# 5.02 EMPAGLIFLOZIN WITH LINAGLIPTIN, Tablet containing 10 mg empagliflozin with 5 mg linagliptin, Tablet containing 25 mg empagliflozin with 5 mg linagliptin, Glyxambi®, Boehringer Ingelheim Pty Limited.

## 1 Purpose of Application

1.1 Authority Required (Streamlined) listing for empagliflozin with linagliptin fixed dose combination (FDC) in combination with metformin for treatment of type 2 diabetes mellitus (T2DM), in patients intolerant or contraindicated to a combination of metformin and a sulfonylurea.

## 2 Requested listing

| 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 mg | 30 | 5 | $[redacted] | Glyxambi® | Boehringer Ingelheim |
| EMPAGLIFLOZIN 25 mg / LINAGLIPTIN 5 mg | 30 | 5 | $[redacted] | | |

**Authority required (Streamlined)**
Triple oral therapy in type 2 diabetes mellitus in combination with metformin
AND
Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR
Patient must not have tolerated a combination of metformin and a sulfonylurea

2.1 The submission did not request changes to the existing restriction for the components, linagliptin and empagliflozin (see TGA status), but indicated it would welcome the PBAC's advice with regards to extending any PBAC recommendation to the components.

2.2 The listing was requested on a cost-minimisation basis of empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDC in combination with metformin compared to:

- Empagliflozin (25 mg or 10 mg) + linagliptin 5 mg in combination with metformin;

The submission claimed that, if listed on this basis, the cost of the FDC would be less than the cost of:

- Insulin glargine in combination with metformin; or
- Exenatide 2 mg weekly or exenatide 10 µg twice daily in combination with metformin.

2.3 Both the ESC and the DUSC had concerns with the proposed restriction including that it would be difficult to implement in practice, that the PBS restrictions for diabetes medicines remain complex, and that the phrase "must not have tolerated" is open to broad interpretation.

2.4 The Pre-PBAC Response argued that the requirement for intolerance or contraindication to sulfonylureas therapy is consistent with the PBS restriction for exenatide. The Pre-PBAC Response also stated that the sponsor would accept a written Authority Required restriction to address concerns regarding inappropriate prescribing outside the PBS restriction and ensure that patients who are

contraindicated or intolerant to sulfonylureas have this treatment option available. The Pre-PBAC Response argued that there are patients for whom a trial of sulfonylurea treatment is not appropriate and could be justifiably considered by their physician as "intolerant" to sulfonylureas. The Pre-PBAC Response also stated that the RACGP 2016-18 guidelines for management of T2DM note that special care needs to be taken with those at increased risk of hypoglycaemia, especially the elderly. The Pre-PBAC Response identified other examples of situations in which sulfonylureas may be considered inappropriate, such as in patients with jobs including driving, physical labour, heavy machinery or working at heights, or patients for whom weight gain is a problem (i.e. obese patients).

2.5 The PBAC noted the sponsor would accept any changes to the restriction wording which would which more clearly identify patients who are intolerant or contraindicated to sulfonylureas, but the sponsor did not provide suggestions about the data that could be collected by a written Authority prescription. The PBAC was concerned that implementation of a restriction based on age, weight and patient's employment would be problematic. In addition, the PBAC noted the substantial costs and resources incurred by clinicians and the Department of Human Services who would be administering a potentially large volume of written Authority prescriptions under the requested listing.

2.6 The PBAC recalled it has previously considered that the requirement for intolerance to sulfonylureas has been interpreted less strictly than intended, and restrictions limiting use of oral diabetes medicines to patients intolerant to sulfonylureas were unlikely to be followed in practice (Alogliptin Public Summary Document (PSD) July 2013; Metformin and sitagliptin PSD November 2013). Subsequently, combination therapy restrictions for dipeptidyl peptidase 4 (DPP4) inhibitor and sodium-glucose co-transporter 2 (SGLT2) inhibitor products were amended to remove the requirement for intolerance or contraindication to sulfonylureas.

2.7 Additionally, as the current PBS restrictions for metformin with a DPP4 inhibitor or metformin with an SGLT2 inhibitor do not require patients to have a metformin + sulfonylurea contraindication or intolerance, a subset of patients will only be eligible for triple therapy with the FDC and metformin (met), if they first demonstrate sulfonylurea (SU) intolerance by trying triple therapy with met + SU + DPP4 inhibitor or met + SU + SGLT2 inhibitor. The PBAC noted this would need to occur in the context where clinicians are considering adding a third oral treatment to a patient's dual oral therapy regimen, rather, than, as is with case with exenatide, considering replacing some oral therapies with an injectable increasing the likelihood that the restriction would not be followed in practice.

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

## 3 Background

3.1 **TGA status at time of PBAC consideration:** Empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDCs were listed 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".

3.2 Empagliflozin 25 mg and 10 mg is registered for use in combination therapy with a DPP4 inhibitor. The indication of empagliflozin on the ARTG is "in the treatment of type 2 diabetes mellitus…" and "in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death".

3.3 Linagliptin is not TGA approved for use in combination therapy with an SGLT2 inhibitor, and an application to extend its indication was expected to have a Clinical Evaluation Report by 31 December 2016 (not available during the evaluation) and TGA approval by mid-2017.

3.4 This fixed dose combination medicine has not previously been considered by the PBAC. Concomitant use of empagliflozin and linagliptin is not subsidised on the PBS, and the PBAC has not previously considered any combination of a DPP4 inhibitor with a SGLT2 inhibitor in dual or triple oral therapy.

## 4 Clinical place for the proposed therapy

4.1 The submission proposed that the FDC would be used for the treatment of type 2 diabetes, as triple oral therapy with metformin in patients unable to achieve glycaemic control on oral dual therapy which included a SGLT2 inhibitor or a DPP4 inhibitor in combination with metformin, and who are intolerant or contraindicated to a combination of metformin and a sulfonylurea.

4.2 The submission proposed that empagliflozin with linagliptin FDC would be used prior to initiating dual therapy with metformin in combination with insulin glargine or exenatide 10 µg twice daily or 2 mg weekly. The ESC noted that there would likely be a preference for an all oral regimen as it is easier to manage in practice.

4.3 The ESC noted that a recent National Prescribing Service Medicinewise News article (Type 2 diabetes: when metformin is not enough, June 2016[1],) included a figure comparing a number of glucose-lowering medicines in the second-line setting. While the article stated "For most patients with type 2 diabetes, sulfonylureas achieve similar reductions in HbA1c compared to other second-line oral agents" the ESC noted this figure in this treatment setting suggested the efficacy of SGLT2 inhibitors and DPP4 inhibitors was less than the efficacy of sulfonylureas for HbA1c reduction.

4.4 The Pre-PBAC Response argued that this figure was based on a narrative review with a comparison of efficacy from different information sources with different levels of evidence and different patient populations. Moreover, it argued that the data presented was based on second-line therapy and is not applicable to the triple oral therapy third-line setting.

4.5 The PBAC was concerned that the submission had not adequately defined the place in therapy of the FDC.

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

[1] "Type 2 diabetes: when metformin is not enough", *National Prescribing Service Medicinewise News,* 1 June 2016, available at: http://www.nps.org.au/publications/health-professional/medicinewise-news/2016/diabetes

## 5 Comparator

5.1 The PBAC, noting the various treatment options for patients listed on the PBS, considered that it was challenging to determine a suitable comparator for the FDC without an adequately justified place in clinical therapy.

5.2 The PBAC noted the submission nominated the individual components of the FDC (empagliflozin 25 mg or 10 mg and linagliptin 5 mg) as a main comparator. In the Pre-PBAC Response, the sponsor argued that this should be the main comparator, including in the circumstance where sulfonylurea contraindication/intolerance is removed from the restriction, on the basis that concomitant use of a DPP4 inhibitor and a SGLT2 inhibitor with metformin is already being prescribed through the PBS to such an extent that this is the therapy most likely to be replaced in practice.

5.3 The PBAC agreed a comparison against the individual components of the FDC is appropriate to demonstrate the additional benefit of empagliflozin 25 mg or 10 mg and linagliptin 5 mg FDCs compared to each of the components. However, concomitant use of empagliflozin and linagliptin is not subsidised on the PBS, and the cost-effectiveness of empagliflozin with linagliptin in triple therapy with metformin has not been established.

5.4 The submission also nominated insulin glargine in combination with metformin and exenatide 10 µg twice daily or 2 mg weekly in combination with metformin, as main comparators. The PBAC agreed these may also be appropriate comparators to demonstrate the cost-effectiveness of empagliflozin 25 mg or 10 mg and linagliptin 5 mg FDCs in triple oral therapy with metformin, but this again depended on there being a better definition of the place in therapy of the FDC.

5.5 The PBAC agreed with its ESC that, if the restriction was amended as described in Section 2 (to remove the requirement for sulfonylurea contraindication/intolerance), then metformin + sulfonylurea + DPP4 and metformin + sulfonylurea + SGLT2 inhibitor may also be appropriate comparators.

*For more detail on 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 submission presented the following discrete comparisons:

1. Empagliflozin with linagliptin FDC vs linagliptin or empagliflozin: both in combination with metformin, based on two head-to-head comparisons:

a. Metformin + empagliflozin with linagliptin FDC vs metformin + linagliptin (1275.9); and
b. Metformin + empagliflozin with linagliptin FDC vs metformin + empagliflozin (1275.10).

2. Empagliflozin with linagliptin FDC vs insulin: both in combination with metformin, based on:
   a. one formal indirect comparison (metformin + DPP4 inhibitor as common reference arm):
      Metformin + empagliflozin with linagliptin FDC vs metformin + linagliptin (1275.1); and
      Metformin + insulin glargine vs metformin + sitagliptin (EASIE).
   b. one informal indirect comparison (no common reference arm):
      Metformin + empagliflozin with linagliptin FDC vs metformin + linagliptin (1275.9); and
      Metformin + sitagliptin + insulin glargine (EASIE Ext).

3. Empagliflozin with linagliptin FDC vs exenatide: both in combination with metformin, based on:
   a. one formal indirect comparison (metformin + DPP4 inhibitor as common reference arm):
      Metformin + empagliflozin with linagliptin FDC vs metformin + linagliptin (1275.1); and
      Metformin + exenatide weekly vs metformin + sitagliptin (Duration 2, Duration Neo 2).
   b. one informal indirect comparison (no common reference arm):
      Metformin + empagliflozin with linagliptin FDC vs metformin + linagliptin (1275.1); and
      Metformin + exenatide twice daily vs metformin + exenatide twice daily + sitagliptin (Violante 2012).

6.4 Both formal indirect comparisons assumed that the outcomes of the common reference arms with linagliptin 5 mg and sitagliptin 100 mg were interchangeable. The ESC noted that in recommending subsidisation, the PBAC had previously considered linagliptin 5 mg and sitagliptin 100 mg as equivalent, but that in the trial based indirect comparison of the FDC and insulin glargine in this submission, there were large differences in the common reference treatment effects.

6.5 The EASIE Extension (EASIE Ext) study was a single arm extension of the EASIE insulin glargine trial and was neither randomised nor blinded, included change in HbA1c only as a secondary outcome, was of short duration and subject to a very high risk of selection bias. Its inclusion in an informal indirect comparison was inappropriate and the results of the analysis should not be relied on and were not presented in the Commentary of the submission.

6.6 Differences between Trial 1275.1 and Violante (2012) in terms of sex, race, BMI and mean baseline metformin dose as well as definition of glycaemic control suggest the trials may not be comparable, and a single arm, informal indirect comparison using these studies was inappropriate. This comparison was also not presented in the Commentary.

6.7 The ESC noted the Pre-Sub-Committee Response (PSCR, ) stated that the sponsor "does not believe it is appropriate for the Commentary to dismiss and not evaluate the best available evidence, especially when it is highly applicable to the proposed PBS population." The PBAC agreed with the ESC that the approach taken in the Commentary was reasonable and did not consider the two indirect comparisons excluded from the Commentary to be sufficiently reliable for decision making.

6.8 Bioequivalence of empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDC to the component products was also presented in the phase 1 Trial 1275.3.

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

**Table 2: Trials and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **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. |
| EASIE Ext (NCT00851903) | Chan JCN, Aschner P, Owens DR, Picard S, Vincent M, Dain MP et al. Triple combination of insulin glargine, sitagliptin and metformin in type 2 diabetes: the EASIE post hoc analysis and extension trial. | Journal of Diabetes and its Complications 2015; 29(1):134-41. |
| **Exenatide randomised trials** | | |
| Violante 2012 (NCT00870194) | Violante R, Oliveira JHA, Yoon KH, Reed VA, Yu MB, Bachmann OP et al. A randomized non-inferiority study comparing the addition of exenatide twice daily to sitagliptin or switching from sitagliptin to | Diabet Med 2012; 29(11):e417-e424. |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| | exenatide twice daily in patients with type 2 diabetes experiencing inadequate glycaemic control on metformin and sitagliptin. | |
| 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 |
| **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. |

Source: Table B2, pp.61-62; Table B3, p.63; Table B72, p.223; Table B73, p.224; Table B114, pp.317-318 of the submission.

6.10 The key features of the randomised trials are summarised in the table below.

**Table 3: Key features of the included evidence**

| Trial | Design | N | Compared interventions | Flow | Primary outcomes | Patient population | Risk of bias |
|---|---|---|---|---|---|---|---|
| **Empagliflozin with linagliptin FDC (with metformin) trials** | | | | | | | |
| 1275.9 | R, DB, PC, MC FAS OC* MMRM | 111<br>112<br>110 | MET+EMPA 25 mg+LINA 5 mg FDC<br>MET+EMPA 10 mg+LINA 5 mg FDC<br>MET+LINA 5 mg+Pbo | 16 week OL run in MET+LINA 5 mg, +1 week OL Pbo added, +24 week RCT +1 week follow up | Mean change in HbA1c | Adult ≥18yrs HbA1c 7.0%-10.5% (post 7 week OL run in) | Low |
| 1275.10 | R, DB, PC, MC FAS OC* MMRM | 114<br>126<br>112<br>130 | MET+EMPA 25 mg+LINA 5 mg FDC<br>MET+EMPA 10 mg+LINA 5 mg FDC<br>MET+EMPA 25 mg+Pbo<br>MET+EMPA 10 mg+Pbo | 16 week OL run in MET+EMPA 10 mg MET+EMPA 25 mg +1 week OL Pbo added +24 week RCT +1 week follow up | Mean change in HbA1c | Adult ≥18yrs HbA1c 7.0%-10.5% (post 7 week OL run in) | Low |
| 1275.1 | R, DB, PC, MC FAS LOCF | 137<br>136<br>141<br>140<br>132 | MET+EMPA 25 mg+LINA 5 mg FDC<br>MET+EMPA 10 mg+LINA 5 mg FDC<br>MET+EMPA 25 mg+Pbo<br>MET+EMPA 10 mg+Pbo<br>MET+LINA 5 mg+Pbo | 2 week SB run in +24/52 week RCT +4 week follow up | Mean change in HbA1c | Adult ≥18yrs HbA1c 7.0%-10.5% (post 2 week SB run in) | Low |
| **Insulin glargine (with metformin) trials** | | | | | | | |
| EASIE | R, OL FAS LOCF | 250<br>265 | MET+insulin glargine†<br>MET+SITA 100 mg | 24 week OL +1-7 days follow up | Mean change in HbA1c | Adult 35-70yrs HbA1c 7% to <11% | High |

| Trial | Design | N | Compared interventions | Flow | Primary outcomes | Patient population | Risk of bias |
|---|---|---|---|---|---|---|---|
| EASIE Ext | OL, SA MITT | 74 | MET+insulin glargine†+SITA (insulin added to MET+SITA or SITA added to MET+insulin) | 12 week follow up to EASIE trial | Proportion achieving HbA1c <7% | Uncontrolled after MET+ insulin or SITA in EASIE | High |
| **Exenatide (with metformin) trials** | | | | | | | |
| Violante 2012 | R, DB, MC MMRM | 127<br>128 | MET+EXE 10 µg BD<br>MET+EXE 10 µg BD+SITA 100 mg | 20 week RCT (first 4 weeks EXE 5 µg BD titration) | Mean change in HbA1c | Adult 18-75yrs HbA1c 7%-9% | Un clear |
| Duration 2 | R, DB, AC, MC PP LOCF | 170<br>172<br>172 | MET+EXE 2 mg wkly+Pbo (oral)<br>MET+SITA 100 mg+Pbo (injected)<br>MET+PIO 45 mg+Pbo (injected) | 26 week RCT | Mean change in HbA1c | Adult ≥18yrs HbA1c 7.1% to <11% | Un clear |
| Duration Neo 2 | R, OL, PC, MC MMRM | 182<br>122<br>61 | MET+EXE 2 mg wkly<br>MET+SITA 100 mg<br>MET+Pbo | 28 week OL | Mean change in HbA1c | Adult ≥18yrs HbA1c 7.1% to <11% | High |
| **Bioequivalence** | | | | | | | |
| 1275.3 | R, OL, Phase 1 | 42 | EMPA 25 mg+LINA 5 mg FDC (normal)<br>EMPA 25 mg+LINA 5 mg concomitant<br>EMPA 25 mg+LINA 5 mg FDC (high fat)<br>EMPA 25 mg+LINA 5 mg FDC (slow) | Single dose | $AUC_{0-tz}$<br>$AUC_{0-72}$<br>$C_{max}$ | Adult 18-55yrs BMI 18.5-29.9 kg/m$^2$ | NA |

Source: Table B.4, p.66; Table B.12, p.83; Table 76, pp.231-233; Table B.86, p.254; Table B.117, pp.327-330; Table B.122, p.342; Table B.124, p.344; Table B.125, p.346; Table B.126, p.347; Table 127, 348; 128, p.349 of the submission; Empalina Bioequivalence, Appendix 7 to the submission.

Abbreviations AC, active control; BD, twice daily; DB, double blind; EMPA, empagliflozin; EXE, exenatide; FAS, full analysis set; FDC, fixed dose combination; HbA1c, glycosylated haemoglobin; LINA, linagliptin; LOCF, last observation carried forward; MC, multi-centre; MET, metformin; MITT, modified intention-to-treat; 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; SA, single arm; SB, single blind; 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.

***Comparative effectiveness***

6.11 1. Empagliflozin with linagliptin FDC vs linagliptin or empagliflozin, both in combination with metformin

**Table 4: Mean change in HbA1c from baseline; head-to-head comparisons of empagliflozin with linagliptin FDC vs linagliptin or empagliflozin (with metformin; FAS, MMRM, OC)**

| Trial ID | Comparison (with metformin) | Mean change in HbA1c, % (SD) (with metformin) | | | | Difference in mean change (95% CI) |
|---|---|---|---|---|---|---|
| | | n | EMPA + LINA FDC | n | LINA + Pbo | |
| 1275.9 (24 wks) | EMPA 25 mg + LINA vs LINA + Pbo | 110 | -0.56 (0.84) | 106 | 0.14 (0.93) | **-0.70 (-0.94, -0.46)** |
| | EMPA 10 mg + LINA vs LINA + Pbo | 109 | -0.65 (0.84) | 106 | 0.14 (0.93) | **-0.79 (-1.03, -0.55)** |
| | | **n** | **EMPA + LINA FDC** | **n** | **EMPA + Pbo** | |
| 1275.10 (24 wks) | EMPA 25 mg + LINA vs EMPA 25 mg + Pbo | 109 | -0.58 (0.73) | 108 | -0.10 (0.73) | **-0.48 (-0.67, -0.29)** |
| | EMPA 10 mg + LINA vs EMPA 10 mg + Pbo | 122 | -0.53 (0.77) | 125 | -0.21 (0.78) | **-0.32 (-0.51, -0.13)** |

Source: Tables B.19, p.97 and B.20, p.100. (Statistically significant results in bold).
Abbreviations: CI, confidence interval; EMPA, empagliflozin; FAS, full analysis set; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MMRM, mixed model repeated measures; OC, observed cases; Pbo, placebo; SD, standard deviation; wks, weeks.

6.12 In the direct head-to-head trials (1275.9 and 1275.10), empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDCs in combination with metformin demonstrated statistically significantly larger reductions in HbA1c from baseline compared to linagliptin 5 mg or empagliflozin 25 mg or 10 mg in combination with metformin over 24 weeks. Results favouring empagliflozin with linagliptin FDC were also reported for change in fasting plasma glucose from baseline, change in body weight from baseline and the proportion of patients achieving a HbA1c <7% (responders).

6.13 The ESC noted that empagliflozin with linagliptin FDC demonstrated superior efficacy compared to linagliptin 5 mg or empagliflozin 25 mg or 10 mg in combination with metformin. The outcomes of trials 1275.9 and 1275.10 suggested the benefits of adding linagliptin 5 mg to empagliflozin in combination with metformin were smaller than the benefits of adding empagliflozin to linagliptin in combination with metformin. The PBAC noted the publications of Trial 1275.1 by DeFronzo et al, 2015 and Lewin et al, 2015 had treatment arms of patients receiving:

1) empagliflozin 25 mg/linagliptin 5 mg FDC,
2) empagliflozin 10 mg/linagliptin 5 mg FDC tablet,
3) empagliflozin 25 mg,
4) empagliflozin 10 mg, or
5) linagliptin 5 mg.

The difference in mean change in HbA1c (%) was not consistently smaller when calculating the difference in the groups receiving empagliflozin (Groups 3 and 4) and the FDCs (Groups 1 and 2) and the groups receiving linagliptin (Group 5) and the FDCs (Groups 1 and 2).

6.14 In all trials, the effect of the combination on HbA1c was less than could be expected if the gains observed in the monotherapy submissions for the SGLT2 inhibitors and the DPP4 inhibitors were summed together. For trials 1275.9 and 1275.10, this is not

unexpected as the entry criteria for the combination drug studies was non-responsiveness to monotherapy (in combination with metformin).

6.15 2. Empagliflozin with linagliptin FDC vs insulin glargine, both in combination with metformin

**Table 5: Mean change in HbA1c from baseline; indirect comparisons of empagliflozin with linagliptin FDC vs insulin glargine (with metformin; linagliptin/sitagliptin as interchangeable common reference; FAS, LOCF)**

| Trial ID | Mean change in HbA1c from baseline % (SD) (in combination with metformin) | | | | | | Difference in mean change (95% CI) |
|---|---|---|---|---|---|---|---|
| | n | EMPA 25 mg + LINA 5 mg | n | LINA 5 mg* or SITA 100 mg* | n | 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 (24 wks) empagliflozin 25 mg + linagliptin 5 mg vs insulin glargine | | | | | | | [redacted] |
| | n | EMPA 10 mg + LINA 5 mg | n | LINA 5 mg* or SITA 100 mg* | n | 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 | | | | | | | [redacted] |

Source: Table B.95, p.275 of the submission. (Statistically significant results in bold).

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

* Common reference linagliptin 5 mg in Trial 1275.1 and sitagliptin 100 mg in the EASIE trial.

6.16 In the indirect comparison of change in HbA1c over 24 weeks, empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDCs showed no statistically significant difference compared to insulin glargine, in combination with metformin.

6.17 Empagliflozin 25 mg with linagliptin 5 mg FDC demonstrated noninferiority with insulin glargine in combination with metformin (upper 95% CI of [redacted]% less than the MCID of 0.40%). However, empagliflozin 10 mg with linagliptin 5 mg FDC did not demonstrate noninferiority (upper 95% CI of the indirect comparison [redacted]%, exceeded the MCID of 0.40%). The MCID of 0.40% HbA1c has previously been accepted by the PBAC (e.g. Dapagliflozin PSD, March 2015; Linagliptin PSD March 2016).

6.18 Large differences in the common reference treatment effects (>0.40%) suggest substantial differences between trial populations or efficacy of the common reference arms (i.e. linagliptin 5 mg and sitagliptin 100 mg). The indirect comparison may have underestimated the comparative efficacy of insulin glargine.

6.19 3. Empagliflozin with linagliptin FDC vs exenatide: both in combination with metformin

**Table 6: Mean change in HbA1c from baseline; indirect comparisons of empagliflozin with linagliptin FDC vs exenatide 2 mg weekly (with metformin; linagliptin/sitagliptin as interchangeable common reference; FAS, OC)**

| Trial ID | Mean change in HbA1c from baseline % (SD) (in combination with metformin) | | | | | | Difference in mean change (95% CI) |
|---|---|---|---|---|---|---|---|
| | n | EMPA 25 mg + LINA 5 mg | n | LINA 5 mg* or SITA 100 mg* | n | Exenatide 2 mg | |
| 1275.1 (24 wks) | 133 | -1.20 (0.69) | 128 | -0.71 (0.79) | - | - | **-0.49 (-0.67, -0.31)** |
| Duration 2 (26 wks) | - | - | 162 | -0.92 (0.94) | 159 | -1.55 (0.90) | **-0.63 (-0.91, -0.35)** |
| Duration Neo 2 (28 wks) | - | - | 122 | -0.75 (0.94) | 181 | -1.13 (0.90) | **-0.59 (-0.72, -0.04)** |
| Indirect comparisons (24 wks) All | | | empagliflozin 25 mg + linagliptin 5 mg vs exenatide | | | | [redacted]) |
| Duration 2 only | | | empagliflozin 25 mg + linagliptin 5 mg vs exenatide | | | | [redacted] |
| | n | EMPA 10 mg + LINA 5 mg | n | LINA 5 mg* or SITA 100 mg* | n | Exenatide 2 mg | |
| 1275.1 (24 wks) | 135 | -1.08 (0.70) | 128 | -0.70 (0.68) | - | - | **-0.38 (-0.55, -0.20)** |
| Duration 2 (26 wks) | - | - | 162 | -0.92 (0.94) | 159 | -1.55 (0.90) | **-0.63 (-0.91, -0.35)** |
| Duration Neo 2 (28 wks) | - | - | 122 | -0.75 (0.94) | 181 | -1.13 (0.90) | **-0.59 (-0.72, -0.04)** |
| Indirect comparisons (24 wks) All | | | empagliflozin 10 mg + linagliptin 5 mg vs exenatide | | | | [redacted] |
| Duration 2 only | | | empagliflozin 10 mg + linagliptin 5 mg vs exenatide | | | | [redacted] |

Source: Table B.137, p.371 of the submission. (Statistically significant results in bold).

Note: Standard deviation and weight mean difference calculated post hoc for the submission. Results in italics calculated during the evaluation.

Abbreviations: CI, confidence interval; EMPA, empagliflozin; FAS, full analysis set; FDC, fixed dose combination; HbA1c, Glycosylated haemoglobin; LINA, linagliptin; MITT, modified intention-to-treat; MMRM, mixed model repeated measures; OC, observed cases; SD, standard deviation; SITA, sitagliptin; wks, weeks.

* Common reference linagliptin 5 mg in Trial 1275.1 and sitagliptin 100 mg in Duration and Duration Neo 2.

6.20 Empagliflozin with linagliptin FDCs in combination with metformin showed statistically significantly larger reductions in HbA1c over 24 weeks compared to linagliptin in combination with metformin in Trial 1275.1. In the Duration 2 and Duration Neo 2 trials, exenatide 2 mg weekly in combination with metformin showed statistically significantly larger reductions in HbA1c over 26-28 weeks compared to sitagliptin in combination with metformin.

6.21 In the indirect comparison of change in HbA1c over 24-28 weeks, empagliflozin 25 mg or 10 mg with linagliptin 5 mg FDCs showed no statistically significant difference compared to exenatide 2 mg weekly, in combination with metformin. The empagliflozin 25 mg with linagliptin 5 mg FDC demonstrated noninferiority with exenatide 2 mg in combination with metformin (upper 95% CI of [redacted]% less than the MCID of 0.40%). However, the empagliflozin 10 mg with linagliptin 5 mg FDC failed to demonstrate noninferiority with exenatide 2 mg (upper 95% CI of the indirect comparison [redacted]%, exceeded the MCID of 0.40%).

6.22 Duration Neo 2 is an unpublished, open label trial with a high risk of bias. As no clinical study report or study publication was available, the study could not be adequately evaluated. Excluding Duration Neo 2 from the indirect comparison (conducted during the evaluation) resulted in empagliflozin 25 mg with linagliptin 5

mg in combination with metformin also failing to demonstrate noninferiority versus exenatide 2 mg in combination with metformin (upper 95% CI of [redacted]% exceeding the MCID of 0.40%).

6.23 Empagliflozin 10 mg with linagliptin 5 mg FDC did not consistently demonstrate noninferiority to insulin glargine or exenatide 2 mg weekly in the indirect comparisons. Empagliflozin 25 mg with linagliptin 5 mg FDC demonstrated noninferiority to insulin glargine and exenatide in combination with metformin in the primary outcome (change in HbA1c), but failed to show noninferiority versus exenatide 2 mg weekly when the Duration Neo 2 trial was excluded from the comparison.

***Comparative harms***

6.24 The comparative harms of empagliflozin with linagliptin FDC in combination with metformin were similar to the component products.

6.25 The safety profile of empagliflozin with linagliptin FDC in combination with metformin was different from both insulin glargine and exenatide 2 mg weekly in combination with metformin, but there was no statistically significantly difference between the treatment regimens in terms of key safety outcomes.

6.26 More patients treated with insulin glargine reported hypoglycaemia events compared to empagliflozin with linagliptin FDC, but the difference was not statistically significant.

6.27 Empagliflozin with linagliptin FDC was associated with more urogenital infections compared to insulin glargine and exenatide 2 mg weekly, but the differences were not statistically significant.

***Clinical claim***

6.28 <u>1. Empagliflozin with linagliptin FDC vs linagliptin or empagliflozin, both in combination with metformin</u>

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. The PBAC agreed this claim was adequately supported in clinical terms.

6.29 <u>2. Empagliflozin with linagliptin FDC vs insulin glargine, both in combination with metformin</u>

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). The PBAC considered this claim was not consistently supported in terms of efficacy and was unclear in terms of safety.

6.30 3. Empagliflozin with linagliptin FDC vs exenatide: both in combination with metformin

The clinical claim was that empagliflozin with linagliptin FDC is noninferior in terms of efficacy and safety to exenatide 10 µg twice daily or 2 mg weekly. The PBAC considered this claim was not adequately supported in terms of efficacy and was unclear in terms of safety.

***Economic analysis***

6.31 The PBAC noted that the cost-effectiveness of the combination of a DPP4 inhibitor with a SGLT2 inhibitor has not been established. Consequently the cost-minimisation based on the sum of the cost of component products as proposed by the submission is not an appropriate methodology for pricing the empagliflozin with linagliptin FDC. The PBAC considered that any economic analysis based on a comparison with the components presented in a future submission for PBS subsidised combination treatment with a DPP4/SGLT2 inhibitor should take into account that the evidence presented in this submission suggests that the effect of the combination on HbA1c is less than could be expected if the gains observed in the monotherapy submissions for the SGLT2 inhibitors and the DPP4 inhibitors were summed together (assuming metformin therapy continues in all cases).

6.32 Furthermore, the PBAC did not consider the cost comparisons with insulin glargine or extenatide to be informative for decision making, as it did not consider noninferiority with these therapies had been demonstrated or that the place in clinical therapy had been well defined. The PBAC noted that the ESC had a number of concerns with each comparison, and considered that each issue would need to be adequately addressed if these comparisons were to be included in any future submission.

6.33 The PBAC considered that it may also be necessary to demonstrate that combination treatment with a DPP4/SGLT2 inhibitor is cost-effective compared to the alternative oral triple combination therapies metformin + sulfonylurea + DPP4 inhibitor and metformin + sulfonylurea + SGLT2 inhibitor, as these regimens may also be alternative therapies to the combination proposed for listing.

***Drug cost/patient/year: $[redacted].***

6.34 The cost of treating one patient over 12 months with empagliflozin with linagliptin FDC was estimated by the submission to be $[redacted]. Compared to treating the same patient with the component products, $[redacted], this represents a savings of $[redacted] over 1 year (cost per calculated as 365.25/30×price).

***Estimated PBS usage & financial implications***

6.35 This submission was considered by DUSC. The submission used a market share approach to estimate the financial implications to the PBS of listing empagliflozin with linagliptin FDC in combination with metformin in patients with a contraindication or intolerance to a sulfonylurea. The submission compared the costs to the PBS if empagliflozin with linagliptin FDC was not listed to the cost to the PBS if it was listed, and presented the difference between these two scenarios as the financial implications to the PBS of listing.

6.36 The estimated number of patients treated with relevant combination treatment regimens was derived from a 10% Medicare longitudinal data analysis, grouped by drug classes and extrapolated over the first five years of listing using linear and power trending functions of Microsoft Excel. Script numbers for drug classes were calculated by average pack size and recommended dose regimens. Average patient copayments were calculated using PBS statistics for each PBS item. 60% of patients treated with exenatide were assumed to be to be treated with exenatide 2 mg weekly.

**Table 7: Estimated number of patients and scripts**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Patients estimated to be using metformin in combination with insulin glargine or exenatide or DPP4 inhibitor + SGLT2 inhibitor** | | | | | |
| Metformin + insulin glargine combinations | [redacted] | | | | |
| Metformin + exenatide combinations | | | | | |
| Metformin + DPP4 + SGLT2 combinations | | | | | |
| Total patients | | | | | |
| Total scripts | | | | | |
| **Patients expected to switch to empagliflozin + linagliptin FDC (market uptake)** | | | | | |
| Uptake rate from Metformin + insulin glargine combinations | | | | | |
| Uptake rate from Metformin + exenatide combinations | | | | | |
| Uptake rate from Metformin + DPP4 + SGLT2 combinations* | | | | | |
| **Estimated utilisation if empagliflozin with linagliptin FDC is listed on the PBS** | | | | | |
| **Empagliflozin + linagliptin FDC** | | | | | |
| Metformin + insulin glargine combinations | | | | | |
| Metformin + exenatide combinations | | | | | |
| Metformin + DPP4 + SGLT2 combinations | | | | | |
| Total patients | | | | | |
| **Total Scripts** | | | | | |

Source: Table E.12, p.478; Table E.17, p.483 of the submission.
Abbreviations: DPP4, dipeptidyl peptidase 4; FDC, fixed dose combination; SGLT2, sodium-glucose co-transporter 2.
* Off restriction utilisation.

The redacted table shows that at year 5, the total number of scripts was over 200,000 per year.

6.37 The submission estimated the total number of patients expected to be prescribed empagliflozin with linagliptin FDC at 10,000 – 50,000 per year in Year 1, increasing to 50,000 – 100,000 per year in Year 5.

**Table 8: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Estimated costs to the PBS/RPBS if empagliflozin with linagliptin NOT listed** | | | | | |
| Metformin | [redacted] | | | | |
| Insulin glargine | | | | | |
| Exenatide | | | | | |
| DPP4 with/without metformin | | | | | |
| SGLT2 with/without metformin | | | | | |
| **Total costs to the PBS/RPBS** | | | | | |
| **Estimated costs to the PBS/RPBS if empagliflozin with linagliptin listed** | | | | | |
| **Empagliflozin + linagliptin FDC** | [redacted] | | | | |
| Metformin | [redacted] | | | | |
| Insulin glargine | | | | | |
| Exenatide | | | | | |
| DPP4 with/without metformin | | | | | |
| SGLT2 with/without metformin | | | | | |
| **Total costs to the PBS/RPBS** | | | | | |

Source: Table E.14, p.480; Table E.12, p.478 of the resubmission.
Abbreviations: DPP4, dipeptidyl peptidase 4 inhibitor; FDC, fixed dose combination; SGLT2, sodium-glucose co-transporter 2 inhibitor.

6.38 The submission estimated the cost of empagliflozin with linagliptin FDC at $20 - 30 million in Year 1, increasing to $60 -100 million in Year 5, a cumulative cost to the PBS of more than $100 million over 5 years.

**Table 9: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Net financial implications to the PBS/RPBS if empagliflozin with linagliptin NOT listed** | | | | | |
| Cost to PBS/RPBS (DPMQ) | [redacted] | | | | |
| Patient copayment | | | | | |
| **Total cost to PBS/RPBS (without copayment)** | | | | | |
| **Net financial implications to the PBS/RPBS if empagliflozin with linagliptin listed** | | | | | |
| Cost to PBS/RPBS (DPMQ) | [redacted] | | | | |
| Patient copayment | | | | | |
| **Total cost to PBS/RPBS (without copayment)** | | | | | |
| **Net change in financial implications to the PBS/RPBS** | | | | | |
| Cost to PBS/RPBS (DPMQ) | [redacted] | | | | |
| Patient copayment | | | | | |
| **Total cost to PBS/RPBS (without copayment)** | | | | | |

Source: Table E.22, p.488 of the submission.

6.39 The submission estimated the net cost to the PBS/RPBS of listing empagliflozin with linagliptin FDC at less than $10 million in Year 1, increasing to less than $10 million in Year 5, a cumulative cost to the PBS of $20 - 30 million over 5 years.

**Table 10: Net financial implications to government including estimated savings to other health budgets**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Number of resources or services avoided if empagliflozin with linagliptin FDC is listed** | | | | | |
| Change in DHS services (script) | [redacted] | | | | |
| Diabetes nurse educator visits (initial) | | | | | |
| (follow up) | | | | | |
| Severe hypoglycaemia hospitalisation | | | | | |
| Injection needles packs | | | | | |
| Lancet testing packs | | | | | |
| Blood glucose testing strips packs | | | | | |
| Needle pens disposal containers | | | | | |
| Needles disposal containers | | | | | |
| **Cost implications to the DHS (costs avoided)** | | | | | |
| Change in DHS services (scripts) | - | - | - | - | - |
| **Costs implications to MBS budget (costs avoided)** | | | | | |
| Diabetes nurse educator visits (initial) | [redacted] | | | | |
| (follow up) | | | | | |
| **Costs implications to State and Territory health budgets (costs avoided)** | | | | | |
| Severe hypoglycaemia hospitalisation | [redacted] | | | | |
| **Costs implications to other health budgets (costs avoided)** | | | | | |
| Injection needles packs | [redacted] | | | | |
| Lancet testing packs | | | | | |
| Blood glucose testing strips packs | | | | | |
| Needle pens disposal containers | | | | | |
| Needles disposal containers | | | | | |
| **Total costs avoided other health budgets** | [redacted] | | | | |
| **Total costs to PBS/RPBS (without copayment)** | [redacted] | | | | |
| **Estimated net cost to government** | [redacted] | | | | |

Source: Tables E.23, p.489, E.24, p.490, E.25, p.490, E.26, p.491, E.27, p.492, E.28, p.493 of the submission.

6.40 The submission estimated a net savings to government health budgets of less than $10 million in Year 1, increasing to $10 - $20 million in Year 5, a cumulative saving of $30- $60 million over 5 years.

6.41 The DUSC considered that the utilisation and financial estimates presented in the submission were unsound. The main issues identified by the DUSC were:

- The method used in the analysis of the 10% PBS prescription sample overestimated the triple therapy market defined as relevant in the submission.
- However, significant markets where this fixed dose combination will be used in practice were not considered, resulting in an underestimate of the number of patients who will be treated. The submission assumed no shift from the sulphonylurea market despite noting the clinical need for a triple oral combination with a lower risk of hypoglycaemia than current sulphonylurea-containing combinations. Other markets not accounted for included substitution of the thiazolidinediones and insulins (other than glargine).
- The submission also did not adequately consider broadening of the market due to a completely new triple therapy opportunity. Patients may be treated with multiple triple oral combinations before progressing to regimens that include injectable therapies.
- The number of patients added from the dual therapy market (ie. metformin +

DPP4 inhibitor or metformin + SGLT2 inhibitor) was not estimated and accounted for.

- The submission's cost offsets due to medicines substituted were likely to be overestimated, as the cheaper sulphonylurea agents are likely to be substituted, rather than the more expensive insulin glargine and exenatide.

6.42 Other issues raised during the evaluation and by the DUSC included:

- It was unclear whether the 10% Medicare longitudinal sample data analysis included undercopayment metformin prescriptions, and metformin utilisation may have been substantially underestimated;
- Use of linear extrapolation to estimate future utilisation of diabetes combination regimens may not have been appropriate for all combination regimens;
- The market uptake of empagliflozin with linagliptin FDC was assumed;
- The assumption that 60% of patients treated with exenatide will be prescribed exenatide 2 mg weekly was not adequately justified, and is unlikely to be realised in the first few years of the estimates, given the recent listing of this formulation on the PBS. In addition, the DUSC considered that the population of patients who use exenatide may differ from the population that will use triple oral therapy and considered that the substitution of exenatide to be overestimated.
- The assumption that an initial and subsequent Nurse Educator visit would be avoided by all patients switching to empagliflozin with linagliptin FDC or opting to take up empagliflozin with linagliptin FDC instead of insulin or exenatide regimens was not supported. Patients switching between regimens may already have used these services, and educator services are not solely provided to address insulin and exenatide related management issues. In the Dapagliflozin November 2014 consideration, the PBAC agreed with the ESC that diabetes educator visits were not solely related to insulin dose titration, and it was unlikely that there would be any reduction in the number of visits. The DUSC agreed that the submission offsets relating to reduced nurse educator visits are unlikely to be achieved and not desirable in a population that has uncontrolled diabetes.
- The event rate for severe hypoglycaemia events related to use of insulin glargine was derived from the EASIE trial, which applied dose titration regimens with aggressive glucose control targets, and may not be representative of the eligible Australian population. A literature search was not conducted to investigate the incidence of severe hypoglycaemia events related to insulin glargine use in the community and the applicable event rate remains uncertain.
- The assumption that all severe hypoglycaemia events require hospitalisation was inconsistent with the definitions of severe hypoglycaemia in the clinical trials. Leese et al. (2003) investigated the frequency of severe hypoglycaemia episodes requiring emergency treatment in patients with Type 2 diabetes, and found that only 28% of events resulted in direct or indirect hospital admission. The costs of managing severe hypoglycaemia events were overestimated. The DUSC agreed that the costs of managing severe hypoglycaemia events were overestimated with the inclusion of hospital separations for catastrophic events.

6.43 DUSC also considered that;

- There was no accounting for wastage that could occur. For example when a patient on metformin and SGLT2 inhibitor dual therapy (in plain form or as an FDC) has the SGLT2 inhibitor component substituted with empagliflozin with linagliptin FDC, then the unused SGLT2 inhibitor plain or FDC form would be wasted.

- There was no accounting for additional treatments for adverse events, notably vulvovaginal candidiasis.
- Uptake of empagliflozin will rapidly increase as a result of the finding of reduced risk of cardiovascular death in the EMPA-REG OUTCOME study, and this is likely across all lines of treatment.

6.44 The Pre-PBAC Response argued while the submission's methods used to estimate the total market likely to be substituted differed from that adopted in the February 2017 DUSC Review, the number of patients receiving different combinations of medicines correlate well between the submission and the DUSC Review (Item 7.5 DUSC February 2017).

***Quality Use of Medicines***

6.45 The sponsor proposed to provide educational resources for prescribers and other health care professionals (no further details provided).

6.46 DUSC considered that FDC products can lead to QUM issues as the patient may be confused as to the contents of each product they are taking. This can lead to doubling up of the DPP4 or SGLT2 component if empagliflozin with linagliptin FDC is added to the regimen of dual therapy patients (ie. metformin + DPP4 or metformin + SGLT2) and the prior DPP4 or SGLT2 product is not ceased.

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

## 7 PBAC Outcome

7.1 The PBAC did not recommend listing empagliflozin (25 mg or 10 mg) + linagliptin 5 mg FDC in combination with metformin for T2DM on the PBS. In making its recommendation, the PBAC considered that the requested restriction would not be implementable in practice, the clinical need and place in therapy were not well defined, the cost-effectiveness of the FDC had not been established compared to the nominated comparators, and the utilisation and costings were likely underestimated.

7.2 The PBAC noted that this application was submitted under the TGA-PBAC parallel process, and considered that the listing of the FDC should not proceed until all single agent TGA indications are aligned with the indications for the FDC.

7.3 The PBAC noted the concerns of ESC and DUSC with the requested listing for the treatment of T2DM in patients intolerant or with contraindications to a sulfonylurea. The PBAC recalled that a similar requirement for second-line listing of SGLT2 and DPP4 inhibitors has previously been interpreted less strictly in practice than intended. The PBAC noted the ESC's advice that under the requested restriction, a subset of patients would only be eligible for the FDC+metformin combination if they first demonstrate SU intolerance by trying triple oral therapy of metformin+SU+DPP4 inhibitor or metformin+SU+SGLT2 inhibitor (as they will not have tried an SU before commencing dual therapy). The PBAC also noted the Pre-PBAC Response that the sponsor would find it acceptable to have a written Authority Required listing to mitigate the risk of prescribing outside the restriction. The PBAC noted a number of issues with this proposal including that the data to be collected by a written Authority was not well defined, and that substantial costs were associated with administering the volume of written Authority prescriptions expected under the requested listing.

Overall, the PBAC considered that the requested listing was both administratively unworkable and unlikely to be adhered to in practice.

7.4 Since interpretation of intolerance to SU may be less strict in clinical practice than proposed in the submission, the PBAC was concerned that patients who may otherwise be successfully treated with triple therapy with metformin + SU + DPP4 (or SGLT2) in the third-line setting, may be prescribed metformin + empagliflozin with linagliptin FDC, particularly those perceived to be at higher risk of hypoglycaemia episodes (e.g. the elderly). This concerned the PBAC as the submission had not provided evidence for a clinical or economic comparison against these triple oral therapies and the utilisation and financial estimates had not accounted for use in this population. The PBAC also noted that the ESC had highlighted the NPS Medicinewise News article suggesting that the efficacy of SGLT2 and DPP4 inhibitors was likely less than that of SUs in the second-line setting. The PBAC noted the Pre-PBAC Response's concerns that "this figure is not applicable to assess relative efficacy of third-line treatments in T2DM and is not informative to the PBAC" . Nonetheless, the PBAC viewed that this article served to illustrate its concern that a substantial proportion of use of the FDC would not be cost-effective if the requested listing does not, in practice, restrict use of the FDC+metformin to an appropriate population with a clear clinical need for this combination.

7.5 The PBAC considered that without a clearly established place in clinical therapy, it was difficult to determine the alternative therapies for the purposes of the *National Health Act 1953*. As noted above, the triple oral therapies of metformin+SU+DPP4 or metformin+SU+SGLT2 may also be appropriate comparators, given that the proposed requirements for intolerance or contraindications to SU are unlikely to be followed in practice.

7.6 Regardless, in consideration of the main comparator proposed by the submission – the individual components of the FDC – the PBAC agreed with the ESC that in the head-to-head comparison (1275.9 and 1275.10 in patients who had insufficient glycaemic control despite dual therapy with linagliptin with metformin or empagliflozin with metformin, respectively), empagliflozin with linagliptin FDC demonstrated superior efficacy compared to linagliptin 5 mg or empagliflozin 25 mg or 10 mg in combination with metformin. The PBAC also noted the ESC's advice that the effect of the combination on HbA1c was less than could be expected if the gains observed in the monotherapy submissions for the SGLT2 inhibitors and the DPP4 inhibitors were summed together (assuming metformin therapy continues in all cases), yet the proposed DPMQ of the FDC was estimated based on the sum of the individual components. The PBAC noted that given the submission claimed superiority of the FDC over the individual components, the ESC's advice was that a cost-effectiveness analysis would be appropriate. The PBAC agreed with the Pre-PBAC Response that the PBAC Guidelines ask for a clinical comparison of the FDC to each of the single agents, and suggest that the FDC should demonstrate an additional benefit over the single agent. However, the PBAC did not agree that "estimating the proposed DPMQ for empagliflozin with linagliptin based on the sum of the individual components is consistent with the PBAC Guidelines" (Pre-PBAC Response). The PBAC considered that this approach would only be appropriate if the combined use of individual components had already been considered by the PBAC to be cost-effective. The PBAC noted that the current use of empagliflozin and linagliptin outside the PBS restriction – as shown in the submission and the DUSC review – could not be assumed to be cost-effective. Consequently, the PBAC could find no basis for

recommending listing the FDC cost-minimised to its individual components.

7.7 As noted above, the PBAC also did not accept that the clinical comparisons presented against insulin glargine or exenatide demonstrated the noninferiority of the FDC against either of these potential comparators. As a result the economic comparisons against exenatide and insulin glargine were not considered informative for decision making. The PBAC did note that the ESC had a number of concerns with each comparison, and considered that each issue would need to be adequately addressed if these comparisons were to be included in any future submission.

7.8 In terms of the estimated utilisation and financial implications, the PBAC agreed with the DUSC's overall advice that the utilisation and costings were unjustifiable and likely underestimated. Not only was use outside the requested restriction highly likely (see paragraphs 7.3 and 7.4), the PBAC also noted that not all relevant markets that the FDC would substitute for were considered by the submission, and that cost-offsets were overestimated for both the medicines substituted and the treatment of hypoglycaemia. As a result of the overestimate of cost-offsets in particular, the PBAC agreed with the DUSC that the total cost to the PBS/RPBS is likely to higher than predicted.

7.9 Although the PBAC could find no basis in this submission for recommending the listing of the empagliflozin with linagliptin FDC on the PBS, it was nonetheless of the view that the drug may provide a clinical effect in some populations. The PBAC expressed that it would welcome a future submission with adequate justification of a clearly defined patient population, with an implementable restriction and justifiable costings. For example, the PBAC considered that an application for a written Authority Required PBS listing for use as first-line treatment of patients with T2DM and moderate renal impairment might be one way forward. The PBAC formed this view noting that it was likely such a population could be clearly defined, and has a high need for oral treatment options without metformin or sulfonylureas, and that estimated utilisation and costings for such a listing could be well justified. Another way forward would be a resubmission that did not restrict use of the FDC to patients with contraindications/intolerance to sulfonylurea therapy.

7.10 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**
Rejected

## 8 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.

## 9 Sponsor's Comment

The sponsor had no comment.