**7.03 EMPAGLIFLOZIN with LINAGLIPTIN FDC,
25 mg/5 mg and 10 mg/5 mg Tablets,
Glyxambi®, Boehringer Ingelheim Pty Ltd**

# Purpose of application

* 1. The resubmission requested an Authority Required listing for empagliflozin with linagliptin fixed dose combination (FDC) in combination with metformin, for the treatment of Type 2 diabetes in patients uncontrolled on metformin and a dipeptidyl peptidase 4 (DPP4) or sodium–glucose co-transporter-2 (SGLT2) inhibitor. The requested listing was for patients uncontrolled on a triple therapy including a sulfonylurea, or who have had a clinically important sulfonylurea-related adverse event necessitating sulfonylurea treatment withdrawal, or who have a contraindication to sulfonylureas. The PBAC considered a similar requested listing at the March 2017 meeting.
	2. The resubmission also requested an additional Authority Required listing for the FDC as dual therapy alone, for the treatment of Type 2 diabetes in patients with mild to moderate renal impairment, uncontrolled on metformin or sulfonylurea monotherapy, or who have had a clinically important sulfonylurea-related adverse event, or who have a contraindication to sulfonylureas.
	3. The key components of the clinical issue addressed in the resubmission are summarised in Table 1.

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

| Component | Description |
| --- | --- |
| Populations | 1. Patients with Type 2 diabetes; 2. Patients with Type 2 diabetes with mild to moderate renal impairment. |
| Interventions | 1. Empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDC, in combination with metformin;2. Empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDC, as dual therapy alone. |
| Comparators | 1. Individual component products; insulin glargine by subcutaneous injection; exenatide 2 mg once weekly by subcutaneous injection; dapagliflozin with saxagliptin; all in combination with metformin.2. Insulin glargine by subcutaneous injection. |
| Outcomes | Mean change from baseline in HbA1c, fasting plasma glucose, total body weight; proportion of patients achieving HbA1c < 7.0%. |
| Clinical claim | 1. The resubmission claimed superiority to the individual component products (accepted at the March 2017 meeting; Empagliflozin with linagliptin FDC PSD, March 2017 para 7.6); noninferiority to insulin glargine (rejected at the March 2017 meeting, Empagliflozin with linagliptin FDC PSD, March 2017 7.7); noninferiority to exenatide 2 mg once weekly (rejected at the March 2017 meeting, Empagliflozin with linagliptin FDC PSD, March 2017 para 7.7); noninferiority to dapagliflozin with saxagliptin.2. The resubmission claimed noninferiority to insulin glargine, but presented a comparison versus the individual component products as no relevant insulin glargine trials could be identified.  |
| Economic analysis | 1. Cost minimisation analysis versus the additive component products;

Cost minimisation analysis versus insulin glargine; andCost minimisation analysis versus exenatide.1. No economic analysis was presented for the additional requested restriction in patients with renal impairment.

A '''''''% price reduction in the ex-manufacturer price was offered, compared to the ex-manufacturer price that would result from the sum of the component prices. This was increased to a ''''''% price reduction in the pre-PBAC response. |

Source: Constructed during the evaluation.

# Requested listing

* 1. In the March 2017 consideration, the PBAC noted that the requested listing for type 2 diabetes in patients intolerant or with contraindications to a sulfonylurea was both administratively unworkable and unlikely to be adhered to in practice, and that similar requirements for second-line listings of SGLT2 and DPP4 inhibitors had previously been interpreted less strictly in practice than intended and had proven impractical (empagliflozin with linagliptin FDC PSD, March 2017 para 7.3). The Pre‑Sub-Committee (PSCR) *and pre-PBAC* responses indicated that the sponsor would accept the wording and restriction that the PBAC considered most appropriate.
	2. The PBAC maintained its previous view that a restriction requiring sulfonylurea intolerance was not practical, and considered that it would be more appropriate for use of triple therapy with empagliflozin + linagliptin + metformin to be restricted to patients with diabetes uncontrolled on combination therapy that included an SGLT2 or DPP4 inhibitor, similar to that outlined below.
	3. The resubmission described the additional requested listing as “early treatment in patients with moderate renal impairment (eGFR 45 to 60 mL/min/1.73 m2)” (p.23 of the resubmission), and described the target population as treatment naïve. The requested restriction requires failure of prior treatment with metformin or a sulfonylurea (despite optimal dosing), or intolerance or contraindication to metformin or a sulfonylurea requiring withdrawal of therapy. The PBAC noted that the restriction for this patient group would be difficult to implement in practice.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Name, Restriction,Manner of administration and form | Max.Qty (packs) | №.ofRpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
| Empagliflozin + linagliptinempagliflozin 10 mg + linagliptin 5 mg tablet, 30empagliflozin 25 mg + linagliptin 5 mg tablet, 30 | 1 | 5 | $'''''''''''' | Glyxambi® 10 mg/5 mgGlyxambi® 25 mg/5 mg | BY |
|  |
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | [ ] Dental [x] Medical Practitioners [x] Nurse practitioners [ ] Optometrists[ ] Midwives |
| **PBS Indication:** | Diabetes mellitus type 2 |
| **Treatment phase:** | - |
| **Restriction Level / Method:** | [x] Streamlined |
| **Clinical criteria:** | The treatment must be in combination with metformin.ANDPatient must have previously been stabilised on dual oral therapy which included a dipeptidyl peptidase 4 inhibitor (gliptin), ORPatient must have previously been stabilised on dual oral therapy which included a sodium-glucose co-transporter 2 (SGLT2) inhibitor, ANDPatient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a gliptin, and an SGLT2 inhibitor; ORPatient 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 gliptin, and an SGLT2 inhibitor. |
| **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 triple oral therapy with a gliptin and an SGLT2 inhibitor is initiated.The HbA1c must be no more than 4 months old at the time triple oral therapy with a gliptin and an SGLT2 inhibitor was initiated.Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/orHad 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 triple oral therapy with a gliptin and 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 and an SGLT2 inhibitor or gliptin does not need to requalify on this criterion before being eligible for PBS subsidised treatment with this fixed dose combination. |
| **Administrative Advice** | Note: 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 fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1, an insulin, another dipeptidyl peptidase 4 inhibitor (gliptin), or another SGLT2 inhibitor. |

Requested restriction: renal impairment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name, Restriction,****Manner of administration and form** | **Max.****Qty** | **№.of****Rpts** | **Dispensed Price for Max. Qty** | **Proprietary Name and Manufacturer** |
| Empagliflozin 10 mg / linagliptin 5 mgEmpagliflozin 25 mg / linagliptin 5 mg | 3030 | 55 | $''''''''''''''$''''''''''''' | Glyxambi® 10 mg / 5 mgGlyxambi® 25 mg / 5 mg | Boehringer Ingelheim |
| Category / Program: | General Schedule |
| Restriction: | Authority Required  |
| PBS Indication: | Type 2 diabetes mellitus |
| Clinical criteria: |  Dual therapy in treatment naïve patients with mild to moderate renal impairment (eGFR ≥ 45 <60 mL/min/1.73 m2), uncontrolled on metformin or sulfonylurea monotherapy, or who have had a clinically important sulfonylurea related adverse event during treatment with a metformin or a sulfonylurea, or contraindication to sulfonylureas, as dual therapy alone. Must be the sole treatment. |
| Prescriber Instructions | A clinically important sulfonylurea related adverse event is defined as follows:* Hypoglycaemia associated with sulfonylurea treatment;
* Hypersensitivity to sulphur containing medicines including skin rash or nausea.

A clinically important sulfonylurea related adverse event does not include weight gain.Any metformin or sulfonylurea related adverse events must be documented in the patient’s records. |

*For more detail on PBAC’s view, see section 7 PBAC outcome*

# Background

## Registration status

* 1. TGA status: empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDCs (Glyxambi®) were registered on the Australian Register of Therapeutic Goods (ARTG) on 19 December 2016, as “an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate”.
	2. Empagliflozin 25 mg and 10 mg is registered for use in combination therapy with a DPP4 inhibitor. Empagliflozin is registered for use in the treatment of type 2 diabetes mellitus as monotherapy, dual therapy with other diabetes medicines (including insulin) and in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death.
	3. The registration of linagliptin 5 mg was extended on 6 July 2017 to include use as an add-on to metformin and a SGLT2 inhibitor.

## Previous PBAC consideration

* 1. The PBAC previously considered a submission for this FDC at its March 2017 meeting.
	2. At the July 2017 meeting the PBAC considered submissions for dapagliflozin with triple therapy with metformin. The PBAC deferred these submissions to allow further work to establish a price that could be considered cost-effective. The PBAC noted that there was no evidence to suggest that the benefit of metformin + dapagliflozin + a DPP4 inhibitor would be of the same magnitude as the incremental benefit of adding either dapagliflozin or a DPP4 inhibitor to metformin, and that this triple therapy would not be cost-effective at the same price as the sum of the components (July 2017 PBAC outcomes).
	3. A minor submission requesting Authority Required (STREAMLINED) listing of empagliflozin, linagliptin and their fixed dose combinations with metformin for use in the triple oral therapy regimen of empagliflozin and linagliptin with metformin for the treatment of type 2 diabetes, and a minor submission for dapagliflozin and saxagliptin for the same indicationwere also considered by the PBAC at the November 2017 meeting.

# Population and disease

* 1. Type 2 diabetes is a long-term progressive metabolic disorder caused by resistance to the glucose modulating effects of insulin in body tissues and/or gradual loss of capacity to produce sufficient insulin. Type 2 diabetes is associated with strong familial and modifiable lifestyle risk factors. Long-term complications include heart disease, stroke, diabetic retinopathy which may lead to blindness, diabetic nephropathy which may lead to end stage renal failure and peripheral vascular disease which may lead to amputation. Type 2 diabetes substantially increases the risk of cardiovascular disease, cardiovascular mortality and chronic kidney disease leading to end stage renal failure.
	2. The submission proposed that empagliflozin with linagliptin FDC would offer an alternative to insulin glargine or exenatide within the current clinical management algorithm, and in addition, offer an alternative to metformin based therapies for patients type 2 diabetes with mild to moderate renal impairment.

# Comparator

Triple therapy

* 1. The resubmission maintained that the component products empagliflozin and linagliptin, and the injectable diabetes medicines insulin glargine and exenatide are the appropriate main comparators, based on the proposed place in therapy, and argued that the proposed restriction and place in therapy (intolerance/contraindication to sulfonylureas) excludes other possible comparators.
	2. At the March 2017 meeting the PBAC considered that a comparison against the individual components of the FDC was appropriate but that the cost-effectiveness of empagliflozin with linagliptin in triple therapy with metformin has not been established (empagliflozin with linagliptin PSD, March 2017 para 7.6). The PBAC also considered that insulin glargine and exenatide may be appropriate comparators to demonstrate cost-effectiveness in triple oral therapy with metformin. The PBAC noted that the requirement for intolerance to sulfonylureas was unworkable and that if removed, triple therapies including metformin, a sulfonylurea and a DPP4 or SGLT2 inhibitor may also be appropriate comparators (empagliflozin with linagliptin PSD, March 2017 para 5.1-5.5).
	3. The ESC noted that the Secretariat proposed wording removed the requirement for intolerance or contraindication to sulfonylureas, and the PSCR indicated that the sponsor would accept proposed amendments to the restriction. The PBAC maintained its previous view that the restriction should not include a requirement for sulfonylurea intolerance, and therefore triple therapy with a sulfonylurea would also be a reasonable comparator. However, the PBAC also noted that the sponsor indicated that a robust comparison would be difficult due to the lack of clinical trial evidence with a common comparator.
	4. The resubmission also included dapagliflozin with saxagliptin FDC as a potential comparator, given this SGLT2 plus DPP4 inhibitor fixed dose combination was considered by the PBAC at the July 2017 meeting. This was appropriate.

Renal impairment

* 1. In the additional requested restriction for dual therapy alone in patients with type 2 diabetes and mild to moderate renal impairment, the resubmission nominated insulin glargine as the main comparator, based on the proposed place in therapy and as defined in the proposed restriction. The nomination of insulin glargine was not adequately justified, and reduced maximum dose metformin or a sulfonylurea in combination with other oral diabetes medicines may also be appropriate comparators.

*For more detail on PBAC’s view, see section 7 PBAC outcome*

# Consideration of the evidence

***Sponsor hearing***

* 1. There was no hearing for this item.

***Consumer comments***

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

***Clinical trials***

* 1. The resubmission presented the three comparisons presented in the March 2017 submission:
* empagliflozin with linagliptin FDC vs components empagliflozin or linagliptin;
* empagliflozin with linagliptin FDC vs insulin glargine; and
* empagliflozin with linagliptin FDC vs exenatide 2 mg weekly.

and two additional comparisons:

* empagliflozin with linagliptin FDC vs dapagliflozin with saxagliptin (previously presented in an attachment to the March 2017 submission);
* empagliflozin with linagliptin FDC dual therapy versus the individual components (empagliflozin and linagliptin) in treatment naïve patients, to support the additional requested restriction for patients with type 2 diabetes and mild to moderate renal impairment (as no relevant insulin glargine trials could be identified):
	1. The resubmission discussed the potential for a comparison with triple therapies including sulfonylureas, and provided a literature search that failed to identify any relevant trials with appropriate common reference arms.
	2. Details of the trials presented in the resubmission are provided in the table below. Table 2: Trials and associated reports presented in the resubmission

| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| --- | --- | --- |
| **Empagliflozin with linagliptin FDC randomised trials**  |
| Trial 1275.9(NCT01734785) | A phase III, randomised, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy.  | Date: 3 Sept 2015. |
| Trial 1275.10(NCT01778049) | A phase III, randomised, double-blind, parallel group study to evaluate efficacy and safety of linagliptin 5 mg compared to placebo, administered as oral fixed dose combinations with empagliflozin 10 mg or 25 mg for 24 weeks, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with empagliflozin 10 mg or 25 mg once daily on metformin background therapy.  | Date: 3 Sept 2015. |
| Trial 1275.1(NCT014 2876) | A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control. | Date: 23 Dec 2013. |
|  | DeFronzo RA, Lewin A, Patel S et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin.  | Diabetes Care 2015; 38(3):384-393. |
|  | Lewin A, DeFronzo RA, Patel S et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes.  | Diabetes Care 2015; 38(3):394-402. |
| **Insulin glargine randomised trials**  |
| EASIE(NCT00751114) | Aschner P, Chan J, Owens DR, Picard S, Wang E, Dain M-P et al. Insulin glargine versus sitagliptin in insulin-naïve patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): A multicentre, randomised open-label trial. | Lancet 2012; 379(9833):2262-2269. |
| **Exenatide randomised trials** |
| Duration 2(NCT00637273) | Bergenstal RM, Wysham C, Macconell L, Malloy J, Walsh B, Yan P et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomised trial. | Lancet 2010; 376(9739):431-439. |
|  | Best JH, Rubin RR, Peyrot M, Li Y, Yan P, Malloy J et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. | Diabetes Care 2011; 34(2):314-319. |
| Duration Neo 2(NCT01652729) | Comparison study of the glycemic effects, safety, and tolerability of exenatide once weekly suspension to sitagliptin and placebo in subjects with type 2 diabetes mellitus (DURATION-NEO-2). | Available from: https://clinicaltrials.gov/ct2/show/study/NCT01652729?sect=X70156 |
|  | Gadde KM, Vetter ML, Iqbal N, Hardy E, Ohman P. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study.  | Diabetes Obes Metab 2017; 19(7):979-988. |
| Duration 8 \*(NCT02229396) | Frías JP, Guja C, Hardy E, Ahmed A, Dong F, Öhman P, Jabbour SA. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial.  | The Lancet Diabetes & Endocrinology 2016;4(12):1004-16 |
| **Supplementary bioequivalence trial** |
| Trial 1275.3(NCT01189201) | Relative bioavailability investigations of a 25 mg BI 10773 / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomised, single dose, crossover, Phase I trial in healthy male and female volunteers). | Date: 20 May 2011. |
| **Dapagliflozin with saxagliptin FDC randomised trials** |
| Mathieu 2015 †(NCT01646320) | Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes.  | Diabetes care 2015;38(11):2009-2017 |
|  | Mathieu C, Herrera Mamolejo M, Gonzalez Gonzalez JG, Hansen L, Chen H, Johnsson E et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes.  | Diabetes Obesity and Metabolism 2016; 18(11):1134-1137.  |
| Matthaei 2015 † (NCT01619059) | Matthaei S, Catrinoiu D, Celinski A, Ekholm E, Cook W, Hirshberg B et al. Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes.  | Diabetes care 2015;38(11):2018-2024. |
|  | Matthaei S, Aggarwal N, Garcia-Hernandez P, Iqbal N, Chen H, Johnsson E et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin.  | Diabetes Obesity and Metabolism 2016; 18(11):1128-1133. |
| Rosenstock 2015 \*(NCT01606007) | Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B et al. 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. | Diabetes care 2015; 38(3):376-383.  |

Source: Tables B.4, pp.81-83; B.5, p.84; B.105, p.313; B.106, p.314; B.140, pp.396-397; B.189, pp.548-550 and Attachment 5 of the resubmission.

\* Trials not identified in or excluded from the March 2017 submission.

† Included in the March 2017 submission (Appendix 9) as supplementary evidence.

* 1. The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

| NA | Design | N | Compared interventions | Flow | Primary outcomes | Patient population | Risk of bias |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Empagliflozin with linagliptin FDC trials** |
| 1275.9 | R, DB, PC, MCFAS OC\*MMRM | 111112110 | MET + EMPA 25 mg + LINA 5 mg FDC MET + EMPA 10 mg + LINA 5 mg FDCMET + LINA 5 mg + Pbo | 16 week OL run inMET + LINA 5 mg,+ 1 week OLPbo added, + 24 week RCT+1 week follow up | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.0% ≤10.5% (post 7 week OL run in) | Low |
| 1275.10 | R, DB, PC, MCFAS OC\*MMRM | 114126112130 | MET + EMPA 25 mg + LINA 5 mg FDC MET + EMPA 10 mg + LINA 5 mg FDC MET + EMPA 25 mg + PboMET + EMPA 10 mg + Pbo | 16 week OL run inMET + EMPA 10 mgMET + EMPA 25 mg+ 1 week OLPbo added + 24 week RCT+1 week follow up | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.0% ≤10.5% (post 7 week OL run in) | Low |
| 1275.1(metformin exposed) | R, DB, PC, MCFAS LOCF | 137136141140132 | MET + EMPA 25 mg + LINA 5 mg FDCMET + EMPA 10 mg + LINA 5 mg FDC MET + EMPA 25 mg + PboMET + EMPA 10 mg + PboMET + LINA 5 mg + Pbo | 2 week SB run in+ 24/52 week RCT+ 4 week follow up | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.0% ≤10.5% (metformin exposed) | Low |
| 1275.1(naïve)‡ | R, DB, PC, MCFAS LOCF | 137136135134135 | EMPA 25 mg + LINA 5 mg FDCEMPA 10 mg + LINA 5 mg FDC EMPA 25 mg + PboEMPA 10 mg + PboLINA 5 mg + Pbo | 2 week SB run in+ 24/52 week RCT+ 4 week follow up | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.0% ≤10.5% (treatment naive) | Low |
| **Insulin glargine trials** |
| EASIE | R, OLFAS LOCF | 250265 | MET + insulin glargine† MET + SITA 100 mg  | 24 week OL RCT+1-7 days follow up | Mean change in HbA1c | Adult 35-70yrsHbA1c ≥7% <11%  | High |
| **Exenatide trials** |
| Duration 2 | R, DB, AC, MCPP LOCF | 170172172 | MET + EXE 2 mg (wkly) + Pbo (oral) MET + SITA 100 mg + Pbo (injected) MET + PIO 45 mg + Pbo (injected)  | 26 week RCT | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.1% <11%  | Unclear |
| Duration Neo 2 | R, OL, PC, MCMMRM | 18212261 | MET + EXE 2 mg (wkly)MET + SITA 100 mg MET + Pbo | 28 week OL RCT | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.1% <11%  | High |
| Duration 8‡ | R, DB, AC, MCITT | 231230121 | MET + EXE 2 mg (wkly) + DAPA 10 mgMET + EXE 2 mg (wkly) + PboMET + DAPA 10 mg + Pbo | 28 week RCT | Mean change in HbA1c | Adult ≥18yrsHbA1c >8.0% ≤12%  | Low |
| **Dapagliflozin with saxagliptin FDC trials** |
| Mathieu 2015 | R, DB, PC, PC24 wks | 160160 | MET + DAPA 10 mg + SAXA 5 mg FDC MET + SAXA 5 mg + Pbo | 16 week OL run inMET + SAXA 5 mg,+ 24 week RCT | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.0% ≤10.5% (post 16 week OL run in) | Low |
| Matthaei 2015 | R, DB, PC, MC24 wks | 153162 | MET + DAPA 10 mg + SAXA 5 mg FDC MET + DAPA 10 mg + Pbo | 8 week OL run inMET + DAPA 10 mg+ 24 week RCT | Mean change in HbA1c | Adult ≥18yrsHbA1c ≥7.0% ≤12.0% (post 8 week OL run in) | Low |
| Rosen-stock 2015‡ | R, DB, AC, MC24 wks  | 179179176 | MET + DAPA 10 mg + SAXA 5 mgMET + DAPA 10 mg + PboMET + SAXA 5 mg + Pbo | 4 week run inMET 1.5-2.0 g daily,+ 24 week RCT | Mean change in HbA1c | Adult ≥18yrsHbA1c >8.0% ≤12%  | Low |
| **Bioequivalence** |
| 1275.3 | R, OL, Phase 1 | 42 | EMPA 25 mg + LINA 5 mg FDC (normal)EMPA 25 mg + LINA 5 mg concomitantEMPA 25 mg + LINA 5 mg FDC (high fat)EMPA 25 mg + LINA 5 mg FDC (slow) | Single dose | AUC0-tz AUC0-72 Cmax | Adult 18-55yrsBMI 18.5–29.9kg/m2  | NA |

Source: Table B.6, pp.89-90; Table B.109, pp.321-323; Table B.143, pp.406-409; Table B.150, p.427; Table B.191, pp.553-555; Empalina Bioequivalence, Attachment 3 to the resubmission.

Abbreviations AC, active control; BMI, body mass index; DB, double blind; EMPA, empagliflozin; EXE, exenatide; FAS, full analysis set; FDC, fixed dose combination; HbA1c, glycosylated haemoglobin; ITT, intention-to-treat; LINA, linagliptin; LOCF, last observation carried forward; MC, multi-centre; MET, metformin; MMRM, mixed model repeated measures; NA, not applicable; OC, observed cases; OL, open label; Pbo, placebo; PC, placebo controlled; PIO, pioglitazone; PP, per protocol; R, randomised; RCT, randomised controlled trial; SITA, sitagliptin; wkly, weekly; wks, weeks

\* Last observation carried forward (LOCF) as sensitivity analysis

† Insulin glargine titrated from an initial subcutaneous dose of 0·2 IU/kg bodyweight to attain fasting plasma glucose of 4·0–5·5 mmol/L

‡ Trial or population not presented in the March 2017 submission, intention-to-treat data set used.

* 1. The Duration 8 trial included patients with poorer glycaemic control (>8.0% ≤12% HbA1c) compared to other trials (≥7% <11% HbA1c), and higher mean baseline HbA1c (9.3% HbA1c compared to 8.4-8.6% HbA1c in the Duration 2 and Duration Neo 2 exenatide trials and 7.9-8.0% in the 1275.9, 1275.10 and 1275.1 empagliflozin with linagliptin FDC trials), and was not comparable with other included trials. The PSCR (p2) provided a sub-group analysis, which showed that in patients in the HbA1c >8.5% group, with similar baseline HbA1c (9.06-9.29% for subgroup of 1275.1, and 9.3% for duration8 trial), had similar improvement in HbA1c to each other and to the whole population.
	2. The Rosenstock (2015) and 1275.1 trials were identified in the resubmission as including a broader range of patients compared to the requested restriction. The populations in trial 1275.1 and Rosenstock (2015) initially included only patients with type 2 diabetes uncontrolled on metformin monotherapy (the broader population). Run in period treatment regimens and randomised treatment regimens in these trials provided a reasonable basis for inclusion in the resubmission. While the resubmission describes comparisons including trials 1275.1 and Rosenstock (2015) as informative, it is unclear why these trials were not included in the indirect comparisons with trials 1275.9, 1275.10, Mathieu (2015) and Matthaei (2015).
	3. The 1275.1 (treatment naïve) trial excluded patients with eGFR <60 mL/min/1.73 m2 and included treatment naïve patients. The trial was not applicable to the eligible population in the additional requested restriction, which included patients uncontrolled on previous therapy with an eGFR ≥45 <60 mL/min/1.73 m2. An applicability study presented in the resubmission may have demonstrated some attenuation of effect for empagliflozin as glomerular filtration rates declined, consistent with precautions included in the empagliflozin Product Information and the empagliflozin mechanism of action.
	4. As noted in the March 2017 submission, the EASIE trial limited inclusion to patients aged between 35-70 years with lower baseline metformin dose regimens (≥1,000 mg/day) compared to other included trials (≥1,500 mg/day).

## Comparative effectiveness

Empagliflozin with linagliptin FDC vs components empagliflozin or linagliptin, in combination with metformin

* 1. The resubmission presented additional pooled results across both doses of empagliflozin in the FDC.

Table 4: Mean change in HbA1c from baseline; direct comparisons of empagliflozin with linagliptin FDC vs linagliptin or empagliflozin (with metformin; FAS, MMRM, OC): Trials 1275.9 and 1275.10

| **Trial ID** | **Comparison (in combination with metformin)** | **Mean change in HbA1c, % (SD)** | **Difference in****mean change** **(95% CI)** |
| --- | --- | --- | --- |
| **1275.9 (24 weeks)** | **n** | **MET + EMPA + LINA FDC** | **n** | **MET + LINA + Pbo** |
| *MET + EMPA 25 mg + LINA vs MET + LINA + Pbo* | *110* | *-0.56 (0.84)* | *106* | *0.14 (0.93)* | ***-0.70 (-0.94, -0.46)*** |
| *MET + EMPA 10 mg + LINA vs MET + LINA + Pbo*  | *109* | *-0.65 (0.84)* | *106* | *0.14 (0.93)* | ***-0.79 (-1.03, -0.55)*** |
| MET + EMPA 25 or 10 mg + LINA 5 mg vs MET + LINA + Pbo (pooled) | 219 | - | 212 | - | **'''''''''' '''''''''''' '''''''''''** |

| **1275.10 (24 weeks)** | **n** | **MET + EMPA + LINA FDC** | **n** | **MET + EMPA + Pbo** |  |
| --- | --- | --- | --- | --- | --- |
| *MET + EMPA 25 mg + LINA vs MET + EMPA 25 mg + Pbo* | *109* | *-0.58 (0.73)* | *108* | *-0.10 (0.73)* | ***-0.48 (-0.67, -0.29)*** |
| *MET + EMPA 10 mg + LINA vs MET + EMPA 10 mg + Pbo*  | *122* | *-0.53 (0.77)* | *125* | *0.21 (0.78)* | ***-0.32 (-0.51, -0.13)*** |
| MET + EMPA 25 or 10 mg + LINA vs MET + EMPA 25 or 10 mg + Pbo (pooled) | 219 | - | 212 | - | **'''''''''' ''''''''''' ''''''''''''** |

Source: Tables B.23, p.135 and B.24, p.136 of the resubmission. (Statistically significant results in bold; results presented in the March 2017 submission are in italics).

Abbreviations: CI, confidence interval; EMPA, empagliflozin; FAS, full analysis set; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MET, metformin; MMRM, mixed model repeated measures; OC, observed cases; Pbo, placebo; SD, standard deviation; wks, weeks.

* 1. The pooled results demonstrated statistically significantly larger reductions in HbA1c from baseline compared to linagliptin or empagliflozin in combination with metformin over 24 weeks.
	2. The results of the head-to-head comparisons in Trial 1275.1, summarised in Table 6, were not included in the March 2017 submission on the basis of including a broader population (those uncontrolled on metformin monotherapy). However, the run-in period and randomised treatment regimens provided a reasonable basis for inclusion in the resubmission.

Table 5: Mean change in HbA1c from baseline; direct comparisons of empagliflozin with linagliptin FDC vs linagliptin or empagliflozin (with metformin; FAS, MMRM, OC)

| **Trial ID / Comparison**  | **Mean change in HbA1c, % (SD)** | **Difference in****mean change** **(95% CI)** |
| --- | --- | --- |
| **1275.1 (24 weeks; metformin exposed)** | **n** | **MET + EMPA + LINA FDC** | **n** | **MET + LINA + Pbo** |
| MET + EMPA 25 mg + LINA vs MET + LINA + Pbo | 133 | -1.20 (0.69) | 128 | -0.71 (0.79) | **-0.49 (-0.67, -0.31)** |
| MET + EMPA 10 mg + LINA vs MET + LINA + Pbo  | 135 | -1.09 (0.70) | 128 | -0.71 (0.79) | **-0.37 (-0.55, -0.20)** |
| MET + EMPA 25 or 10 mg + vs MET + LINA + Pbo (pooled) | 268 | **-** | 256 | **-** | **'''''''''' '''''''''''' ''''''''''** |

| **1275.1 (24 weeks; metformin exposed)** | **n** | **MET + EMPA + LINA FDC** | **n** | **MET + EMPA + Pbo** |  |
| --- | --- | --- | --- | --- | --- |
| MET + EMPA 25 mg + LINA vs MET + EMPA 25 mg + Pbo | 133 | -1.20 (0.69) | 139 | -0.64 (0.71) | **-0.56 (-0.74, -0.39)** |
| MET + EMPA 10 mg + LINA vs MET + EMPA 10 mg + Pbo  | 135 | -1.09 (0.70) | 137 | -0.68 (0.70) | **-0.41 (-0.58, -0.23)** |
| MET + EMPA 25 or 10 mg + LINA vs MET + EMPA 25 or 10 mg + Pbo (pooled) | 219 | **-** | 212 | **-** | **'''''''''' ''''''''''' '''''''''''** |

Source: Tables B.51, p.182 and B.52, p.184 of the resubmission. (Statistically significant results in bold).

Abbreviations: CI, confidence interval; EMPA, empagliflozin; FAS, full analysis set; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MET, metformin; MMRM, mixed model repeated measures; OC, observed cases; Pbo, placebo; SD, standard deviation; wks, weeks.

* 1. The results demonstrated statistically significantly larger reductions in HbA1c from baseline compared to linagliptin or empagliflozin in combination with metformin. In contrast to the treatment naïve population (Table 11), and the results presented in Table 5, the addition of linagliptin 5 mg to empagliflozin 25 mg or 10 mg achieved clinically important treatment effects (i.e. a minimal clinically important difference of > 0.40% MCID). The ESC noted that these data indicated that the benefit of adding empagliflozin and linagliptin to metformin (triple oral therapy) was less than the sum of benefit observed when adding empagliflozin or linagliptin to metformin in the dual therapy setting.

Empagliflozin with linagliptin FDC vs insulin glargine, in combination with metformin

* 1. At the March 2017 meeting the PBAC did not accept that the clinical comparisons presented against insulin glargine demonstrated the noninferiority (empagliflozin with linagliptin FDC PSD, March 2017 para 7.7). The resubmission presented additional pooled results across both doses of empagliflozin in the FDC in the indirect comparison with insulin glargine and the EASIE extension study was removed from the comparison.

Table 6: Mean change in HbA1c from baseline; indirect comparisons of empagliflozin with linagliptin FDC vs insulin glargine (with metformin; linagliptin/sitagliptin as common reference; FAS, LOCF)

| **Trial ID** | **Mean change in HbA1c from baseline % (SD)** | **Difference in****mean change****(95% CI)** |
| --- | --- | --- |
| **N** | **MET + EMPA 25 mg****+ LINA 5 mg** | **n** | **MET + LINA 5 mg or SITA 100 mg** | **N** | **MET +****Insulin glargine** |
| *1275.1 (24 wks)* | *134* | *-1.19 (0.69)* | *128* | *-0.70 (0.68)* | *-* | *-* | ***-0.49 (-0.66, -0.32)*** |
| *EASIE (24 wks)* | *-* | *-* | *248* | *-1.13 (0.94)* | *224* | *-1.72 (0.90)* | ***-0.59 (-0.76, -0.42)*** |
| *Indirect comparison Empagliflozin 25 + linagliptin 5 mg vs insulin glargine* | *'''''''''' '''''''''''''''' ''''''''''''''* |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **MET + EMPA 10 mg****+ LINA 5 mg** | **n** | **MET + LINA 5 mg or SITA 100 mg** | **N** | **MET +****Insulin glargine** |  |
| *1275.1 (24 wks)* | *135* | *-1.08 (0.70)* | *128* | *-0.70 (0.68)* | *-* | *-* | ***-0.38 (-0.55, -0.21)*** |
| *EASIE (24 wks)* | *-* | *-* | *248* | *-1.13 (0.94)* | *224* | *-1.72 (0.90)* | ***-0.59 (-0.76, -0.42)*** |
| *Indirect comparison (24 wks)**empagliflozin 10 mg + linagliptin 5 mg vs insulin glargine* | *'''''''''''' '''''''''''''''' ''''''''''''* |
| Pooled indirect comparison Empagliflozin 25 or 10 mg + linagliptin 5 mg vs insulin glargine | ''''''''''' '''''''''''''' ''''''''''' |

Source: Table B.123, p.355 of the submission. (Statistically significant results in bold; results presented in the March 2017 submission are in italics).

Abbreviations: CI, confidence interval; EMPA, empagliflozin; FAS, full analysis set; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; LOCF, last observation carried forward; MET, metformin; SD, standard deviation; SITA, sitagliptin; wks, weeks.

* 1. The pooled indirect comparison showed no statistically significant difference for empagliflozin with linagliptin FDC compared to insulin glargine, in combination with metformin, and demonstrated noninferiority compared to insulin glargine in combination with metformin. However, empagliflozin 10 mg with linagliptin 5 mg FDC failed to demonstrate noninferiority to insulin glargine in change in HbA1c from baseline (upper 95% CI of the indirect comparison ''''''''%, exceeded the MCID of 0.40%). The PBAC noted that this is relevant given that the expected use of the 10mg FDC is not small; the use of the 10mg FDC in the dual setting is around 40%, and it would be reasonable that this strength be similarly used in the triple setting.

Empagliflozin with linagliptin FDC vs exenatide 2 mg weekly, in combination with metformin

* 1. The Violante (2012) trial was removed from the comparison with exenatide 2 mg weekly, and the recently identified Duration 8 trial was included. This trial enabled an indirect comparison of empagliflozin with linagliptin FDC with exenatide 2 mg weekly using an SGLT2 inhibitor as the common comparator.
	2. In the indirect comparison, empagliflozin 25 mg with linagliptin 5 mg FDC demonstrated statistical superiority over exenatide 2 mg weekly (in combination with metformin). Empagliflozin 10 mg with linagliptin 5 mg FDC demonstrated noninferiority compared to exenatide 2 mg weekly (upper 95% CI of ''''''''% less than the MCID of 0.40%). Similar results were reported in a post-hoc subgroup analysis comparing patients in the 1275.1 trial with HbA1c ≥8.0% or ≥8.5% (Table 153, p.433 of the resubmission).

Table 7: Mean change in HbA1c from baseline; indirect comparisons of empagliflozin with linagliptin FDC vs exenatide 2 mg weekly (with metformin; dapagliflozin/empagliflozin as common reference)

| **Trial ID** | **Mean change in HbA1c from baseline % (SD)** | **Difference in****mean change****(95% CI)** |
| --- | --- | --- |
| **N** | **MET + EMPA 25 mg** **+ LINA 5 mg** | **n** | **MET + EMPA 25 mg or DAPA 10 mg\*** | **N** | **MET + EXE 2 mg** |
| 1275.1 (24 wks) | 133 | -1.20 (0.69) | 128 | -0.64 (0.71) | - | - | **-0.56 (-0.74, -0.39)** |
| Duration 8 (28 wks) | - | - | 198 | -1.40 (1.44) | 192 | -1.60 (1.41) | -0.20 (-0.48, 0.08) |
| Indirect comparisons (24 wks) empagliflozin 25 mg + linagliptin 5 mg vs exenatide 2 mg | **'''''''''' '''''''''''' ''''''''''''** |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **MET + EMPA 10 mg** **+ LINA 5 mg** | **n** | **MET + EMPA 10 mg or DAPA 10 mg\*** | **N** | **MET + EXE 2 mg** |  |
| 1275.1 (24 wks) | 135 | -1.09 (0.70) | 128 | -0.68 (0.70) | - | - | **-0.41 (-0.58, -0.23)** |
| Duration 8 (28 wks) | - | - | 198 | -1.40 (1.44) | 192 | -1.60 (1.41) | -0.20 (-0.48, 0.08) |
| Indirect comparisons (24 wks) empagliflozin 10 mg + linagliptin 5 mg vs exenatide 2 mg | ''''''''''' ''''''''''''''' '''''''''''''' |

Source: Table B.160, pp.451-452 of the resubmission. (Statistically significant results in bold).

Note: Standard deviation and weight mean difference calculated post hoc for the submission.

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; EMPA, empagliflozin; EXE, exenatide; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MET, metformin; SD, standard deviation; SITA, sitagliptin; wks, weeks.

\* Common reference empagliflozin 25 mg or 10 mg in Trial 1275.1 and dapagliflozin 10 mg in Duration 8.

* 1. Overall, the results of this indirect comparison of empagliflozin with linagliptin FDC versus exenatide 2 mg once weekly (in combination with metformin) generally favoured empagliflozin with linagliptin FDC. However, there were large differences in the magnitude of effect between common reference arms in the indirect comparison, and differences in baseline HbA1c between the 1275.1 (7.9% HbA1c) and Duration 8 trials (9.3% HbA1c), consistent with the inclusion criteria for each trial. The indirect analysis based on a defined subgroup (for patients with HbA1c >8.5%) which showed closer baseline values and treatment effects between trials, was consistent with non-inferiority. However, since this was for a subgroup of patients, this did not overcome the issue of differences between the trials.
	2. Empagliflozin with linagliptin FDC vs dapagliflozin with saxagliptin, in combination with metformin
	3. The resubmission presented a more detailed comparison with dapagliflozin with saxagliptin (previously presented in an attachment to the March 2017 submission), and including Rosenstock (2015), which was previously excluded from the March 2017 submission on the basis that it included a broader population (those uncontrolled on metformin monotherapy). However, the run-in period and randomised treatment regimens provided a reasonable basis for inclusion in the resubmission.

**Table 8: Mean change in HbA1c from baseline; indirect comparisons of empagliflozin with linagliptin FDC vs dapagliflozin 10 mg + saxagliptin 5 mg (with metformin; DPP4 as common reference; 1275.9 vs Mathieu 2015)**

|  |  |  |
| --- | --- | --- |
| **Trial ID** | **Mean change in HbA1c from baseline % (SD)** | **Difference in****mean change****(95% CI)** |
| **N** | **MET + EMPA 25 mg** **+ LINA** | **n** | **MET +** **LINA or SAXA\*** | **N** | **MET + DAPA + SAXA** |
| 1275.9 (24 wks) | 110 | -0.56 (0.84) | 106 | 0.14 (0.94) | - | - | **-0.70 (-0.94, -0.46)** |
| Mathieu 2015 (24 wks) | - | - | 160 | -0.10 (0.88) | 160 | -0.82 (0.86) | **-0.72 (-0.91, -0.53)** |
| Indirect comparison: empagliflozin 25 mg + linagliptin 5 mg vs dapagliflozin 10 mg + saxagliptin 5 mg | ''''''''''' ''''''''''''''' '''''''''''' |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **MET + EMPA 10 mg** **+ LINA** | **n** | **MET +** **LINA or SAXA\*** | **N** | **MET + DAPA + SAXA** |  |
| 1275.9 (24 wks) | 109 | -0.65 (0.84) | 106 | 0.14 (0.94) | - | - | **-0.79 (-1.03, -0.55)** |
| Mathieu 2015 (24 wks) | - | - | 160 | -0.10 (0.88) | 160 | -0.82 (0.86) | **-0.72 (-0.91, -0.53)** |
| Indirect comparison: empagliflozin 10 mg + linagliptin 5 mg vs dapagliflozin 10 mg + saxagliptin 5 mg | ''''''''''''' '''''''''''''' ''''''''''''' |
| Indirect comparison: pooled | '''''''''''''' '''''''''''''''' '''''''''''' |

Source: Table B.205, p.578 of the resubmission. (Statistically significant results in bold).

Note: Standard deviation and weight mean difference calculated post hoc for the March 2017 submission.

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; EMPA, empagliflozin; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MET, metformin; SD, standard deviation; SAXA, saxagliptin; wks, weeks.

\* Common reference linagliptin 5 mg in Trial 1275.9 and saxagliptin 5 mg in Matthieu 2015.

**Table 9: Mean change in HbA1c from baseline; indirect comparisons of empagliflozin with linagliptin FDC vs dapagliflozin 10 mg + saxagliptin 5 mg (with metformin; SGLT2 as common reference; 1275.10 vs Matthaei 2015)**

|  |  |  |
| --- | --- | --- |
| **Trial ID** | **Mean change in HbA1c from baseline % (SD)** | **Difference in****mean change****(95% CI)** |
| **N** | **MET + EMPA 25 mg** **+ LINA** | **n** | **MET +** **EMPA or DAPA\*** | **N** | **MET + DAPA** **+ SAXA** |
| 1275.10 (24 wks) | 109 | -0.58 (0.73) | 108 | -0.10 (0.73) | - | - | **-0.48 (-0.67, -0.29)** |
| Matthaei 2015 (24 wks) | - | - | 162 | -0.16 (0.78) | 153 | -0.51 (0.75) | **-0.35 (-0.52, -0.18)** |
| Indirect comparison: empagliflozin 25 mg + linagliptin 5 mg vs dapagliflozin 10 mg + saxagliptin 5 mg | ''''''''''''' '''''''''''''''' ''''''''''''' |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **MET + EMPA 10 mg** **+ LINA** | **n** | **MET +** **EMPA or DAPA\*** | **N** | **MET + DAPA** **+ SAXA** |  |
| 1275.10 (24 wks) | 122 | -0.53 (0.77) | 125 | 0.21 (0.78) | - | - | **-0.32 (-0.51, -0.13)** |
| Matthaei 2015 (24 wks) | - | - | 162 | -0.16 (0.78) | 153 | -0.51 (0.75) | **-0.35 (-0.52, -0.18)** |
| Indirect comparison: empagliflozin 10 mg + linagliptin 5 mg vs dapagliflozin 10 mg + saxagliptin 5 mg | ''''''''''' '''''''''''''''' '''''''''''''' |
| Indirect comparison: pooled | '''''''''''' '''''''''''''''' ''''''''''''' |

Source: Table B.206, p.581 of the resubmission. (Statistically significant results in bold).

Note: Standard deviation and weight mean difference calculated post hoc for the March 2017 submission.

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; EMPA, empagliflozin; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MET, metformin; SD, standard deviation; SAXA, saxagliptin; wks, weeks.

\* Common reference empagliflozin 25 mg or 10 mg in Trial 1275.10 and dapagliflozin 10 mg in Matthaei 2015.

* 1. There were no statistically significant differences between empagliflozin with linagliptin FDC and dapagliflozin with saxagliptin in terms of the primary outcome (mean change in HbA1c), and empagliflozin with linagliptin FDC demonstrated noninferiority to dapagliflozin with saxagliptin, the upper confidence intervals falling below the MCID of 0.40% HbA1c.
	2. The comparison between trials 1275.1 (sub group of patients previously exposed to metformin) and Rosenstock 2015 using an SGLT2 inhibitor (empagliflozin 25 or 10 mg or dapagliflozin) as a common reference, showed superiority of empagliflozin 25 mg with linagliptin FDC over dapagliflozin with saxagliptin. However, this result may be due to the larger treatment effect of the common reference arm in the Rosenstock 2015 trial (metformin with dapagliflozin).
	3. Overall, empagliflozin with linagliptin FDC demonstrated noninferiority to dapagliflozin with saxagliptin, in combination with metformin.

Empagliflozin with linagliptin FDC vs triple therapies containing sulfonylureas.

* 1. The PBAC was concerned that the March 2017 submission had not provided evidence for a clinical or economic comparison against triple oral therapies including metformin, a sulfonylurea and either a DPP4 or SGLT2 inhibitor.
	2. Several potentially relevant trials were identified in a literature search conducted for the resubmission, including metformin in combination with a sulfonylurea and a DPP4 or SGLT2 inhibitor (1245.23, Study 5, 1218.18, Study 229, Study 253 and Study 035). These trials were appropriately excluded as they could not be compared with empagliflozin with linagliptin FDC given the absence of common reference arms (none of the FDC trials included a metformin with a sulfonylurea arm). No evidence was presented for this comparison. The PSCR (pp1-2) reiterated that it was not possible to conduct an indirect comparison due to the lack of a common treatment arm. The PBAC noted the literature search provided in the submission and considered that it was unlikely that a robust indirect comparison could be conducted for this comparator.

Empagliflozin with linagliptin FDC vs insulin glargine in treatment naïve patients with type 2 diabetes and impaired renal function

* 1. The results of Trial 1275.1 (treatment naïve population), summarised in Table 10, were presented to support the resubmission’s additional requested restriction for patients with impaired renal function.

Table 11: Mean change in HbA1c from baseline; direct comparisons of empagliflozin with linagliptin FDC vs linagliptin or empagliflozin (FAS, MMRM, OC)

| **Trial ID / Comparison**  | **Mean change in HbA1c, % (SD)** | **Difference in****mean change** **(95% CI)** |
| --- | --- | --- |
| **1275.1 (24 wks; treatment naïve)** | **n** | **EMPA + LINA FDC** | **n** | **LINA + Pbo** |
| EMPA 25 mg + LINA vs LINA + Pbo | 134 | -1.07 (0.81) | 133 | -0.69 (0.81) | **-0.38 (-0.58, -0.18)** |
| EMPA 10 mg + LINA vs LINA + Pbo  | 134 | -1.26 (0.81) | 133 | -0.69 (0.81) | **-0.57 (-0.77, -0.36)** |
| EMPA 25 or 10 mg + vs LINA + Pbo (pooled) | 268 | **-** | 266 | **-** | **'''''''''' ''''''''''' ''''''''''** |
| **1275.1 (24 wks; treatment naïve)** | **n** | **EMPA + LINA FDC** | **n** | **EMPA + Pbo** |  |
| EMPA 25 mg + LINA vs EMPA 25 mg + Pbo | 134 | -1.07 (0.81) | 133 | -0.95 (0.81) | -0.12 (-0.32, 0.08) |
| EMPA 10 mg + LINA vs EMPA 10 mg + Pbo  | 134 | -1.26 (0.81) | 131 | -0.84 (0.80) | **-0.41 (-0.62, -0.21)** |
| EMPA 25 or 10 mg + LINA vs EMPA 25 or 10 mg + Pbo (pooled) | 219 | **-** | 212 | **-** | '''''''''''' '''''''''''''''' ''''''''''''' |

Source: Tables B.228, p.637 and B.229, p.640 of the resubmission. (Statistically significant results in bold).

Abbreviations: CI, confidence interval; EMPA, empagliflozin; FAS, full analysis set; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MET, metformin; MMRM, mixed model repeated measures; OC, observed cases; Pbo, placebo; SD, standard deviation; wks, weeks.

* 1. In the treatment naïve sub-population of Trial 1275.1, empagliflozin with linagliptin FDC demonstrated statistically significantly larger reductions in HbA1c from baseline compared to linagliptin monotherapy over 24 weeks. However, all upper 95% CIs as well as the mean difference for empagliflozin 25 mg with linagliptin compared to linagliptin alone were below the MCID of 0.4%.
	2. There was no statistically significant difference between empagliflozin 25 mg with linagliptin FDC compared to empagliflozin 25 mg alone, nor was there a statistically significant difference between empagliflozin with linagliptin compared to empagliflozin alone in the pooled analysis. This was consistent with the results presented in the March 2017 submission for the metformin exposed populations in trials 1275.9 and 1275.10.
	3. Results favouring empagliflozin 25 mg with linagliptin FDC were also reported for change in fasting plasma glucose (FPG) from baseline (empagliflozin 25 mg FDC FPG -1.22 mmol/L, 95% CI [-1.6, -0.85]; and for empagliflozin 10 mg FDC FPG -1.10 mmol/L, 95% CI [-1.47, -0.73]. Similar to the primary outcome and consistent with the metformin exposed population presented in the March 2017 submission, the benefits of adding linagliptin 5 mg to empagliflozin 10 or 25 mg in combination with metformin were small and may not be clinically important (empagliflozin 25 mg FDC FPG -0.29 mmol/L, 95% CI [-0.66, 0.08]; empagliflozin 10 mg FDC FPG -0.17 mmol/L, 95% CI [-0.54, 0.20]).
	4. The primary and key secondary results in the treatment naïve population of Trial 1275.1 were similar to those reported for metformin exposed patients in trials 1275.9 and 1275.10 in the March 2017 submission. The results showed that adding empagliflozin 25 mg or 10 mg to linagliptin 5 mg resulted in a statistically significant benefit to treatment naïve patients with type 2 diabetes, but the magnitude of treatment effect was inconsistently reported between the empagliflozin 25 mg and 10 mg dose strength FDCs. In addition, adding linagliptin 5 mg to empagliflozin 25 mg or 10 mg showed inconsistent results with many outcomes failing to achieve statistical significance. The ESC noted that the data suggested that the benefit to adding a second agent in this setting was lower.

## Comparative harms

* 1. The comparative harms for empagliflozin with linagliptin FDC versus the comparators were unchanged from the March 2017 submission.

## Clinical claim

Empagliflozin with linagliptin FDC vs linagliptin or empagliflozin, in combination with metformin

* 1. The clinical claim was that empagliflozin with linagliptin FDC is superior in terms of efficacy and noninferior in terms of safety compared to either linagliptin or empagliflozin (in combination with metformin), and that empagliflozin with linagliptin FDC is bioequivalent to concomitant empagliflozin and linagliptin. This claim is adequately supported, and was accepted by the PBAC at the March 2017 meeting (Empagliflozin with linagliptin PSD, March 2017 para 7.6).

Empagliflozin with linagliptin FDC vs insulin glargine, in combination with metformin

* 1. The clinical claim was that empagliflozin with linagliptin FDC is noninferior in terms of efficacy and safety compared to insulin glargine (in combination with metformin).
	2. The PBAC considered that while the pooled analysis supported a claim of non-inferiority, there was some remaining uncertainty due to the 10 mg empagliflozin does not demonstrating noninferiority*.*

Empagliflozin with linagliptin FDC vs exenatide, in combination with metformin

* 1. The PBAC considered that the clinical claim that empagliflozin with linagliptin FDC is noninferior in terms of efficacy and safety to exenatide 10 µg twice daily or 2 mg weekly was reasonable.

Empagliflozin with linagliptin FDC vs dapagliflozin with saxagliptin, in combination with metformin

* 1. The PBAC considered that the clinical claim that empagliflozin with linagliptin FDC is noninferior in terms of efficacy and safety to dapagliflozin with saxagliptin FDC was adequately supported.

Empagliflozin with linagliptin FDC vs insulin glargine (patients with renal impairment)

* 1. No evidence was presented comparing empagliflozin with linagliptin FDC versus insulin glargine (the nominated comparator) in the requested population.

The PBAC considered that the clinical claim that empagliflozin with linagliptin FDC is superior in terms of efficacy and noninferior in terms of safety compared to either linagliptin or empagliflozin, in treatment naïve patients was not adequately supported by the data. The PBAC noted that some comparisons did not meet the minimum clinically important difference of 0.4% to demonstrate the benefit of adding a second agent. However, the PBAC acknowledged the clinical need for further treatment options for this patient group.

## Economic analysis

* 1. The resubmission did not present any economic analysis directly relating to the renal impairment population. The submission claimed that the price reduction was intended to account for the uncertainty regarding the cost-effectiveness of this listing. However, the benefit of this treatment was not adequately supported.
	2. The pre‑PBAC response proposed a discount of ''''''% on the previously requested approved ex‑manufacturer price (AEMP) to account for uncertainty around the cost effectiveness of the FDC (the initial resubmission proposed a '''''% price reduction).
	3. The resubmission presented the three cost minimisation analyses presented in the March 2017 submission using the same methodology, with changes addressing some of the concerns raised by the PBAC, ESC and DUSC at that time:
	+ The published prices of insulin glargine and exenatide 2 mg once weekly were updated to the July 2017 PBS Schedule.
	+ The number of nurse educator visits was reduced to one initial visit ($79.85).
	+ The cost of hospitalisation for severe hypoglycaemia events was reduced, assuming 28% of hospital admissions would be day stay or multi day stay admissions, and the remainder (78%) accident and emergency department presentations, consistent with Leese et al. (2003).
	+ The cost of linagliptin was removed from the comparator costs.

Empagliflozin with linagliptin FDC vs insulin glargine

* 1. The resubmission estimated an incremental cost saving over a two-year period for empagliflozin with linagliptin FDC versus insulin glargine per person. When drug costs only were included, the treatment with empagliflozin with linagliptin FDC was associated with an additional cost (based on insulin glargine listed price and the proposed equi‑effective doses; Table D(ii).2.5 of the Commentary). The analysis could not incorporate the impact of insulin glargine’s special pricing arrangement. The cost minimisation analysis therefore overestimates the costs of treatment with insulin glargine. The ESC also noted that the proposed equieffective dose of 41.4 IU was based on the EASIE trial which had aggressive glycaemic targets, and that the PBAC has previously recommended equieffective doses in the range of 24-28.2 IU, which although in different settings, were considerably lower.

Empagliflozin with linagliptin FDC vs exenatide

* 1. The resubmission estimated an incremental cost saving over a two-year period for empagliflozin with linagliptin FDC versus exenatide 2 mg once weekly. When drug costs only were included, the estimated incremental cost savings was slightly increased (Table D.2.2 of the Commentary). The analysis could not incorporate the impact of the exenatide special pricing arrangement. The cost minimisation analysis therefore overestimates the costs of treatment with exenatide.
	2. The ESC noted that the cost offsets may be overestimated because of a number of issues around the resource costs and drug costs used in the cost minimisation analyses:
* The costs of glucose monitoring (blood test strips and lancets) and sharps disposal have not previously been accepted by the PBAC, and may not be reasonable;
* Diabetes education in patients with poor glycaemic control may continue for patients taking oral diabetes medicines. The costs of a nurse educator visit may not be reasonable. The ESC noted that the PBAC previously considered that offsets relating to reduced nurse educator visits were unlikely to be achieved and may not be desirable in an uncontrolled population;
* Costs of hospitalisation due to severe hypoglycaemia events may not be reasonable, given that it was assumed that all patients experiencing severe hypoglycaemia events required either hospitalisation or accident and emergency admission.
	1. The PBAC considered that in the context of the remaining uncertainties with the economic analyses with insulin glargine and exenatide, the most appropriate approach would be to determine the price based on the benefit of both agents used in triple therapy, compared to the sum of the magnitude of benefit when each of the agents are used in dual therapy.
	2. Applying this approach to the results from study 1275.1 at 24 weeks (Tables 5 and 10 for metformin exposed and treatment naïve, respectively), rather than the 52 weeks results used by the sponsor, the benefit of adding both empagliflozin and linagliptin is '''''% (range ''''''''''''%) of the sum of components for the metformin experienced patients, and ''''''% (range ''''''''''''%) for the metformin naïve (renally impaired) populations (averages unweighted for dose utilisations) – see Table 12 and 13.

Table 11: Proportional HbA1c reduction between the empagliflozin with linagliptin FDC vs the reduction in HbA1c in dual therapy of linagliptin plus empagliflozin (metformin exposed patients)

| **1275.1 (24 weeks; metformin exposed)** | **MET + LINA + Pbo plus MET + EMPA + Pbo** | **MET + EMPA + LINA FDC**  | **Proportion of benefit compared to sum of components** |
| --- | --- | --- | --- |
| MET + LINA + Pbo added to MET + EMPA 25 + Pbo vs MET + EMPA 25 mg + LINA  | ''''''''''''' | -1.20 | **'''''''''** |
| MET + LINA + Pbo added to MET + EMPA 10 + Pbo vs MET + EMPA 10 mg + LINA  | ''''''''''' | -1.09 | **''''''''** |
| Average (unweighted) | **'''''''''** |

Table 12: Proportional HbA1c reduction between the empagliflozin with linagliptin FDC vs the reduction in HbA1c in dual therapy of linagliptin plus empagliflozin (treatment naïve patients)

| **1275.1 (24 weeks; treatment naïve)** | **LINA + Pbo plus EMPA + Pbo** | **EMPA + LINA FDC**  | **Proportion of benefit compared to sum of components** |
| --- | --- | --- | --- |
| EMPA 25 + Pbo plus LINA + Pbo vs EMPA 25 + LINA | '''''''''''' | -1.07 | **'''''''''** |
| EMPA 10 + Pbo plus LINA + Pbo vs EMPA 10 + LINA | '''''''''''' | -1.26 | **''''''''** |
| Average (unweighted) | **'''''''''** |

Table 13: AEMP of FDC based on additive benefit on HbA1c

|  | **Proportion of benefit compared to sum of components** | **Discount based on additive HbA1c** | **Price based on additive benefit on HbA1c**  |
| --- | --- | --- | --- |
| 52 weeks |
| Treatment Naïve | '''''''''' | '''''''' | '''''''''''''''' |
| Treatment Experienced | '''''''''' | ''''''''''' | '''''''''''''''' |
| Average (unweighted) | '''''''''' | '''''''''' | ''''''''''''''' |
| 24 weeks |
| Treatment Naïve | '''''''''' | ''''''''''' | '''''''''''''''' |
| Treatment Experienced | '''''''''' | ''''''''''' | ''''''''''''''''' |
| Average (unweighted) | ''''''''''' | '''''''''' | ''''''''''''''' |
| Proposed price (AEMP) |
|  | ''''''''' | ''''''''' | '''''''''''' |

* 1. The pre-PBAC response argued that it was more reasonable to use the week 52 results over the week 24 results because diabetes is a long-term condition. However, the PBAC considered that any benefits of treatment should be observable by week 24, and noted that the submission used the data at week 24 as the basis of the clinical claim. The ESC had considered that the price reduction offered in the PSCR ('''''% at AEMP) may not be sufficient to address the uncertainty associated with this approach. The PBAC noted that the pre-PBAC response proposed an increased price reduction, to '''''% off the AEMP of the sum of components. The PBAC considered this adequately addressed the reduced benefit of adding the third drug in triple therapy, any remaining uncertainty regarding the cost-effectiveness of this combination use and accounted for use of this triple therapy combination through other fixed‑dose combination products available on the PBS.

## Drug cost/patient/year: $'''''''''''''''''

* 1. The estimated cost of treating one patient over 12 months with empagliflozin with linagliptin FDC was $'''''''''''''''' (cost per year calculated as 365.25 / 30 × price), this is a reduction of '''''''''% (DPMQ) compared to the March 2017 submission ($''''''''''''''''). The PBAC noted that this cost would be further lowered following the additional price reduction offered in the pre-PBAC response.

## Estimated PBS usage & financial implications

* 1. This resubmission was not considered by DUSC. The resubmission used a mixed epidemiological and market share approach to estimate the extent of use and financial implications of listing empagliflozin with linagliptin FDC on the PBS as:
* triple therapy with metformin for the treatment of type 2 diabetes in patients intolerant/contraindicated to metformin and sulfonylurea combination therapy; and
* dual therapy (empagliflozin with linagliptin FDC alone) for the treatment of type 2 diabetes in patients with moderate renal impairment.
	1. The resubmission applied the same methodology used in the March 2017 submission, adjusted for updated drug prices and reductions in selected non-drug related cost offsets as recommended by the PBAC.

Triple therapy in combination with metformin

Table 14: Estimated use and financial implications in triple therapy

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated extent of use (other therapies)** |
| Total patients treated | ''''''''''''''''' | '''''''''''''''' | '''''''''''''''' | '''''''''''''''''' | '''''''''''''''''' | ''''''''''''''''''''' |
| **Estimated extent of use (uptake from other therapies)** |
| Number of scripts empagliflozin/linagliptin FDC | **''''''''''''''''** | **'''''''''''''''** | **'''''''''''''''** | **'''''''''''''''** | **'''''''''''''''''** | **'''''''''''''''''''** |
| **Estimated cost of empagliflozin with linagliptin FDC** |
| Cost empagliflozin/linagliptin FDC (DPMQ) | **'''''''''''''''''''''''** | **''''''''''''''''''''''''** | **'''''''''''''''''''''''''** | **''''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **'''''''''''''''''''''''''** |
| **Net change in financial implications to the PBS/RPBS** |
| **Net PBS/RPBS cost** | **'''''''''''''''''''''** | **'''''''''''''''''''''''''** | **'''''''''''''''''''''''** | **''''''''''''''''''''''** | **''''''''''''''''''''''''** | **''''''''''''''''''''''** |
| **Costs implications to other health budgets (costs avoided)** |
| Total costs to other health budgets | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' |
| **Net cost to government** | **'''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **'''''''''''''''''''''''** | **'''''''''''''''''''''''''''** | **'''''''''''''''''''''''''** |

Source: Tables E.4, p.751; Table E.11, p.756; Table E.12, p.757; Table E.13, p.758; Table E.21, p.766, Tables E.22 to E.27, pp.766-769 and ‘Att 8\_Glyxambi Section E’ Excel workbook

The redacted table shows that at year 6, the estimated number of patients was 100,000 – 200,000 per year

* 1. The resubmission estimated the net cost savings to the PBS/RPBS of listing empagliflozin with linagliptin FDC at less than $10 million per yearin Year 1, increasing to $20 - $30 million per year in Year 6, a total cost savings of $30 - $60 million over 6 years..
	2. The evaluation considered that the estimated utilisation and financial estimates for triple therapy were uncertain. The resubmission did not adequately address DUSC’s concerns about the exclusion of other triple and dual therapy markets likely to be substituted (particularly those including sulfonylureas), the costs of hospitalisation due to severe hypoglycaemia events and other non-drug related resources. The estimates also failed to address all other issues raised by the DUSC at the March 2017 meeting:
* methodology of the 10% Medicare sample analysis
* exclusion of undercopayment data from the analysis
* broadening of the market due introduction of a novel therapy option
* exclusion of costs related to adverse events such as vulvovaginal candidiasis and
* quality use of medicine issues around patient understanding of combination medicine use.
	1. At the March 2017, meeting the DUSC also noted that uptake of empagliflozin across all lines of the treatment (single or FDC) may rapidly increase because of the finding of reduced risk of cardiovascular death in the EMPA-REG OUTCOME study.
	2. Additionally, the cost offsets from medicines substituted were overestimated due to the use of the published prices of insulin glargine and exenatide 2 mg weekly that are subject to special pricing arrangements.

Dual therapy in treatment naïve patients with mild to moderate renal impairment

* 1. The resubmission used an epidemiological approach to estimate the use and financial implications of listing empagliflozin with linagliptin for use in dual therapy in patients with mild to moderate renal impairment.

**Table 15: Estimated utilisation and financial implications of PBS-listed empagliflozin with linagliptin FDC in dual therapy**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimate utilisation and cost of empagliflozin with linagliptin FDC**  |
| Eligible patients with CKD stage 3  | '''''''''''''''' | ''''''''''''''' | ''''''''''''''''' | '''''''''''''''' | '''''''''''''''' | '''''''''''''''' |
| Market uptake  | 40% | 50% | 60% | 70% | 80% | 90% |
| Total patients | ''''''''''''''''' | '''''''''''''''' | ''''''''''''''''' | '''''''''''''''' | ''''''''''''''' | ''''''''''''''''' |
| Total scripts (12.18/year) | '''''''''''''''''''' | '''''''''''''''''' | ''''''''''''''''' | '''''''''''''''''' | ''''''''''''''''''' | '''''''''''''''''''' |
| Total cost to PBS/RPBS less copayments | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''' |
| **Drug cost offsets due to substitution of insulin glargine** |
| Total offsets less copayments | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''' |
| **Net financial implications of empagliflozin with linagliptin FDC substituting for insulin glargine** |
| Net cost to PBS less copayments | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''' | '''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' |
| **Costs implications to MBS budget (costs avoided)** |
| Diabetes nurse educator | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' |
| **Costs implications to State and Territory health budgets (costs avoided)** |
| Severe hypoglycaemia  | ''''''''''''''''''''''' | '''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | '''''''''''''''''''''''''' |
| **Costs implications to other health budgets (costs avoided)** |
| Needles, lancets, glucose strips, needle disposal | ''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | '''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''' |
| **Net costs to PBS/RPBS** | **'''''''''''''''''''''** | **'''''''''''''''''''** | **'''''''''''''''''''''''** | **'''''''''''''''''''''** | **'''''''''''''''''''''** | **''''''''''''''''''''** |
| **Net cost to government** | **''''''''''''''''''''''''** | **'''''''''''''''''''''''** | **''''''''''''''''''''''** | **'''''''''''''''''''''''''** | **''''''''''''''''''''''''** | **''''''''''''''''''''''''''** |

Source: Tables E.35-E.53, pp.778-789 Tables E.22 to E.27, pp.766-769 of the submission.

Abbreviations: CKD, chronic kidney disease; FDC, fixed dose combination; eGFR, estimated glomerular filtration rate.

Note: Insulin glargine is subject to a special pricing arrangement. Estimates are based on published prices.

The redacted table shows that at year 6, the estimated number of patients was 10,000 – 50,000 per year

* 1. The resubmission estimated the net cost to the PBS/RPBS of listing empagliflozin with linagliptin FDC for patients with mild to moderate renal impairment at less than $10 million per year in Year 1, increasing to less than $10 million per year in Year 6, a total cost savings of $20 - $30 million over 6 years. DUSC has not previously considered this population.
	2. The evaluation considered that utilisation/financial estimates for this patient population were substantially underestimated due to the following issues:
* The overly complex derivation of patient numbers based on multiple sources of data with different population characteristics and definitions of renal impairment resulted in only 0.0015% of Australians being considered eligible for treatment. This proportion does not appear reliable given other sources identify much larger proportions of patients with diabetes and renal impairment (e.g. 1.7% of total Australian population, AIHW 2014).
* The assumption that all use of PBS-listed empagliflozin with linagliptin FDC would be from substitution of insulin glargine alone (100%) was not justified. The drug cost offsets are likely to be overestimated.
* Insulin glargine is subject to a special pricing arrangement and the estimated savings, at the published price, from substitution of insulin glargine were therefore overestimated.
* The number of scripts of insulin glargine that are substituted are likely to be overestimated as it was calculated based on a proposed equi-effective dose of 41.4 IU with empagliflozin and linagliptin from the EASIE extension study.
* The resubmission used the same assumptions and cost offsets as for triple therapy based on differences in methods of administration and management of severe hypoglycaemia events. These did not adequately address DUSC’s concerns and likely overestimate the savings to other health budgets.
	1. The ESC considered that the financial estimates were highly dependent on the proposed restriction, and were therefore uncertain. The PBAC noted that as the requirement for sulfonylurea intolerance was proposed to be removed from the restriction, and the restriction for the renally impaired population would not be included, these financial estimates would need to be re-calculated.

## Quality use of medicines

* 1. The sponsor proposed to work with a third party provider to build a Decision Support System (CAT Plus Technology) and to provide an Ongoing HCP Education program to prescribers.
	2. The PBAC noted previous advice in relation to DPP4 + SGLT2 inhibitor fixed dose combinations that these combinations may allow for more flexibility in metformin dose titration and reduce the risk of confusion with metformin-containing products.

*For more detail on PBAC’s view, see section 7 PBAC outcome*

1. **PBAC Outcome**

*Triple therapy with metformin*

* 1. The PBAC recommended the listing of empagliflozin with linagliptin for use in combination with metformin for the treatment of type 2 diabetes in patients uncontrolled on dual or triple therapy including metformin and a DPP4 or SGLT2 inhibitor.
	2. The PBAC considered that the evidence presented in the submission supported a claim of non-inferior efficacy and safety for empagliflozin with linagliptin, compared to exenatide or insulin glargine, all in combination with metformin. The PBAC noted that while a relevant comparator, the submission indicated that a robust comparison with triple therapies including a sulfonylurea would be difficult due to the lack of clinical trial evidence with a common comparator.
	3. The PBAC also considered that the data presented in the submission supported the claim of non-inferior efficacy and safety for empagliflozin with linagliptin, compared to dapagliflozin with saxagliptin. The equi-effective doses are empagliflozin 10 mg or 25 mg plus linagliptin 5 mg compared to dapagliflozin 10 mg plus saxagliptin 5 mg.
	4. The PBAC also considered that the evidence presented in the submission supported the claim that empagliflozin with linagliptin in combination with metformin provides a significant improvement in efficacy over either empagliflozin or linagliptin in dual combination therapy with metformin. However, the PBAC maintained its previous view that the benefit of adding empagliflozin or linagliptin in the triple therapy setting was smaller than the magnitude of benefit when either of these agents are added in the dual therapy setting, and therefore that the price should be lower than the sum of the price of the individual components.
	5. The PBAC was of the view that there may be some potential quality use of medicines benefits for patients as use of the FDC may reduce the risk of confusion in DPP4 and SGLT2 inhibitor dosing, and provide greater flexibility in metformin dosing.
	6. The PBAC noted that triple therapy of oral agents was already occurring and that this application would enable more cost effective triple therapy than currently exists.
	7. The PBAC noted that the submission presented cost-minimisation analyses for empagliflozin and linagliptin against insulin glargine or exenatide. However, the PBAC considered that there remained a number of uncertainties in these analyses. The PBAC considered that the presented alternative approach where the decrement of benefit of empagliflozin and linagliptin in triple therapy with metformin compared to the sum of benefit when each is added to metformin in dual therapy was a more robust approach. The PBAC noted that the price reduction offered in the pre-PBAC response of '''''% exceeded the decrement of benefit observed in most of the patient groups in the clinical trials and as such also addressed any residual uncertainties. The PBAC therefore considered that the price proposed for the empagliflozin with linagliptin fixed dose combination was acceptable.
	8. The PBAC noted the restriction changes for the requested FDCs would be similarly applied to the components and that this is a complex restriction. In addition, the PBAC noted that these additional restrictions would add further complexity to the PBS subsidised treatments for type 2 diabetes and reiterated its recommendation that a general statement for type 2 diabetes may be appropriate.
	9. The PBAC noted that the financial estimates would need to be adjusted to reflect the change in the proposed restriction to remove the requirement for sulfonylurea intolerance, and that these should be consistent with the previous DUSC advice.
	10. The PBAC advised that, under subsection 101(3BA) of the *National Health Act, 1953* empagliflozin with linagliptin should be treated as interchangeable on an individual patient basis with dapagliflozin with saxagliptin.
	11. The PBAC advised that empagliflozin with linagliptin is suitable for prescribing by nurse practitioners for continuing therapy only. However, the PBAC considered that it may be appropriate for nurse practitioners to initiate some treatments for type 2 diabetes and requested that this be investigated further.
	12. The PBAC recommended that the Early Supply Rule should apply.
	13. The PBAC noted that this submission is not eligible for an Independent Review because it was recommended.

*Use in moderate renal impairment*

* 1. The PBAC did not recommended the listing of empagliflozin with linagliptin for the treatment of patients with type 2 diabetes and moderate renal impairment for whom metformin or sulfonylureas are contraindicated or not tolerated.
	2. The PBAC considered that the efficacy of empagliflozin and linagliptin for the treatment of patients with mild to moderate renal impairment was not adequately supported by the data presented. Further, the submission did not address relevant comparators, such as reduced dose metformin or sulfonylureas. The PBAC also noted that the data suggested that the benefit to adding a second agent in this setting was lower, particularly in adding linagliptin to empagliflozin, and that some did not exceed the minimum clinically important difference of 0.4%.
	3. However, the PBAC acknowledged the clinical need for further treatment options for this patient group and requested the Department work with the sponsor on potential ways forward.

**Outcome:**

Recommended

1. **Recommended listing**
	1. Add new item:

|  |  |  |  |
| --- | --- | --- | --- |
| Name, Restriction,Manner of administration and form | Max.Qty (packs) | №.ofRpts | Proprietary Name and Manufacturer |
| Empagliflozin + linagliptinempagliflozin 10 mg + linagliptin 5 mg tablet, 30empagliflozin 25 mg + linagliptin 5 mg tablet, 30 | 1 | 5 | Glyxambi® 10 mg/5 mgGlyxambi® 25 mg/5 mg | BY |
|  |
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | [ ] Dental [x] Medical Practitioners [x] Nurse practitioners [ ] Optometrists[ ] Midwives |
| **PBS Indication:** | Diabetes mellitus type 2 |
| **Treatment phase:** | - |
| **Restriction Level / Method:** | [x] Streamlined |
| **Clinical criteria:** | The treatment must be in combination with metformin.ANDPatient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 4 inhibitor (gliptin), ORPatient must have previously been stabilised on dual or triple oral therapy which included a sodium-glucose co-transporter 2 (SGLT2) inhibitor, ANDPatient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a gliptin, and an SGLT2 inhibitor; ORPatient 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 gliptin, and an SGLT2 inhibitor. |
| **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 triple oral therapy with a gliptin and an SGLT2 inhibitor is initiated.The HbA1c must be no more than 4 months old at the time triple oral therapy with a gliptin and an SGLT2 inhibitor was initiated.Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/orHad 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 triple oral therapy with a gliptin and 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 and an SGLT2 inhibitor or gliptin does not need to requalify on this criterion before being eligible for PBS subsidised treatment with this fixed dose combination. |
| **Administrative Advice** | Note: 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 fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1, an insulin, another dipeptidyl peptidase 4 inhibitor (gliptin), or another SGLT2 inhibitor. |

# 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.

# Sponsor’s Comment

The sponsor had no comment.