

**6.04 ERTUGLIFLOZIN with SITAGLIPTIN,
Fixed dose combination tablet, 5 mg/100 mg;
15 mg/100 mg,
Steglujan[®],
Merck Sharp & Dohme**

NOTE: Add-on components in the clinical trials are denoted using square bracket, for example [ertugliflozin] or [placebo] was added to dual therapy consisting of sitagliptin plus metformin.

1 Purpose of Application

- 1.1 The submission requested an Authority Required (Streamlined) listing for ertugliflozin with sitagliptin fixed dose combination (FDC) in combination with metformin, for the treatment of Type 2 diabetes mellitus (T2DM) in patients uncontrolled on metformin and a dipeptidyl peptidase 4 (DPP4) or sodium-glucose co-transporter 2 (SGLT2) inhibitor.
- 1.2 The submission was for:
 - the addition of ertugliflozin with sitagliptin (5 mg/100 mg, 15 mg/100 mg) FDC products to the PBS; and
 - for changes to the PBS restrictions of ertugliflozin (5 mg, 15 mg), ertugliflozin with metformin (2.5 mg/500 mg, 2.5 mg/1 g, 7.5 mg/500 mg, 7.5 mg/1 g) FDC products, sitagliptin (25 mg, 50 mg, 100 mg) and sitagliptin with metformin (50 mg/500 mg, 50 mg/850 mg, 50 mg/1 g, 50 mg/1 g extended release (XR), 100 mg/1 g XR) FDC products to allow their use as triple therapies.
- 1.3 The combination of ertugliflozin plus sitagliptin has not been considered by the PBAC previously.
- 1.4 In March 2018 ertugliflozin (5 mg, 15 mg) as a single agent and ertugliflozin with metformin (2.5 mg/500 mg, 2.5 mg/1 g, 7.5 mg/500 mg, 7.5 mg/1 g) FDC products were considered for listing.
- 1.5 The PBAC recommended ertugliflozin 5 mg and ertugliflozin with metformin 2.5 mg/500 mg and 2.5 mg/1 g FDC products for PBS listing. The PBAC did not recommend ertugliflozin 15 mg and ertugliflozin with metformin 7.5 mg/500 mg and 7.5 mg/1 g FDC products as the TGA Delegate's Overview was not positive and the evidence did not support a clinical need (paragraph 7.2, March 2018 Public Summary Document (PSD) for ertugliflozin and ertugliflozin with metformin).

- 1.6 Following the 8 April ACM, the TGA registered ertugliflozin 5 mg and 15 mg and all strengths of the related FDC products.
- 1.7 Consequently, a minor resubmission for ertugliflozin 15 mg and ertugliflozin with metformin 7.5 mg/500 mg and 7.5 mg/1 g FDC products was considered and the items were recommended for PBS listing at the July 2018 PBAC meeting.
- 1.8 In November 2017, the PBAC recommended two SGLT2 inhibitor plus DPP4 inhibitor plus metformin triple oral combination therapies:
 - Dapagliflozin plus saxagliptin plus metformin, including the addition of the dapagliflozin with saxagliptin FDC product (10 mg/5 mg) to the PBS and changes to the relevant PBS restrictions of the associated single agent and FDC products;
 - Empagliflozin plus linagliptin plus metformin, including the addition of the empagliflozin with linagliptin FDC products (10 mg/5 mg and 25 mg/1 g) to the PBS and changes to the relevant PBS restrictions of the associated single agent and FDC products.
- 1.9 The submission presented a cost-minimisation analysis for ertugliflozin with sitagliptin (5 mg/100 mg, 15 mg/100 mg) FDC products based on non-inferior efficacy and safety compared to dapagliflozin with saxagliptin and empagliflozin with linagliptin FDC products.

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

Component	Description
Population	Patients with T2DM with inadequate glycaemic control, who have been previously stabilised on dual or triple oral therapy which included a SGLT2 or DPP4 inhibitor.
Intervention	Ertugliflozin 5 mg with sitagliptin 100 mg FDC, in combination with metformin Ertugliflozin 15 mg with sitagliptin 100 mg FDC, in combination with metformin
Comparator	Triple oral combination therapy consisting of either: - Dapagliflozin plus saxagliptin plus metformin; or - Empagliflozin plus linagliptin plus metformin.
Outcomes	Mean change in HbA _{1c} , proportion of HbA _{1c} responders (< 7.0%), mean change in FPG, body weight, safety, hypoglycaemic events
Clinical claim	In triple oral combination therapy, ertugliflozin (5 mg or 15 mg) is non-inferior to dapagliflozin (10 mg) and empagliflozin (10 mg or 25 mg); sitagliptin (100 mg) is non-inferior to saxagliptin (5 mg) and linagliptin (5 mg). For the FDC of ertugliflozin with sitagliptin, there is bioequivalence compared with the individual components taken concurrently at corresponding doses.
Economic analysis	Cost-minimisation analysis versus the comparator FDC products, dapagliflozin 10 mg with saxagliptin 5 mg and empagliflozin 10 mg or 25 mg with linagliptin 5 mg.

Source: Table 1-1, Section 1.1.1 of the submission

DPP4 = dipeptidyl peptidase-4; FDC = fixed dose combination; FPG = fasting plasma glucose; HbA_{1c} = glycated haemoglobin; SGLT2 = sodium-glucose co-transporter-2; T2DM = Type 2 diabetes mellitus

2 Requested listing

- 2.1 The requested PBS listing for ertugliflozin with sitagliptin FDC products is presented below. Following the PBS listing of the dapagliflozin with saxagliptin and empagliflozin with linagliptin FDC products on 1 April 2018, the Pre-PBAC response

requested the same restriction wording and dispensed price for the maximum quantity (DPMQ).

2.2 As per the PBS listings of dapagliflozin and saxagliptin and empagliflozin and linagliptin on 1 April 2018 for use as triple oral therapies in combination with metformin, the Pre-PBAC response requested that:

- the note precluding use with a DPP4 inhibitor be deleted from the PBS restrictions for ertugliflozin and ertugliflozin with metformin FDC products. This amendment was also requested in the July 2018 minor resubmission for ertugliflozin 15 mg and ertugliflozin with metformin 7.5 mg/500 mg and 7.5 mg/1 g; and
- the note precluding use with a SGLT2 inhibitor be deleted from the PBS restrictions for sitagliptin and sitagliptin with metformin FDC products.

Name, Restriction, Manner of administration and form	Max. qty packs	No. of Rpts	DPMQ	Proprietary Name and Manufacturer
ERTUGLIFLOZIN WITH SITAGLIPTIN				
ertugliflozin 5 mg + sitagliptin 100 mg tablet, 28	1	5	\$79.43	Steglujan [®] Merck, Sharp & Dohme
ertugliflozin 15 mg + sitagliptin 100 mg tablet, 28	1	5	\$79.43	

Category/Program:	General Schedule, Section 85
PBS indication:	Diabetes mellitus type 2
Restriction:	Streamlined
Treatment phase:	Initial treatment
Clinical criteria:	<p>The treatment must be in combination with metformin;</p> <p>AND</p> <p>Patient must have an HbA1c measurement greater than 7% despite treatment with dual oral combination therapy with metformin and a dipeptidyl peptidase 4 inhibitor (gliptin) or a sodium-glucose co-transporter 2 (SGLT2) inhibitor;</p> <p>OR</p> <p>Patient must have, 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 prior to initiation of triple oral therapy with a sodium-glucose co-transporter 2 (SGLT2) inhibitor, metformin and a gliptin.</p> <p>The date and level of the qualifying HbA1c measurement must be documented in the patient's medical records at the time triple oral therapy with an SGLT2 inhibitor, metformin and a gliptin is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with an SGLT2 inhibitor, metformin and a gliptin is initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p>

	The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of triple oral therapy with an SGLT2 inhibitor, metformin and a gliptin, must be documented in the patient's medical records.
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Category/Program:	General Schedule, Section 85
PBS indication:	Diabetes mellitus type 2
Restriction:	Streamlined
Treatment phase:	Continuing treatment
Clinical criteria:	The treatment must be in combination with metformin; AND Patient must have previously received a PBS-subsidised regimen of oral diabetic medicines which included a sodium-glucose co-transporter 2 (SGLT2) inhibitor, metformin and a gliptin for this condition.

- 2.3 Although the submission did not propose a special pricing arrangement, it acknowledged that the proposed DPMQ may not reflect the actual price of the comparator products and stated a willingness to adjust the proposed price to ensure the cost-minimisation framework was maintained.

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

3 Background

Registration status

- 3.1 The submission for the ertugliflozin with sitagliptin FDC products was made under TGA/PBAC Parallel Process. At the time of PBAC consideration (following the 8 April ACM), the TGA had registered ertugliflozin with sitagliptin 5 mg/100 mg and 15 mg/100 mg for the following indication:

“As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.”

- 3.2 Ertugliflozin 5 mg and 15 mg as a single agent and ertugliflozin with metformin FDC products were also approved by the TGA in April 2018 for the same indication.
- 3.3 The TGA indications for sitagliptin and sitagliptin-based FDC products do not allow for use as triple oral therapy in combination with a SGLT2 inhibitor and metformin.

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

4 Population and disease

- 4.1 T2DM is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, insufficient insulin secretion or both. The

submissions target population was patients with T2DM who were inadequately controlled, but had been previously stabilised, on dual or triple oral combination therapy which included a SGLT2 inhibitor or a DPP4 inhibitor and metformin. Inadequate control was defined in existing PBS criteria as glycated haemoglobin (HbA_{1c}) greater than 7.0%.

- 4.2 The submission stated that the listing of ertugliflozin plus sitagliptin plus metformin would result in no change to the current clinical management algorithm for T2DM. Triple therapy would be initiated in patients who were uncontrolled on dual therapy consisting of metformin plus either a SGLT2 inhibitor or a DPP4 inhibitor.
- 4.3 The place in therapy for ertugliflozin plus sitagliptin plus metformin would be the same as for the PBS-recommended triple therapy combinations of a SGLT2 inhibitor plus a DPP4 inhibitor plus metformin.

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

5 Comparator

- 5.1 For the triple therapy combination of ertugliflozin 5 mg or 15 mg plus sitagliptin 100 mg plus metformin, the submission nominated two primary comparators:
 - dapagliflozin 10 mg plus saxagliptin 5 mg plus metformin; and
 - empagliflozin 10 mg or 25 mg plus linagliptin 5 mg plus metformin.
- 5.2 For ertugliflozin plus sitagliptin 5 mg/100 mg or 15 mg/100 mg FDC products, the nominated comparators were:
 - the individual components taken concurrently at the corresponding doses;
 - dapagliflozin with saxagliptin (10 mg/5 mg) FDC product; and
 - empagliflozin with linagliptin (10 mg/5 mg, 25 mg/5 mg) FDC products.
- 5.3 The PBAC considered that the nominated comparators were appropriate.

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

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 primary clinical comparison was an indirect comparison of ertugliflozin plus sitagliptin plus metformin with dapagliflozin plus saxagliptin plus metformin and empagliflozin plus linagliptin plus metformin. Placebo plus a DPP4 inhibitor plus metformin was the common reference arm. The comparison included the results from three key randomised controlled trials:

- P006 – a comparison of [ertugliflozin or placebo] plus sitagliptin plus metformin (N = 462);
- Mathieu 2015 – a comparison of [dapagliflozin or placebo] plus saxagliptin plus metformin (N = 320); and
- Softeland 2017 – a comparison of [empagliflozin or placebo] plus linagliptin plus metformin (N = 327).

6.4 Supporting information was provided by three additional randomised controlled trials:

- Jabbour 2014 – a comparison of [dapagliflozin or placebo] plus sitagliptin plus metformin (N = 226);
- Matthaei 2015 – a comparison of [saxagliptin or placebo] plus dapagliflozin plus metformin (N = 315); and
- Tinahones 2016 – a comparison of [linagliptin or placebo] plus empagliflozin plus metformin (N = 467).

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

Table 2: Randomised controlled trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
[ERTU] + SITA + MF versus [PBO] + SITA + MF		
P006	Study P006 – A Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group clinical trial to evaluate the safety and efficacy of ertugliflozin (MK-8835/PF-04971729) in the treatment of subjects with Type 2 diabetes mellitus who have inadequate glycaemic control on metformin and sitagliptin. Dagogo-Jack S, Liu J, Eldor R, Amorn G, Johnson J, <i>et al.</i> 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 randomised study. Eldor R, Liu J, Dagogo-Jack S, Amorn G, Johnson J, <i>et al.</i> Safety and efficacy of ertugliflozin after 52 weeks in patients with Type 2 diabetes inadequately controlled on metformin and sitagliptin: VERTIS SITA2 trial extension. Lauring B, Eldor R, Liu J, Dagogo-Jack S, Amorn G, <i>et al.</i> Efficacy and safety of ertugliflozin in subjects with Type 2 diabetes mellitus inadequately controlled on the dual combination of metformin and sitagliptin: The VERTIS SITA2 trial.	27 October 2016 <i>Diabetes, Obesity and Metabolism.</i> 2017; 20(3): 530-540. Conference abstract: <i>Diabetologia.</i> 2017; 60: 1 Supp 1 (S21). Conference abstract: <i>Diabetologia.</i> 2016; 59(1): S93.

Trial ID	Protocol title/ Publication title	Publication citation
	Liu J, Eldor R, Dagogo-Jack S, Amarin G, Johnson J, <i>et al.</i> Safety and efficacy of ertugliflozin after 52 weeks in subjects with T2DM inadequately controlled on metformin and sitagliptin: Results from the extension phase of the VERTIS SITA2 trial.	Conference abstract: <i>Diabetes</i> . 2017; 66: A35.
[DAPA] + SAXA + MF versus [PBO] + SAXA + MF		
Mathieu 2015	Mathieu C, Ranetti AE, Li D, <i>et al.</i> Randomised, double-blind, Phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in Type 2 diabetes. Mathieu C, Herrera Marmolejo M, Gonzalez Gonzalez JG, <i>et al.</i> Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with Type 2 diabetes. Mathieu C, Ranetti AE, Li D, <i>et al.</i> A randomised, double-blind, Phase 3 trial of dapagliflozin add-on to saxagliptin plus metformin in Type 2 diabetes. Mathieu C, Ranetti AE, Li D, <i>et al.</i> A randomised, double-blind, Phase 3 trial of dapagliflozin add-on to saxagliptin plus metformin in Type 2 diabetes.	<i>Diabetes Care</i> . 2015; 38: 2009-2017. <i>Diabetes, Obesity and Metabolism</i> . 2016; 18: 1134-1137. Conference abstract: <i>Diabetologia</i> . 2015; 58: S356. Conference abstract: <i>Diabetes</i> . 2015; 64: A28.
[EMPA] + LINA + MF versus [PBO] + LINA + MF		
Softeland 2017	Softeland E, Meier JJ, Vangen B, <i>et al.</i> Empagliflozin as add-on therapy in patients with Type 2 diabetes inadequately controlled with linagliptin and metformin: A 24-week randomised, double-blind parallel-group trial.	<i>Diabetes Care</i> . 2017; 40: 201-209.
	Maldonado-Lutomirsky M, Softeland E, Meier JJ, <i>et al.</i> Empagliflozin as add-on to linagliptin and metformin in patients with Type 2 diabetes: A 24-week randomised, double-blind, parallel-group trial. Seufert J, Softeland E, Toorawa R, <i>et al.</i> HbA _{1c} response to open-label linagliptin with metformin in patients with Type 2 diabetes. Seufert J, Naderali E, Maldonado M, <i>et al.</i> Empagliflozin as add-on to linagliptin and metformin in patients with Type 2 diabetes: Subgroup analysis by baseline demographics in a 24-week randomised trial. Softeland E, Meier JJ, Vangen B, <i>et al.</i> Empagliflozin as add-on to linagliptin and metformin in patients with Type 2 diabetes: Subgroup analysis by region in a 24-week randomised trial. Wanner C, Naderali E, Maldonado M, <i>et al.</i> Empagliflozin as add-on to linagliptin and metformin in patients with Type 2 diabetes: Subgroup analysis by region in a 24-week randomised trial.	Conference abstract: <i>Diabetologia</i> . 2016; 59: S93. Conference abstract: <i>Diabetes</i> . 2017; 66: A345. Conference abstract: <i>Diabetes</i> . 2016; 65 Supp 1: A292. Conference abstract: <i>Diabetes</i> . 2016; 65 Supp 1: A295. Conference abstract: <i>Diabetes</i> . 2016; 65 Supp 1: A228-A289.
Supportive trials: SGLT2 + DPP4 + MF		
Matthaei 2015	Matthaei S, Catrinou D, Celinski A, <i>et al.</i> Randomised, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with Type 2 diabetes. Matthaei S, Aggarwal N, Garcia-Hernandez P, <i>et al.</i> One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Matthaei S, Catrinou D, Celinski A, <i>et al.</i> A randomised, double-blind trial of saxagliptin add-on to dapagliflozin plus metformin. Blonde L, Mathieu C, Sheehan JJ, <i>et al.</i> Quality measures assessment of triple therapy with saxagliptin plus dapagliflozin plus metformin in Type 2 diabetes mellitus patients with inadequate response to dapagliflozin plus metformin or saxagliptin plus metformin. Catrinou D, Matthaei S, Celinski A, <i>et al.</i> A randomised, double-blind trial of saxagliptin add-on to dapagliflozin plus metformin.	<i>Diabetes Care</i> . 2015; 38: 2018-2024. <i>Diabetes, Obesity and Metabolism</i> . 2016; 18: 1128-1133. Conference abstract: <i>Diabetes</i> . 2015; 64: A27-A28. Conference abstract: <i>Diabetes</i> . 2016; 65 Supp 1: A296. Conference abstract: <i>Diabetologia</i> . 2015; 58: S386.
Tinahones 2016	Tinahones FJ, Gallwitz B, Nordaby M, <i>et al.</i> Linagliptin as add-on to empagliflozin and metformin in patients with Type 2 diabetes: Two 24-week randomised, double-blind, double-dummy, parallel-group trials.	<i>Diabetes, Obesity and Metabolism</i> . 2017; 19: 266-274.

Trial ID	Protocol title/ Publication title	Publication citation
	Tinahones FJ, Gallwitz B, Nordaby M, <i>et al.</i> Linagliptin as add-on to empagliflozin and metformin in patients with Type 2 diabetes: Two 24-week, randomised, double-blind, parallel-group trials. Kis SG, Khunti K, Maldonado M, <i>et al.</i> Linagliptin as add-on to empagliflozin and metformin in patients with Type 2 diabetes: Subgroup analysis by baseline demographics in two 24-week randomised, double-blind, parallel-group trials. Tinahones FJ, Gallwitz B, Nordaby M, <i>et al.</i> Linagliptin as add-on to empagliflozin and metformin in patients with Type 2 diabetes: Two 24-week randomised, double-blind, parallel-group trials.	Conference abstract: <i>Diabetes</i> . 2016; 65 Supp 1: A50. Conference abstract: <i>Diabetes</i> . 2016; 65 Supp 1: A297-A298. Conference abstract: <i>Diabetologia</i> . 2016; 59: S371-S372.
Jabbour 2014	Jabbour S, Hardy E, Sugg J, <i>et al.</i> Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: A 24-week multicentre, randomised, double-blind, placebo-controlled study. Jabbour S, Hardy E, Sugg J, <i>et al.</i> Dapagliflozin is safe and effective as add on therapy to sitagliptin with or without background metformin. Jabbour S, Hardy E, Sugg J, <i>et al.</i> Dapagliflozin as add-on therapy to sitagliptin with or without metformin: A randomised, double-blind, placebo-controlled study.	<i>Diabetes Care</i> . 2014; 37: 40-750. Conference abstract: <i>Diabetologia</i> . 2012; 55: S311. Conference abstract: <i>Diabetes</i> . 2012; 61: A275-A276.

Source: Table 2-6, Section 2.2.3 of the submission

DAPA = dapagliflozin; DPP4 = dipeptidyl peptidase-4; EMPA = empagliflozin; ERTU = ertugliflozin; LINA = linagliptin; MF = metformin; PBO = placebo; SAXA = saxagliptin; SGLT2 = sodium-glucose co-transporter-2; SITA = sitagliptin

6.6 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
[ERTU] + SITA + MF versus [PBO] + SITA + MF					
P006	462	R, DB, MC 26/52 weeks	Low ^a	T2DM; HbA _{1c} ≥ 7.0% to ≤ 10.5%	Δ HbA _{1c} , % HbA _{1c} < 7.0%, Δ FPG, Δ weight, safety
[SGLT2] + DPP4 + MF versus [PBO] + DPP4 + MF					
Mathieu 2015	320	R, DB, MC 24/52 weeks	Low ^a	T2DM; HbA _{1c} ≥ 7.0% to ≤ 10.5%	Δ HbA _{1c} , % HbA _{1c} < 7.0%, Δ FPG, Δ weight, safety
Softeland 2017	327	R, DB, MC 24 weeks	Low ^a	T2DM; HbA _{1c} ≥ 7.0% to ≤ 10.5%	Δ HbA _{1c} , % HbA _{1c} < 7.0%, Δ FPG, Δ weight, safety
Jabbour 2014	226	R, DB, MC 24/48 weeks	Low ^a	T2DM; HbA _{1c} ≥ 7.0% to ≤ 10.0%	Δ HbA _{1c} , % HbA _{1c} < 7.0%, Δ FPG, Δ weight
Meta-analysis	873	Supplementary indirect comparison versus P006; included Mathieu 2015, Softeland 2017 and Jabbour 2014			
[DPP4] + SGLT2 + MF versus [PBO] + SGLT2 + MF					
Matthaei 2015	315	R, DB, MC 24/52 weeks	Low ^a	T2DM; HbA _{1c} ≥ 7.0% to ≤ 10.5%	Δ HbA _{1c} , % HbA _{1c} < 7.0%, Δ FPG, Δ weight, safety
Tinahones 2016	467	R, DB, MC 24 weeks	Low ^a	T2DM; HbA _{1c} ≥ 7.0% to ≤ 10.5%	Δ HbA _{1c} , % HbA _{1c} < 7.0%, Δ FPG, Δ weight, safety
Meta-analysis	782	Supplementary indirect comparison versus P006; included Matthaei 2015 and Tinahones 2016			

Source: Section 2 of the submission and individual trial papers

DB = double blind; DPP4 = dipeptidyl peptidase-4; ERTU = ertugliflozin; FPG = fasting plasma glucose; HbA_{1c} = glycated haemoglobin; MC = multi-centre; MF = metformin; PBO = placebo; R = randomised; SGLT2 = sodium-glucose co-transporter-2; SITA = sitagliptin; T2DM = Type 2 diabetes mellitus

^a Sponsored by a pharmaceutical company, which might have resulted in an overall high risk of bias

Comparative effectiveness

6.7 The primary outcome presented in each of the trials was change in glycated haemoglobin (HbA_{1c}) from baseline after a treatment duration of 24 or 26 weeks.

For the indirect comparisons a non-inferiority margin of 0.4% was nominated. The primary outcome and non-inferiority margin were reasonable and the PBAC noted that they were accepted by the PBAC previously.

6.8 The submission presented an indirect comparison between ertugliflozin plus sitagliptin plus metformin (P006) and:

- dapagliflozin plus saxagliptin plus metformin (Mathieu 2015); and
- empagliflozin plus linagliptin plus metformin (Softeland 2016).

[Placebo] plus a DPP4 inhibitor plus metformin was the common comparator.

6.9 Supportive indirect comparisons presented by the submission compared ertugliflozin plus sitagliptin plus metformin (P006) to a meta-analysis of:

- three trials of a SGLT2 inhibitor plus a DPP4 inhibitor plus metformin (Mathieu 2015, Softeland 2016 and Jabbour 2014); and
- two trials of a DPP4 inhibitor plus a SGLT2 inhibitor plus metformin (Matthaei 2015 and Tinahones 2016).

Table 4: Results of the indirect comparisons for change from baseline in HbA_{1c} at 24 or 26 weeks

Trial	Arm	Change from baseline in HbA _{1c} LSM (SD)			LSM difference (95% CI)
		[ERTU] + SITA + MF	[PBO] + DPP4 + MF	[SGLT2] + DPP4 + MF	
P006	ERTU 5 mg	N = 156 -0.78 (0.83)	N = 153 -0.09 (0.85)	-	-0.69 (-0.88, -0.50)
	ERTU 15 mg	N = 153 -0.86 (0.85)	N = 153 -0.09 (0.85)	-	-0.77 (-0.96, -0.58)
Pooled: ertugliflozin					WMD = -0.73 (-0.86, -0.60)
				[DAPA] + SAXA + MF	
Mathieu 2015	-	-	N = 158 -0.10 (0.81)	N = 158 -0.82 (0.87)	-0.72 (-0.91, -0.53)
Indirect WMD, P006 (ERTU 5 mg) vs. Mathieu 2015 (95% CI)					WMD = 0.03 (-0.24, 0.30)
Indirect WMD, P006 (ERTU 15 mg) vs. Mathieu 2015 (95% CI)					WMD = -0.05 (-0.32, 0.22)
Indirect WMD, P006 (ERTU 5 mg + 15 mg) vs. Mathieu 2015 (95% CI)					WMD = -0.01 (-0.24, 0.22)
				[EMPA] + LINA + MF	
Softeland 2017	EMPA 10 mg	-	N = 108 0.14 (0.84)	N = 100 -0.65 (0.80)	-0.79 (-1.02, -0.55)
	EMPA 25 mg	-		N = 100 -0.56 (0.80)	-0.70 (-0.93, -0.46)
Pooled: empagliflozin					WMD = -0.74 (-0.91, -0.58)
Indirect WMD, P006 (ERTU 5 mg) vs. Softeland 2017 (EMPA 10 mg) (95% CI)					WMD = 0.10 (-0.20, 0.40)
Indirect WMD, P006 (ERTU 15 mg) vs. Softeland 2017 (EMPA 10 mg) (95% CI)					WMD = -0.07 (-0.37, 0.23)
Indirect WMD, P006 (ERTU 5 mg) vs. Softeland 2017 (EMPA 25 mg) (95% CI)					WMD = 0.01 (-0.29, 0.31)
Indirect WMD, P006 (ERTU 15 mg) vs. Softeland 2017 (EMPA 25 mg) (95% CI)					WMD = 0.02 (-0.28, 0.32)
Indirect WMD, P006 (ERTU 5 mg + 15 mg) vs. Softeland 2017 (EMPA 10 mg + 25 mg) (95% CI)					WMD = 0.05 (-0.20, 0.30)
				[DAPA] + SITA + MF	
Jabbour 2014	-	-	N = 113 0.00 (0.81)	N = 113 -0.40 (0.81)	-0.40 (-0.61, -0.19)
Meta-analysis: Mathieu 2015, Softeland 2017 and Jabbour 2014 I ² = 59%; p = 0.06					WMD = -0.65 (-0.82, -0.48)
Indirect WMD, P006 (ERTU 5 mg) vs. meta-analysis (95% CI)					WMD = -0.04 (-0.29, 0.21)
Indirect WMD, P006 (ERTU 15 mg) vs. meta-analysis (95% CI)					WMD = -0.12 (-0.37, 0.13)
Indirect WMD, P006 (ERTU 5 mg + 15 mg) vs. meta-analysis (95% CI)					WMD = -0.08 (-0.29, 0.13)
				[PBO] + SGLT2 + MF	
Matthaei 2015	-	-	N = 149 -0.16 (0.75)	N = 139 -0.51 (0.72)	-0.35 (-0.52, -0.18)
				[LINA] + EMPA + MF	
Tinahones 2016	EMPA 10 mg	-	N = 110 -0.21 (0.73)	N = 111 -0.53 (0.74)	-0.32 (-0.51, -0.13)
	EMPA 25 mg	-	N = 98 -0.10 (0.69)	N = 98 -0.58 (0.69)	-0.48 (-0.67, 0.29)
Meta-analysis: Matthaei 2015 and Tinahones 2016 I ² = 0%; p = 0.47					WMD = -0.38 (-0.49, -0.27)
Indirect WMD, P006 (ERTU 5 mg) vs. meta-analysis (95% CI)					WMD = -0.31 (-0.53, -0.09)
Indirect WMD, P006 (ERTU 15 mg) vs. meta-analysis (95% CI)					WMD = -0.39 (-0.61, -0.17)
Indirect WMD, P006 (ERTU 5 mg + 15 mg) vs. meta-analysis (95% CI)					WMD = -0.35 (-0.52, -0.18)

Source: Figure 2-11 and Table 2-20, Section 2.6.2, and Attachment 11 of the submission
CI = confidence interval; DAPA = dapagliflozin; DPP4 = dipeptidyl peptidase-4; EMPA = empagliflozin; ERTU = ertugliflozin; HbA_{1c} = glycated haemoglobin; LINA = linagliptin; LSM = least square mean; MF = metformin; PBO = placebo; SAXA = saxagliptin; SD = standard deviation; SGLT2 = sodium-glucose co-transporter-2; SITA = sitagliptin; vs. = versus; WMD = weighted mean difference; **bold** = WMD met the non-inferiority margin proposed by the submission (upper bound 95% CI: ≤ 0.4%)

6.10 The results of the indirect comparisons suggested that for change in HbA_{1c} from baseline at 24 or 26 weeks, [ertugliflozin 5 mg or 15 mg] plus sitagliptin plus metformin:

- demonstrated no statistically significant differences to the comparators; and
- met the pre-specified non-inferiority margin of 0.4%, with the upper bound of all the 95% confidence intervals less than or equal to this value.

6.11 The PBAC considered that there were no statistically significant differences between patients treated with ertugliflozin 5 mg-based triple therapy or ertugliflozin 15 mg-based triple therapy.

6.12 The PBAC considered that all clinical claims for ertugliflozin plus sitagliptin plus metformin triple therapies administered as individual agents also applied for regimens comprising of the ertugliflozin with sitagliptin FDC products on the basis of bioequivalence. The TGAs First Round Clinical Evaluation Report stated that:

“Each of the proposed dose strengths of the ertugliflozin with sitagliptin FDC tablets were bioequivalent with their matching dose of the free combination of ertugliflozin and sitagliptin tablets given in combination.”

Comparative harms

6.13 Safety data was reported in all trials, with the exception of Jabbour 2014, at 24 or 26 weeks. The submission presented three adverse events of interest, the incidence of hypoglycaemic events, urinary tract infections and genital infections.

Table 5: Summary of key adverse events in the randomised trials at 24 or 26 weeks

	Primary analysis								Supportive analysis					
	[SGLT2] or [PBO] + DPP4 + MF								[DPP4] or [PBO] + SGLT2 + MF					
	P006			Mathieu 2015		Softeland 2017			Matthaei 2015		Tinahones 2016			
	ERTU 5 mg	ERTU 15 mg	PBO	DAPA	PBO	EMPA 10 mg	EMPA 25 mg	PBO	SAXA	PBO	LINA + EMPA 10 mg	PBO + EMPA 10 mg	LINA + EMPA 25 mg	PBO + EMPA 25 mg
N	156	153	153	160	160	112	110	110	153	162	126	128	112	112
Any AE	65 (42%)	67 (44%)	74 (48%)	90 (56%)	94 (59%)	62 (55%)	57 (52%)	75 (68%)	73 (48%)	70 (43%)	61 (48%)	71 (56%)	59 (53%)	66 (59%)
SAE	7 (5%)	3 (2%)	4 (3%)	5 (3%)	3 (2%)	5 (5%)	4 (4%)	10 (9%)	5 (3%)	5 (3%)	4 (3%)	5 (4%)	3 (3%)	4 (4%)
Withdrawal	5 (3%)	1 (1%)	1 (1%)	8 (5%)	2 (1%)	2 (2%)	0	2 (2%)	1 (1%)	3 (2%)	4 (3%)	3 (2%)	3 (3%)	3 (3%)
Death	0	0	0	NR	NR	0	0	0	NR	NR	0	0	0	0
Hypo event	7 (4%)	3 (2%)	5 (3%)	2 (1%)	0	0	3 (3%)	1 (1%)	2 (1%)	4 (3%)	0	0	0	3 (3%)
UTI	4 (3%)	7 (5%)	3 (2%)	8 (5%)	10 (6%)	8 (7%)	4 (4%)	7 (6%)	8 (5%)	6 (4%)	12 (10%)	10 (8%)	15 (13%)	9 (8%)
Genital infection	10 (6%)	12 (8%)	1 (1%)	8 (5%)	1 (1%)	2 (2%)	5 (5%)	2 (2%)	0	4 (3%)	3 (2%)	4 (3%)	3 (3%)	9 (8%)

Source: Table 2-18, Section 2.5.2 of the submission; and corrected during evaluation

AE = adverse event; DAPA = dapagliflozin; DPP4 = dipeptidyl peptidase-4; EMPA = empagliflozin; ERTU = ertugliflozin; Hypo = hypoglycaemic; LINA = linagliptin; MF = metformin; NR = not reported; PBO = placebo; SAE = serious adverse event; SAXA = saxagliptin; SGLT2 = sodium-glucose co-transporter-2; UTI = urinary tract infection

- 6.14 At 24 or 26 weeks, in all trials (with the exception of Matthaei 2015), the proportion of patients reporting any adverse events in the active treatment arms were less than in the respective placebo arms. The reports of serious adverse events ($\leq 9\%$) and withdrawals from trials due to adverse events ($\leq 5\%$) were consistent across all trials.
- 6.15 In relation to hypoglycaemic events, the incidence was consistent ($\leq 4\%$) across all trial arms at 24 or 26 weeks.
- 6.16 The rates of urinary tract infections were consistent ($\leq 7\%$) in all trials at 24 or 26 weeks, with the exception of Tinahones 2016, which had rates up to 13%. The incidence of genital infections was 8% or lower in all trials.
- 6.17 The PBAC considered that there were no significant differences in the proportions of patients reporting adverse events between ertugliflozin 5 mg-based triple therapy and ertugliflozin 15 mg-based triple therapy.

Clinical claim

- 6.18 The submission described the triple therapy combination of ertugliflozin plus sitagliptin plus metformin as non-inferior in terms of effectiveness and safety compared with the comparators, dapagliflozin plus saxagliptin plus metformin and empagliflozin plus linagliptin plus metformin. The PBAC and ESC considered that the therapeutic conclusions presented in the submission were adequately supported.
- 6.19 The PBAC considered that there were no statistically significant differences in terms of efficacy or safety between triple therapy regimens based on ertugliflozin 5 mg or ertugliflozin 15 mg. However, both the PBAC and ESC noted that both strengths of the empagliflozin with linagliptin FDC products (10 mg/5 mg and 25 mg/5 mg) were listed on the PBS despite not demonstrating statistically significant differences in terms of efficacy.
- 6.20 The PBAC considered that the FDC products of ertugliflozin with sitagliptin (5 mg/100 mg, 15 mg/100 mg) were bioequivalent to the individual components taken concurrently. This conclusion was supported by the TGAs Clinical Evaluation Report.
- 6.21 The submission stated that all claims for ertugliflozin plus sitagliptin plus metformin compared with dapagliflozin plus saxagliptin plus metformin and empagliflozin plus linagliptin plus metformin administered as individual agents also applied to regimens comprising of FDC products on the basis of bioequivalence. Therefore, ertugliflozin with sitagliptin FDC products (5 mg/100 mg, 15 mg/100 mg) were non-inferior to dapagliflozin with saxagliptin (10 mg/5 mg) and empagliflozin with linagliptin (10 mg/5 mg, 25 mg/5 mg) FDC products when used in triple therapy with metformin. This conclusion was reasonable. This was supported by the PBAC and ESC.

- 6.22 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.23 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.24 For the economic evaluation the submission presented a cost-minimisation approach.

Table 6: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Effectiveness of [ERTU] + SITA + MF compared to the comparators, [DAPA] + SAXA + MF and [EMPA] + LINA + MF, was assumed to be non-inferior
Therapeutic claim: safety	Safety of [ERTU] + SITA + MF compared to the comparators, [DAPA] + SAXA + MF and [EMPA] + LINA + MF, was assumed to be non-inferior
Key evidence base	Indirect comparison of [ERTU] + SITA + MF with: - [DAPA] + SAXA + MF triple therapy; and - [EMPA] + LINA + MF triple therapy. PLUS Bioequivalence data that ERTU with SITA (5 mg/100 mg, 15 mg/100 mg) FDC products were bioequivalent to the co-administration of the individual doses and are non-inferior to the comparator FDC products (DAPA with SAXA 10 mg/5 mg and EMPA with LINA 10 mg/5 mg, 25 mg/5 mg).
Equi-effective doses	ERTU 5 mg or 15 mg = DAPA 10 mg = EMPA 10 mg or 25 mg SITA 100 mg = SAXA 5 mg = LINA 5 mg
Direct medicine costs	Costs of the proposed medicine, ERTU with SITA (5 mg/100 mg, 15 mg/100 mg) FDCs per patient year are equivalent to the costs of the comparators, DAPA with SAXA (10 mg/5 mg) and EMPA with LINA (10 mg/5 mg, 25 mg/5 mg) FDC products
Other costs/cost offsets	None

Source: Table 3-1, Section 3.1.1 of the submission

DAPA = dapagliflozin; EMPA = empagliflozin; ERTU = ertugliflozin; FDC = fixed dose combination; LINA = linagliptin; MF = metformin; SAXA = saxagliptin; SITA = sitagliptin

- 6.25 The equi-effective doses were estimated by the submission as:

Ertugliflozin (5 mg or 15 mg) plus sitagliptin (100 mg)
= Dapagliflozin (10 mg) plus saxagliptin (5 mg)
= Empagliflozin (10 mg or 25 mg) plus linagliptin (5 mg)

- 6.26 The PBAC accepted in March 2018 that ertugliflozin 5 mg = dapagliflozin 10 mg = empagliflozin 10 mg or 25 mg (paragraph 7.4, March 2018 PSD, ertugliflozin and ertugliflozin with metformin). At the July 2018 meeting the PBAC accepted that ertugliflozin 5 mg or 15 mg = dapagliflozin 10 mg = empagliflozin 10 mg or 25 mg.
- 6.27 The PBAC has previously accepted that sitagliptin 100 mg = saxagliptin 5 mg = linagliptin 5 mg (PBS Therapeutic Relativity sheets, February 2018).
- 6.28 In addition, ertugliflozin with sitagliptin FDC products (5 mg/100 mg, 15 mg/100 mg) were considered bioequivalent to the co-administration of the

individual components at corresponding doses. The PBAC considered this was reasonable.

- 6.29 The requested DPMQ for ertugliflozin with sitagliptin (5 mg/100 mg, 15 mg/100 mg) FDC products was \$79.43. This was based on the DPMQs of the primary comparators (i.e. dapagliflozin with saxagliptin, and empagliflozin with linagliptin). The submission acknowledged that the DPMQs might not reflect the effective prices of the FDC products. The Sponsor was willing to adjust the proposed DPMQ to ensure the cost-minimisation framework was maintained.
- 6.30 The PBAC noted there were no major issues with the cost-minimisation approach.

Drug cost/patient/year = \$1,036.14

- 6.31 The estimated cost of treating one patient for 12 months using the proposed DPMQ of \$79.43 was \$1,036.14.

Estimated PBS usage & financial implications

- 6.32 This submission was not considered by DUSC.
- 6.33 The submission presented a market share approach to estimate the utilisation and financial implications associated with recommending ertugliflozin plus sitagliptin plus metformin for listing on the PBS as triple oral therapy for the treatment of T2DM.

Table 7: Estimated utilisations and financial implications of recommending ERTU + SITA + MF as triple oral therapy to the PBS/RPBS *

	Year 1: 2019	Year 2: 2020	Year 3: 2021	Year 4: 2022	Year 5: 2023	Year 6: 2024
Estimated extent of use						
Utilisation of ERTU and ERTU/MF FDCs						
Utilisation of SITA and SITA/MF FDCs						
Utilisation of ERTU/SITA FDCs						
Estimated financial implications of ERTU + SITA + MF triple oral therapy						
Cost of ERTU and ERTU/MF FDCs	\$	\$	\$	\$	\$	\$
Cost of SITA and SITA/MF FDCs	\$	\$	\$	\$	\$	\$
Cost PBS/RPBS of ERTU/SITA FDC	\$	\$	\$	\$	\$	\$
Total cost	\$	\$	\$	\$	\$	\$
Estimated financial implications for DAPA + SAXA + MF and EMPA + LINA + MF triple oral therapies						
Cost offsets of ERTU and ERTU/MF FDCs	\$	\$	\$	\$	\$	\$
Cost offsets of SITA and SITA/MF FDCs	\$	\$	\$	\$	\$	\$
Cost offsets of ERTU/SITA FDCs	\$	\$	\$	\$	\$	\$
Total cost offsets	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost of ERTU and ERTU/MF FDCs	\$	\$	\$	\$	\$	\$
Net cost of SITA and SITA/MF FDCs	\$	\$	\$	\$	\$	\$
Net cost of ERTU/SITA FDCs	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS	\$	-\$	-\$	\$	\$	\$

Source: Attachment 13 of the submission

DAPA = dapagliflozin; EMPA = empagliflozin; ERTU = ertugliflozin; FDC = fixed dose combination; LINA = linagliptin; MF = metformin; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAXA = saxagliptin; SITA = sitagliptin

* Financial estimates were based on a proposed DPMQ of \$103.56, which was nominated in the submission. It was expected that the net cost to the PBS/RPBS would remain negligible if the Pre-PBAC proposed DPMQ of \$79.43 was used.

The redacted table shows that at year 6, the estimated number of patients less than \$10 million and the net cost to the PBS would be less than \$10 million.

6.34 The net financial impact of recommending ertugliflozin plus sitagliptin plus metformin for triple oral therapy was minimal for Years 1 to 6 as a cost-minimisation approach was used in Section 3.

6.35 The PBAC considered that although the utilisation and cost estimates were uncertain, the overall net financial effect is expected to remain small.

Quality Use of Medicines

6.36 The submission outlined a number of initiatives to promote the safe and effective use of ertugliflozin plus sitagliptin plus metformin in the treatment of T2DM, including educational material for clinicians, nurses, pharmacists, diabetes educators and patients and an 1800-telephone service.

Financial Management – Risk Sharing Arrangements

6.37 The submission did not propose a risk sharing arrangement.

For more detail on the PBAC’s view, see Section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of ertugliflozin with sitagliptin FDC products for use in triple oral therapy in combination with metformin in patients with T2DM who are inadequately controlled on metformin and a DPP4 or SGLT2 inhibitor based on cost-minimisation to dapagliflozin with saxagliptin plus metformin and empagliflozin with linagliptin plus metformin. The PBAC also recommended restriction changes to currently listed ertugliflozin, ertugliflozin with metformin, sitagliptin and sitagliptin with metformin products to allow triple therapy in patients with T2DM.
- 7.2 The PBAC considered that the comparators presented in the submission, dapagliflozin with saxagliptin and empagliflozin with linagliptin, were appropriate.
- 7.3 The PBAC considered that the evidence presented in the submission supported a claim of non-inferior efficacy and safety for ertugliflozin with sitagliptin, compared to dapagliflozin with saxagliptin and empagliflozin with linagliptin, all in combination with metformin. The PBAC considered that there were no statistically significant differences in terms of efficacy or safety between triple therapy regimens based on ertugliflozin 5 mg or ertugliflozin 15 mg.
- 7.4 The PBAC considered that the evidence presented in the submission supported a claim of non-inferiority efficacy and safety for ertugliflozin with sitagliptin FDC products compared to the individual components. The PBAC considered that the FDC products met the pre-specified bioequivalence margins against the individual components. The equi-effective doses of the FDC products were considered to be equivalent to the same dose of individual components taken concomitantly.
- 7.5 The PBAC recalled that it recommended the PBS listing of the dapagliflozin with saxagliptin FDC product and the empagliflozin with linagliptin FDC products at the November 2017 meeting at the price proposed in the submission. The PBAC noted that the incremental benefit of adding a third oral agent was smaller in magnitude than the benefit observed when adding either agent in the dual therapy setting. However, the PBAC recalled that the price reduction proposed by the sponsors accounted for this decrement of benefit in triple oral therapy as well as the uncertainty inherent in this approach. Therefore, the PBAC considered that a similar approach would be appropriate for the listing of ertugliflozin with sitagliptin when used in this setting.
- 7.6 The PBAC noted that the submission presented a cost-minimisation analysis. The PBAC considered that the price proposed for ertugliflozin with sitagliptin FDC products was acceptable. The equi-effective doses are ertugliflozin 5 mg or 15 mg with sitagliptin 100 mg, dapagliflozin 10 mg with saxagliptin 5 mg and empagliflozin 10 mg or 25 mg with linagliptin 5 mg.
- 7.7 The PBAC noted that the restriction was complex, and that the restrictions for the individual components and the respective FDCs with metformin should be

consistent. The PBAC also reiterated its recommendation that a general statement for T2DM may be appropriate.

- 7.8 The PBAC advised that, under subsection 101(3BA) of the *National Health Act, 1953*, ertugliflozin with sitagliptin should be treated as interchangeable on an individual patient basis with dapagliflozin with saxagliptin and empagliflozin with linagliptin.
- 7.9 The PBAC considered that ertugliflozin with sitagliptin FDC, ertugliflozin, sitagliptin and their respective FDCs with metformin are suitable for prescribing by nurse practitioners for continuing therapy only, where a medical practitioner has initiated the therapy.
- 7.10 The PBAC recommended that the Early Supply Rule should apply to ertugliflozin with sitagliptin FDC products as the Early Supply Rule applies to the current PBS listings for other SGLT2 inhibitor with DPP4 inhibitor listings.
- 7.11 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 packs	No. of repeats	Proprietary name	Manufacturer
ERTUGLIFLOZIN WITH SITAGLIPTIN				
<i>ertugliflozin 5 mg + sitagliptin 100 mg tablet, 28</i>	1	5	Steglujan [®]	Merck, Sharp & Dohme
<i>ertugliflozin 15 mg + sitagliptin 100 mg tablet, 28</i>	1	5		

Category/Program:	GENERAL - General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Diabetes mellitus type 2
Restriction:	Authority Required (STREAMLINED)
Treatment phase:	Initial treatment
Clinical criteria:	The treatment must be in combination with metformin; AND Patient must have an HbA1c measurement greater than 7% despite treatment with dual oral combination therapy with metformin and a dipeptidyl peptidase 4 inhibitor (gliptin) or a sodium-glucose co-transporter 2 (SGLT2) inhibitor; OR Patient must have, 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 prior to initiation of triple oral therapy with a sodium-glucose co-transporter 2 (SGLT2) inhibitor, metformin and a gliptin.
Prescriber Instructions:	The date and level of the qualifying HbA1c measurement must be documented in the patient's medical records at the time triple oral therapy with an SGLT2 inhibitor, metformin and a gliptin is initiated.

	<p>The HbA1c must be no more than 4 months old at the time triple oral therapy with an SGLT2 inhibitor, metformin and a gliptin is initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <ul style="list-style-type: none"> (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. <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of triple oral therapy with an SGLT2 inhibitor, metformin and a gliptin, must be documented in the patient's medical records.</p>
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Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Diabetes mellitus type 2
Restriction:	Authority Required (STREAMLINED)
Treatment phase:	Continuing treatment
Clinical criteria:	<p>The treatment must be in combination with metformin; AND Patient must have previously received a PBS-subsidised regimen of oral diabetic medicines which included a sodium-glucose co-transporter 2 (SGLT2) inhibitor, metformin and a gliptin for this condition.</p>
Administrative Advice:	<p>Note: Continuing Therapy Only:</p> <p>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.</p>

8.2 Amend existing listings:

Name, Restriction, Manner of administration and form	Max qty packs	No. of repeats	Proprietary Name and Manufacturer	
SITAGLIPTIN				
25 mg tablet, 28	1	5	Januvia®	Merck, Sharp & Dohme
50 mg tablet, 28	1	5		
100 mg tablet, 28	1	5		

Category/program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS indication:	Diabetes mellitus type 2
Treatment Phase:	Initial treatment
Restriction Level/ Method:	<input checked="" type="checkbox"/> Authority Required (Streamlined)

<p>Clinical criteria:</p>	<p>The treatment must be in combination with metformin; AND <i>The treatment must be in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor;</i> AND Patient must have been previously stabilised on dual or triple oral therapy which includes a dipeptidyl peptidase 4 inhibitor (gliptin); OR Patient must have been previously stabilised on dual or triple oral therapy which includes a sodium glucose co-transporter 2 (SGLT2) inhibitor;</p> <p>Patient must have, or have had, an HbA1c measurement greater than 7% <i>despite treatment with dual oral combination therapy with metformin and an SGLT2 inhibitor; prior to the initiation of the initiation of triple oral therapy with a dipeptidyl peptidase 4 inhibitor (gliptin) and a sodium glucose co-transporter 2 (SGLT2) inhibitor;</i> 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 prior to initiation of triple oral therapy with a dipeptidyl peptidase 4 inhibitor (gliptin), <i>metformin</i> and an SGLT2 inhibitor.</p>
<p>Prescriber Instructions:</p>	<p>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 triple oral therapy with an SGLT2 inhibitor, <i>metformin</i> and a gliptin is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with an SGLT2 inhibitor, <i>metformin</i> and a <i>gliptin</i> is was initiated.</p> <p>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.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of triple oral therapy with an SGLT2 inhibitor, gliptin and <i>metformin</i> is initiated, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled by dual therapy with metformin and a gliptin or an SGLT2 inhibitor does not need to requalify on this criterion before being eligible for PBS subsidised treatment with this drug.</p>
<p>Administrative advice:</p>	<p>This drug is not PBS-subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1 analogue or an SGLT2 inhibitor.</p> <p><u>Note</u> <i>PBS-subsidised dual oral therapy does not include combination use of:</i></p> <ul style="list-style-type: none"> • <i>a gliptin with an SGLT2 inhibitor; or</i> • <i>a gliptin with a glitazone; or</i> • <i>an SGLT2 inhibitor with a glitazone.</i>

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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment Phase	<i>Continuing treatment</i>
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (Streamlined)
Clinical criteria:	<p><i>The treatment must be in combination with metformin</i></p> <p>AND</p> <p><i>The treatment must be in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor</i></p> <p>AND</p> <p><i>Patient must have previously received a PBS-subsidised regimen of oral diabetic medicines which included an SGLT2 inhibitor, metformin and a dipeptidyl peptidase 4 inhibitor (gliptin) for this condition.</i></p>
Administrative advice:	<p>Continuing Therapy Only:</p> <p>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.</p> <p>Note:</p> <p>This drug is not PBS-subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1 analogue or an SGLT inhibitor.</p> <p><i>PBS-subsidised dual oral therapy does not include combination use of:</i></p> <ul style="list-style-type: none"> • <i>a gliptin with an SGLT2 inhibitor; or</i> • <i>a gliptin with a glitazone; or</i> • <i>an SGLT2 inhibitor with a glitazone.</i>

Name, Restriction, Manner of administration and form	Max qty packs	No. of repeats	Proprietary Name and Manufacturer	
SITAGLIPTIN WITH METFORMIN				
<i>sitagliptin 50 mg + metformin 500 mg tablet, 56</i>	1	5	Janumet®	Merck, Sharp & Dohme
<i>sitagliptin 50 mg + metformin 850 mg tablet, 56</i>	1	5		
<i>sitagliptin 50 mg + metformin 1 g tablet, 56</i>	1	5		
<i>sitagliptin 50 mg + metformin 1 g modified release tablet, 56</i>	1	5	Janumet XR®	Merck, Sharp & Dohme
<i>sitagliptin 100 mg + metformin 1 g modified release tablet, 28</i>	1	5		

Category/program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS indication:	Diabetes mellitus type 2
Treatment Phase:	<i>Initial treatment</i>
Restriction:	<input checked="" type="checkbox"/> Authority Required (Streamlined)

<p>Clinical criteria:</p>	<p><i>The treatment must be in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor;</i> AND Patient must have been previously stabilised on dual or triple oral therapy which includes a dipeptidyl peptidase 4 inhibitor (gliptin); OR Patient must have been previously stabilised on dual or triple oral therapy which includes a sodium-glucose co-transporter 2 (SGLT2) inhibitor; AND Patient must have, or have had, an HbA1c measurement greater than 7% prior to the initiation <i>with a PBS-subsidised regimen or oral diabetic medicines which includes metformin and an SGLT2 inhibitor for this condition;</i> of the initiation of triple oral therapy with a dipeptidyl peptidase 4 inhibitor (gliptin) and a sodium-glucose co-transporter 2 (SGLT2) inhibitor; 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 prior to initiation of triple oral therapy with an SGLT2 inhibitor, <i>metformin</i> and a gliptin.</p>
<p>Prescriber Instructions</p>	<p>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 triple oral therapy with an SGLT2 inhibitor, <i>metformin</i> and a gliptin is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with an SGLT2 inhibitor, <i>metformin</i> and a gliptin is <i>was</i> initiated.</p> <p>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.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of triple oral therapy with an SGLT2 inhibitor, <i>metformin</i> and a gliptin is <i>initiated</i>, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled by dual therapy with metformin and a gliptin or an SGLT2 inhibitor does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.</p>
<p>Administrative advice:</p>	<p>PBS-subsidised dual oral therapy does not include concomitant use of a combination of a gliptin, a glitazone or an SGLT2 inhibitor. This fixed dose combination is not PBS-subsidised for initiating dual oral combination treatment or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 analogue or an SGLT2 inhibitor <i>another dipeptidyl peptidase 4 inhibitor (gliptin)</i></p> <p><i>PBS-subsidised dual oral therapy does not include combination use of:</i></p> <ul style="list-style-type: none"> • <i>a gliptin with an SGLT2 inhibitor; or</i> • <i>a gliptin with a glitazone; or</i> • <i>an SGLT2 inhibitor with a glitazone.</i>

<p>Category / Program</p>	<p>GENERAL – General Schedule (Code GE)</p>
<p>Prescriber type:</p>	<p><input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input checked="" type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
<p>Condition:</p>	<p>Diabetes mellitus type 2</p>
<p>PBS Indication:</p>	<p>Diabetes mellitus type 2</p>
<p>Treatment Phase</p>	<p><i>Continuing treatment</i></p>

Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (Streamlined)
Clinical criteria:	<p><i>The treatment must be in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor,</i></p> <p>AND</p> <p><i>Patient must have previously received a PBS-subsidised regimen of oral diabetic medicines which included an SGLT2 inhibitor, metformin and a dipeptidyl peptidase 4 inhibitor (gliptin) for this condition</i></p>
Administrative Advice	<p>Note: Continuing Therapy Only:</p> <p>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.</p> <p>Note:</p> <p><i>This fixed dose combination is not PBS-subsidised for initiating dual oral combination treatment or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 analogue or another dipeptidyl peptidase 4 inhibitor (gliptin).</i></p> <p><i>PBS-subsidised dual oral therapy does not include combination use of:</i></p> <ul style="list-style-type: none"> • <i>a gliptin with an SGLT2 inhibitor; or</i> • <i>a gliptin with a glitazone; or</i> • <i>an SGLT2 inhibitor with a glitazone.</i>

8.3 Amend proposed listings:

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Name, Restriction, Manner of administration and Form	Max qty packs	No. of repeats	Proprietary Name and Manufacturer	
ERTUGLIFLOZIN				
<i>ertugliflozin 5 mg tablet, 28</i>	1	5	Steglatro®	Merck Sharp & Dohme
<i>ertugliflozin 15 mg tablet, 28</i>	1	5		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS indication:	Diabetes mellitus type 2
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be in combination with metformin;</p> <p>OR</p> <p>The treatment must be in combination with a sulfonylurea,</p> <p>AND</p> <p>Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with either metformin or a sulfonylurea;</p> <p>OR</p> <p>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.</p>
Prescriber instructions:	<p>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.</p> <p>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.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>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.</p> <p>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.</p>
Administrative advice:	<p>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.</p> <p>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.</p>

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Name, Restriction, Manner of administration and Form	Max qty packs	No. of repeats	Proprietary Name and Manufacturer	
ERTUGLIFLOZIN WITH METFORMIN				
ertugliflozin 2.5 mg + metformin 500 mg tablet, 56	1	5	Segluromet®	Merck Sharp & Dohme
ertugliflozin 2.5 mg + metformin 1 g tablet, 56	1	5		
ertugliflozin 7.5 mg + metformin 500 mg tablet, 56	1	5		
ertugliflozin 7.5 mg + metformin 1 g tablet, 56				
Category / Program:	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Diabetes mellitus type 2			
PBS indication:	Diabetes mellitus type 2			
Treatment phase:	Initial treatment			
Restriction Level / Method:	<input checked="" type="checkbox"/> 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:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> 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.