4-I reference**	**Sulfonylurea reference**
12/16 week results			
ERTU 5 mg vs. DAPA 10 mg	[redacted]	NR	NR
ERTU 5 mg vs. EMPA 10 mg	[redacted]	[redacted]	NR
ERTU 5 mg vs. EMPA 25 mg	[redacted]	[redacted]	NR
ERTU 15 mg vs. DAPA 10 mg	NR	NR	NR
ERTU 15 mg vs. EMPA 10 mg	NR	NR	NR
ERTU 15 mg vs. EMPA 25 mg	NR	NR	NR
24/26 week results			
ERTU 5 mg vs. DAPA 10 mg	-0.21 (-0.47, 0.05)	**0.35 (0.07, 0.63)**	NR
ERTU 5 mg vs. EMPA 10 mg	-0.13 (-0.35, 0.09)	-0.01 (-0.25, 0.23)	NR
ERTU 5 mg vs. EMPA 25 mg	-0.06 (-0.28, 0.16)	-0.05 (-0.29, 0.19)	NR
ERTU 15 mg vs. DAPA 10 mg	-0.39 (-0.65, -0.13)	**0.29 (0.01, 0.57)**	NR
ERTU 15 mg vs. EMPA 10 mg	**-0.31 (-0.54, -0.08)**	-0.07 (-0.31, 0.17)	NR
ERTU 15 mg vs. EMPA 25 mg	**-0.24 (-0.47, -0.01)**	-0.11 (-0.35, 0.13)	NR
52 week results			
ERTU 5 mg vs. DAPA 10 mg	NR	NR	NR
ERTU 5 mg vs. EMPA 10 mg	NR	0.07 (-0.18, 0.32)	NR
ERTU 5 mg vs. EMPA 25 mg	NR	0.02 (-0.24, 0.28)	**0.25 (0.11, 0.39)**
ERTU 15 mg vs. DAPA 10 mg	NR	NR	NR
ERTU 15 mg vs. EMPA 10 mg	NR	0.10 (-0.15, 0.35)	NR
ERTU 15 mg vs. EMPA 25 mg	NR	0.05 (-0.21, 0.31)	**0.17 (0.03, 0.31)**

Note: bolded numbers indicate statistically significant differences between treatment groups.

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; DPP4-I, dipeptidyl peptidase 4 inhibitor; EMPA, empagliflozin; ERTU, ertugliflozin; NR, not reported

Source: Figure 2-5, p5; Figure 2.6, p7; Table 2-23, pp5-6; Table 2-24, p7 of the submission; Table 3, pp12-14; Table 4, pp16-17; Table 8, p27; Table 9, p29, Attachment 2 of the submission

6.22 The results of change from baseline in HbA1c in the primary indirect analysis (with placebo as common reference) generally favoured ertugliflozin over dapagliflozin and empagliflozin. Differences between treatments did not exceed the nominated non-inferiority margin.

6.23 The results of the supportive indirect analysis using DPP4 inhibitors as common reference generally favoured dapagliflozin over ertugliflozin with statistically significant differences between treatments. The results also tended to favour empagliflozin over ertugliflozin although these differences were generally small.

6.24 The results of the supportive indirect analysis using sulfonylureas as common reference generally favoured empagliflozin over ertugliflozin with some statistically

significant differences between high dose empagliflozin (25 mg) and ertugliflozin 5 mg and 15 mg.

6.25 The reliability of results from the primary indirect analysis is uncertain, given the limitations of the available evidence (uncertain comparability of trials, inappropriate handling of multi-arm trials, potentially relevant data from additional time points excluded from some analyses, pooling treatment effect estimates from different drugs).

6.26 The results of the ertugliflozin with metformin FDC bioequivalence studies are presented in Table 8.

Table 8: Bioequivalence of ertugliflozin with metformin FDC to individual components

Trial	Adjusted Geometric Mean Ratio (90% CI)		
	AUC_{INF} (ng.h/mL)	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)
Study P027 (n=16)			
ERTU 7.5 mg	[redacted]	[redacted]	[redacted]
MET 1000 mg	[redacted]	[redacted]	[redacted]
Study P047 (n=16)			
ERTU 7.5 mg	[redacted]	[redacted]	[redacted]
MET 1000 mg	[redacted]	[redacted]	[redacted]
Study P050 (n=16)			
ERTU 2.5 mg	[redacted]	[redacted]	[redacted]
MET 500 mg	[redacted]	[redacted]	[redacted]
Study P052 (n=16)			
MET 500 mg fed, n=7	[redacted]	[redacted]	[redacted]
MET 500 mg fasted, n=9	[redacted]	[redacted]	[redacted]

Abbreviations: AUC, area under the curve; CI, confidence intervals; C_{max}, peak serum concentration; ERTU, ertugliflozin; FDC, fixed dose combination; MET, metformin

Source: Table 1-17, p16; Table 1-19, p17; Table 1-21, p18; Table 1-23, p19; Table 1-25, p20; Table 1-27, p21; Table 1-29, p22; Table 1-31, p23, Attachment 1 of the submission.

6.27 The fixed dose combinations in the included ertugliflozin studies met the pre-specified bioequivalence margins against the individual components, with 90% confidence intervals of the geometric mean ratios for the FDC compared to individual components contained within the criterion interval of (80%, 125%). The TGA delegate will assess bioequivalence. At the time of the evaluation and consideration by ESC the TGA delegate's report was not available. The PBAC noted that the Delegate's report was silent on bioequivalence, but saw no reason not to recommend approval of the ertugliflozin 2.5 mg/metformin 500 mg or ertugliflozin 2.5mg/metformin 1 g strengths.

Comparative harms

6.28 Rates of specific adverse events and treatment related adverse events for the ertugliflozin trials are presented in Table 9. Genital infections and urinary tract infections are adverse events of special interest for SGLT2 inhibitors.

Table 9: Summary of key adverse events in the randomised ertugliflozin trials

Trial ID and time point	Treatment arm	Treatment-related AEs	Hypoglycaemia	UTIs	Genital infections
Ertugliflozin + metformin vs placebo + metformin					
P016 12 weeks	ERTU 5 mg + MET	[redacted]	[redacted]	[redacted]	[redacted]
	PBO + MET				
P007 26 weeks	ERTU 5 mg + MET	24/207 (11.6)	8/207 (3.9)	5/207 (2.4)	7/207 (3.4)
	ERTU 15 mg + MET	25/205 (12.2)	10/205 (4.9)	5/205 (2.4)	8/205 (3.9)
	PBO + MET	13/209 (6.2)	6/209 (2.9)	2/209 (1.0)	1/209 (0.5)
Ertugliflozin + metformin vs sitagliptin + metformin					
P016 12 weeks	ERTU 5 mg + MET	[redacted]	[redacted]	[redacted]	[redacted]
	SITA 100 mg + MET				
P005 26 weeks	ERTU 5 mg + MET	42/250 (16.8)	8/250 (3.2)	11/250 (4.4)	7/250 (2.8)
	ERTU 15 mg + MET	30/248 (12.1)	9/248 (3.6)	11/248 (4.4)	11/248 (4.4)
	SITA 100 mg + MET	12/247 (4.9)	6/247 (2.4)	8/247 (3.2)	1/247 (0.4)
P005 52 weeks	ERTU 5 mg + MET	49/250 (19.6)	12/250 (4.8)	20/250 (8.0)	8/250 (3.2)
	ERTU 15 mg + MET	40/248 (16.1)	13/248 (5.2)	19/248 (7.7)	12/248 (4.8)
	SITA 100 mg + MET	21/247 (8.5)	11/247 (4.5)	13/247 (5.3)	2/247 (0.8)
Ertugliflozin + metformin vs glimepiride + metformin					
P002 52 weeks	ERTU 5 mg + MET	82/448 (18.3)	17/448 (3.8)	23/448 (5.1)	2/448 (0.5)
	ERTU 15 mg + MET	95/440 (21.6)	25/440 (5.7)	20/440 (4.6)	4/440 (0.9)
	GLIM + MET	78/437 (17.8)	96/437 (22.0)	24/437 (5.5)	0/437 (0.0)

Note: Trials P007, P002 and P005 26 week analysis excluded safety data after initiation of glycaemic rescue therapy, while P005 52 week analysis included this safety data. Rescue medicine was not offered in trial P016

Abbreviations: AE, adverse event; ERTU, ertugliflozin; GLIM, glimepiride; MET, metformin; PBO, placebo; SITA, sitagliptin; UTI, urinary tract infection

Source: Table 2-21, Section 2.5.2.1 of the submission

6.29 Treatment related adverse events were higher in the ertugliflozin arms than in the comparator arms of the included trials, mainly due to the higher number of adverse events in the categories of gastrointestinal disorders, infections and infestations (e.g. urinary tract infections), and reproductive system and breast disorders (genital infections). Overall, the adverse events observed in the included ertugliflozin trials occurred in relatively few patients and were consistent with the known safety profile of SGLT2 inhibitors.

6.30 The submission summarised the indirect analyses of any adverse event, serious adverse events, adverse events leading to discontinuation, hypoglycaemia events, urinary tract infections or genital infections. There were no statistically significant differences in adverse events between ertugliflozin, dapagliflozin and empagliflozin. These analyses were largely uninformative given the methodological limitations of the indirect analyses and the lack of statistical power to detect differences in adverse event incidence.

Clinical claim

6.31 The submission described ertugliflozin 5 mg and 15 mg as non-inferior in terms of effectiveness compared with dapagliflozin 10 mg or empagliflozin 10 mg or 25 mg, when used in dual oral combination with metformin for the treatment of patients with type 2 diabetes. The submission described ertugliflozin 5 mg and 15 mg as non-inferior in terms of safety compared to dapagliflozin or empagliflozin, when

used in dual oral combination with metformin in patients with type 2 diabetes. The PBAC considered that this claim was supported by the evidence presented in the submission.

6.32 The PBAC considered that the evidence provided in the submission did not support the clinical need for the 15 mg ertugliflozin or 7.5 mg ertugliflozin with 500 mg/1 g metformin fixed dose combinations for listing, especially given the doubt as to the non-inferior safety profile compared to their respective comparators.

6.33 The PBAC noted the limitations of the available evidence from indirect analyses (uncertain comparability of trials, inappropriate handling of multi-arm trials, potentially relevant data from additional time points being excluded from some analyses, pooling treatment effect estimates from different drugs), but considered the data submitted was acceptable despite a potential lack of transitivity.

6.34 The PBAC noted that there was no direct evidence supporting ertugliflozin dual therapy in combination with a sulfonylurea, although the proposed PBS listing would allow use of ertugliflozin with either metformin or a sulfonylurea. The PBAC recalled that this was consistent with the dual oral therapy listing for the comparator empagliflozin, which was recommended on the basis of evidence with metformin only.

6.35 The PBAC considered that the limited availability of long-term efficacy and safety data for ertugliflozin was consistent with other SGLT2 inhibitors and some DPP4 inhibitors and was not an impediment to listing.

6.36 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.37 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.38 The equi-effective doses were estimated as ertugliflozin 5 mg or 15 mg, once daily and dapagliflozin 10 mg or empagliflozin 10 mg or 25 mg, once daily. Estimates of equi-effectiveness were trial based. Equi-effectiveness of the comparators was derived from Therapeutic Relativity Sheets. The PBAC considered that as the TGA delegate was only inclined to list the 5 mg strength of ertugliflozin, this was the only strength that could be recommended for PBS listing at this time, and therefore considered that the equi-effective doses were ertugliflozin 5 mg (once daily), and dapagliflozin 10 mg or empagliflozin 10 mg or 25 mg (once daily).

6.39 Results of the cost-minimisation analysis for ertugliflozin are presented in Table 10.

Table 10: Results of the cost-minimisation analysis, ertugliflozin

Component	ERTU 5 mg	ERTU 15 mg	DAPA 10 mg	EMPA 10 mg	EMPA 25 mg
PBS item code	-	-	10011X	10206E	10202Y
Maximum quantity	28	28	28	30	30
AEMP per max quantity	$43.88	$43.88	$43.88	$47.01	$47.01
AEMP per day	$1.57	$1.57	$1.57	$1.57	$1.57
DPMQ	$58.27	$58.27	$58.27	$61.64	$61.64

Abbreviations: AEMP, approved ex-manufacturer price; DAPA, dapagliflozin; DPMQ, dispensed price for maximum quantity; EMPA, empagliflozin; ERTU, ertugliflozin; max, maximum
Source: Table 3.4.1-1, Section 3.4.1 of the submission

6.40 The AEMP per day for ertugliflozin is the same as for all doses of the comparators, dapagliflozin and empagliflozin. The DPMQ for both dose strengths of empagliflozin is slightly higher than the other SGLT2 inhibitors due to differences in pack size (30 days of therapy compared to 28).

6.41 The estimated equi-effective doses for ertugliflozin with metformin FDC, noting that the based on the TGA delegates report the PBAC has only supported listing of the 2.5 mg ertugliflozin FDCs, and the individual components are as follows:

- Ertugliflozin with metformin 2.5 mg/500 mg FDC (twice daily) is equivalent to ertugliflozin 5 mg once daily and metformin 500 mg twice daily;
- Ertugliflozin with metformin 2.5 mg/1 g FDC (twice daily) is equivalent to ertugliflozin 5 mg once daily and metformin 1 g twice daily;

6.42 Results of the cost-minimisation analysis for ertugliflozin with metformin FDC are presented in Table 11. The AEMP per day for ertugliflozin and the relevant strength of metformin were added to give the AEMP per day for the corresponding FDC dose strength. The submission noted that the AEMP proposed in this submission is equivalent to other SGLT2 inhibitor with metformin FDCs, when adjusted for pack size.

Table 11: Results of the cost-minimisation analysis, ertugliflozin with metformin FDC

Component	ERTU 5 mg or 15 mg	MET 500 mg	MET 1000 mg	FDC with MET 500 mg	FDC with MET 1000 mg
PBS item code	-	2430X	8607B	-	-
Maximum quantity	28	100	90	56	56
AEMP per max quantity	$43.88	$2.50	$4.36	$45.28	$46.59
AEMP per day	$1.57	$0.05 [a]	$0.10 [a]	$1.62	$1.67
DPMQ	$58.27	$13.78	$15.78	$59.78	$61.18

[a] assuming twice-daily regimen
Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, dispensed price for maximum quantity; ERTU, ertugliflozin; FDC, fixed dose combination; MET, metformin
Source: Table 3.4.1-2, Table 3.4.1-3 Section 3.4.1 of the submission

Drug cost/patient/year

6.43 The cost of ertugliflozin 5 mg or 15 mg per patient per year is $759.84 (DPMQ $58.27 for 28 days treatment x 13.04), which is the same as the cost per patient per year for dapagliflozin 10 mg. The cost of empagliflozin 10 mg and 25 mg per patient per year is $749.95 (DPMQ $61.64 for 30 days treatment x 12.17). The small difference in

costs per year for empagliflozin is due the larger pack size which requires fewer prescriptions per year. Treatment is ongoing.

6.44 The cost of ertugliflozin with metformin FDC per patient per year varies depending on metformin dose:

- Ertugliflozin 2.5 mg or 7.5 mg with metformin 500 mg: $779.53 (DMPQ $59.78 for 28 days treatment x 13.04)
- Ertugliflozin 2.5 mg or 7.5 mg with metformin 1 g: $797.79 (DPMQ $61.18 for 28 days treatment x 13.04).

Estimated PBS usage & financial implications

6.45 This submission was not considered by DUSC. A market share approach was used to estimate utilisation and financial impact of ertugliflozin and ertugliflozin with metformin FDC.

6.46 Table 12 presents the estimated use and financial impact of a PBS listing for ertugliflozin, and ertugliflozin with metformin FDC.

Table 12: Estimated use and financial implications

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Extrapolated dapagliflozin single agent scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolated empagliflozin single agent scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolated empagliflozin with metformin FDC scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total gliflozin scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of gliflozin scripts for dual therapy[b]	33.2%	33.7%	34.1%	34.4%	34.7%	34.8%
Dual therapy gliflozin scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated uptake rate of ertugliflozin	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Total ertugliflozin scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ertugliflozin single agent scripts (78%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of ertugliflozin single agent (DPMQ $58.27)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated ertugliflozin with metformin 500 mg FDC scripts (4%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of ertugliflozin with metformin 500 mg FDC scripts (DPMQ $59.78)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated ertugliflozin with metformin 1000 mg FDC scripts (18%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of ertugliflozin with metformin 1000 mg FDC scripts (DPMQ $61.19)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Patient copayments (average $16.79 per script)	-$	-$	-$	-$	-$	-$
Total cost	$	$	$	$	$	$
Change in dapagliflozin single agent scripts						
Cost of substituted single agent dapagliflozin	-$	-$	-$	-$	-$	-$
Change in empagliflozin single agent scripts[a]						
Cost of substituted single agent empagliflozin	-$	-$	-$	-$	-$	-$
Change in empagliflozin with metformin 500 mg FDC scripts[a]						
Cost of substituted empagliflozin with metformin 500 mg FDC scripts	-$	-$	-$	-$	-$	-$
Change in empagliflozin with metformin 1000 mg FDC scripts[a]						
Cost of substituted empagliflozin with metformin 1000 mg FDC scripts	-$	-$	-$	-$	-$	-$
Net cost to the PBS/RPBS	$	$	$	$	$	$

Source: Constructed during the evaluation based on Att 8 Excel workbook

Abbreviations: DPMQ, dispensed price for maximum quantity; FDC, fixed dose combination; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

[a] The PBS script duration for empagliflozin covers 30 days of therapy. Estimates were adjusted to 28-day equivalents (consistent with dapagliflozin and ertugliflozin script duration) to estimate the market size. Estimates were then converted back to 30-day equivalents when estimating the change in use of substituted therapies

[b] Based on 30% dual therapy use for PBS item 10011X, 10206E, 10202Y, 10626G, 10627H, 10633P, 10677Y and 100% dual therapy use for PBS item 10650M, 10649L, 10639Y, 10640B

The redacted table shows that the estimated total number of ertugliflozin scripts dispensed in Year 1 was in the range of 10,000 – 50,000 per year, increasing to 50,000 – 100,000 per year in Year 6. The redacted table also shows that the estimated cumulative net cost to the PBS over 6 years would be substantially less than $10 million.

6.47 Overall, the budget impact estimates appear to be reasonable given that the requested listing was based on a cost-minimisation analysis of similar products using drug costs only with no obvious expectation of market growth. However, the expected utilisation patterns of ertugliflozin, dapagliflozin and empagliflozin are uncertain, given the dynamics of the SGLT2 inhibitor market are rapidly changing with the recent listings of dapagliflozin with metformin and empagliflozin with metformin FDCs as well as the potential introduction of dapagliflozin with saxagliptin FDC (considered at the July 2017 PBAC meeting) and empagliflozin with linagliptin FDC (considered at the November 2017 PBAC meeting). The potential future availability of ertugliflozin with sitagliptin FDC (the most widely used DPP4 inhibitor therapy) may also affect uptake rates of other ertugliflozin products.

6.48 The PBAC considered that the growth rate assumption regarding SGLT2 inhibitors in the financial estimates was uncertain given the changes to the dynamics of the SGLT2 market.

6.49 The proposed restriction for ertugliflozin (dual therapy only) is narrower than other available PBS listed SGLT2 therapies (dual, triple and combination with insulin) which may cause confusion amongst physicians and lead to potential leakage outside the proposed restriction.

Quality Use of Medicines

6.50 The submission detailed educational material for health care professionals to ensure the appropriate use of ertugliflozin.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of the 5 mg dose strength ertugliflozin for dual oral therapy with metformin or a sulfonylurea, and the 2.5 mg ertugliflozin with 500 mg metformin, and 2.5 mg ertugliflozin with 1 g metformin fixed dose combinations, for the treatment of type 2 diabetes in patients inadequately controlled with metformin or a sulfonylurea.

7.2 The PBAC advised that given a positive TGA Delegate's Overview was not received for the ertugliflozin 15 mg dose strength, a recommendation for listing of the 15 mg dose strength could not be made. However, the PBAC considered that the evidence provided in the submission did not support the clinical need for the 15 mg ertugliflozin or 7.5 mg ertugliflozin with 500 mg/1 g metformin fixed dose combinations for listing, especially given the doubt as to the non-inferior safety profile compared to their respective comparators.

7.3 The PBAC considered that the nominated primary comparators dapagliflozin and empagliflozin were acceptable.

7.4 The PBAC considered that the evidence presented in the submission supported a claim of non-inferior efficacy and safety for ertugliflozin compared to dapagliflozin or empagliflozin. The equi-effective doses are ertugliflozin 5 mg (once daily) and dapagliflozin 10 mg or empagliflozin 10 mg or 25 mg (once daily).

7.5 The PBAC considered that the evidence presented in the submission supported a claim of non-inferior efficacy and safety for ertugliflozin with metformin FDC (2.5 mg ertugliflozin with 500 mg metformin, and 2.5 mg ertugliflozin with 1 g metformin) compared to the individual components. The PBAC considered that the fixed dose combinations in the included ertugliflozin studies met the pre-specified bioequivalence margins against the individual components. The equi-effective doses for the FDC were considered to be equivalent to the same dose of individual components taken concomitantly.

7.6 The PBAC considered that there was no statistically significant difference in HbA1c change from baseline between treatment with ertugliflozin 5 mg and dapagliflozin or empagliflozin, with the difference between treatments meeting the nominated non-inferiority margin (upper 95% CI < 0.40%).

7.7 The PBAC noted that there was no statistically significant difference in HbA1c responders at Week 24/26 between ertugliflozin, dapagliflozin and empagliflozin treatment groups.

7.8 The PBAC considered that, overall, the adverse events observed in the included ertugliflozin 5 mg trials occurred in relatively few patients and were consistent with the known safety profile of SGLT2 inhibitors. The PBAC noted that the TGA delegate considered that the rate of adverse events was higher for the patients taking a 15 mg dose.

7.9 In making their recommendation for listing, the PBAC noted that the 15 mg dose strength of ertugliflozin did not receive a positive recommendation in the TGA Delegate's Overview, [redacted]. The PBAC also advised that no direct evidence was provided to indicate that there were improved outcomes from an increase in dose from 5 to 15 mg in patients with poor glycaemic control on the 5 mg ertugliflozin dose, and therefore the clinical need for availability of the 15 mg dose strength of ertugliflozin to the market had not been established.

7.10 The PBAC considered that the proposed restriction for ertugliflozin (dual therapy only) being narrower than other available PBS listed SGLT2 therapies may cause confusion amongst physicians and lead to potential leakage outside the proposed restriction. It therefore recommended the addition of appropriate wording in the administrative advice to preclude the use of ertugliflozin in triple therapy.

7.11 The PBAC considered that the growth rate assumption regarding SGLT2 inhibitors in the financial estimates was uncertain given the changes to the dynamics of the SGLT2 market.

7.12 The PBAC advised that, under subsection 101(3BA) of the *National Health Act 1953* ertugliflozin and ertugliflozin with metformin should be treated as interchangeable on an individual patient basis with dapagliflozin and empagliflozin, and their corresponding fixed dose combinations with metformin, respectively.

7.13 The PBAC advised that ertugliflozin and ertugliflozin with metformin is suitable for prescribing by nurse practitioners for continuing therapy only, consistent with the current PBS listings for other SGLT2 inhibitors.

7.14 The PBAC recommended that the Early Supply Rule should apply to ertugliflozin and ertugliflozin with metformin as the Early Supply Rule applies to the current PBS listings for other SGLT2 inhibitors.

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it has received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ERTUGLIFLOZIN				
ertugliflozin 5 mg tablet, 28	1	5	Steglatro®	Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☒Streamlined
Clinical criteria:	The treatment must be in combination with metformin; OR The treatment must be in combination with a sulfonylurea, AND Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with either metformin or a sulfonylurea; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period despite treatment with either metformin or a sulfonylurea.

Prescriber Instructions	The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) Had red cell transfusion within the previous 3 months. The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records. A patient whose diabetes was previously demonstrated unable to be controlled with metformin or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.
Administrative Advice	Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. This drug is not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin), insulin or a glucagon-like peptide-1.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ERTUGLIFLOZIN + METFORMIN				
ertugliflozin 2.5 mg + metformin 500 mg tablet, 56	1	5	Segluromet®	Merck Sharp & Dohme (Australia) Pty Ltd
ertugliflozin 2.5 mg + metformin 1 g tablet, 56	1	5		

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	Initial *treatment*
Restriction Level / Method:	☒Streamlined
Clinical criteria:	Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with metformin; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period despite treatment with metformin.

Prescriber Instructions	The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) Had red cell transfusion within the previous 3 months. The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records. A patient whose diabetes was previously demonstrated unable to be controlled with metformin does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.
Administrative Advice	This fixed dose combination is not PBS subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin), insulin or a glucagon-like peptide-1.

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	Continuing *treatment*
Restriction Level / Method:	☒Streamlined
Clinical criteria:	Patient must have previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and ertugliflozin.
Administrative Advice	*Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.* This fixed dose combination is not PBS subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin), insulin or a glucagon-like peptide-1.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.