Medicines for the treatment of type 2 diabetes

Drug utilisation sub-committee (DUSC)

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## Abstract

### Purpose

To review the utilisation of medicines for the treatment of type 2 diabetes mellitus (T2DM), with a focus on the use of glucagon-like peptide‑1 receptor agonists (GLP‑1 RAs), sodium-glucose cotransporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors outside the Pharmaceutical Benefits Scheme (PBS) restrictions.

In July 2022, the PBAC noted that the PBS restrictions for GLP-1 RAs required patients to be contraindicated or intolerant to the combination of metformin and a sulfonylurea (SU) to receive subsidised access to a GLP-1 RA in dual therapy with metformin or a SU. The PBAC considered that clinicians may have a broader interpretation of contraindication to SUs in clinical practice than in the clinical trials and estimates of use that supported the PBS listing of GLP‑1 RAs. The PBAC recommended an updated review of the utilisation of T2DM medicines, which would include an estimation of the extent of use of GLP-1 RAs outside the PBS restrictions, such as use in monotherapy, and in dual therapy in patients not contraindicated/intolerant to a combination of metformin and a SU.

### Date of listing on the Pharmaceutical Benefits Scheme (PBS)

The DUSC reviewed medicines for the treatment of T2DM in October 2012/February 2013, and for diabetes more broadly in February 2017.

Key changes to T2DM medicines since 2017 include the listing of two GLP-1 RAs (dulaglutide in June 2018 and semaglutide in July 2020) for use in dual therapy with metformin or triple therapy with metformin and a sulfonylurea (SU), and extensions to these listings in 2021 to allow concomitant use with insulin and metformin (except where metformin is contraindicated or not tolerated). The first fixed dose combinations (FDCs) of SGLT2 inhibitors with DPP4 inhibitors were listed in April 2018, for use in triple therapy with metformin. Further details are provided in Table 1 of this report.

### Data Source / Methodology

Data extracted from the PBS claims database maintained by the Department of Health and Aged Care, and processed by Services Australia, were used for the analyses. Prescription data were extracted from 1 January 2015 up to and including 30 June 2022 based on the date of supply. Patients who were only supplied insulin in this period were excluded as likely to be patients with type 1 diabetes. Analyses included:

* Use of metformin, SU or insulin prior to GLP-1 RA initiation.
* Use of GLP-1 RAs in combination with another GLP-1 RA, an SGLT2 inhibitor or a DPP4 inhibitor.
* Use of a GLP-1 RA, SGLT2 inhibitor or a DPP4 inhibitor without concomitant use of metformin, a SU or insulin.

### Key Findings

* In 2021, the total number of people supplied a medicine for the treatment of T2DM through the PBS was around 1.42 million.
* In mid-2022, biguanides (metformin) were the most commonly supplied class of medicines for the treatment of T2DM, followed by (in order of most commonly supplied), DPP4 inhibitor + metformin FDCs, GLP-1 RAs, SU and SGLT2 inhibitors.
* Total expenditure based on the published list prices on T2DM medicines has increased from around $516 million in 2017-2018 to around $756 million in 2021-22.
* GLP‑1 RAs are now the highest expenditure class of medicines on the PBS for the treatment of T2DM accounting for 26% of expenditure in 2021-22 ($194 million).
* There are several examples of apparent use outside the PBS restrictions:
  + From 2017 to mid-2022, 18% of people initiating GLP-1 RA therapy were not supplied metformin, a SU or insulin prior to or at initiation, indicating clear use outside of the PBS restrictions. A further 57% were supplied only insulin, a SU, or metformin prior to or at initiation of a GLP-1 RA, indicating possible use outside of the PBS restrictions.
  + According to analysis of the prevalent population in 2021, almost 60% of people supplied a GLP-1 RA received this medicine in a regimen that is inconsistent with the PBS restrictions:
    - 42% were supplied a GLP-1 RA in combination with another GLP‑1 RA, a DPP4 inhibitor, an SGLT2 inhibitor or a combination of these medicines.
    - 27% were supplied a GLP-1 RA without concomitant use of metformin, SU or insulin.
    - 9.5% crossed both above categories and were supplied a GLP-1 RA without concomitant use of metformin, SU or insulin and in combination with another GLP‑1 RA, a DPP4 inhibitor, an SGLT2 inhibitor, or a combination of these medicines.
* In 2021, around 15% of people supplied an SGLT2 inhibitor and 16% of people supplied a DPP4 inhibitor received these medicines without concomitant use of metformin, SU or insulin, as required by the PBS restrictions.
* In 2021, around 14% of people supplied an SGLT2 inhibitor and 7% of people supplied a DPP4 inhibitor received these medicines in combination with a GLP‑1 RA, use which is inconsistent with the PBS restrictions.

# Purpose of analysis

To review the utilisation of medicines for the treatment of T2DM, with a focus on the use of GLP‑1 RAs, SGLT2 inhibitors and DPP4 inhibitors outside the PBS restrictions.

In July 2022, the PBAC noted that the PBS restrictions for GLP-1 RAs required patients to be contraindicated or intolerant to the combination of metformin and a SU to receive subsidised access to a GLP-1 RA in dual therapy with metformin or a SU. The PBAC considered that clinicians may have a broader interpretation of contraindication to SUs in clinical practice than in the clinical trials and estimates of use that supported the PBS listing of GLP‑1 RAs. The PBAC recommended an updated review of the utilisation of T2DM medicines, which would include an estimation of the extent of use of GLP-1 RAs outside the PBS restrictions, such as use in monotherapy, and in dual therapy in patients not contraindicated/intolerant to a combination of metformin and a SU.

# Background

## Clinical situation

Diabetes mellitus is a chronic condition in which insulin deficiency results in high blood glucose levels (hyperglycaemia). In the long term, high blood glucose levels can result in complications affecting the kidneys, eyes, heart, and nerves in the feet and other parts of the body. There are three types of diabetes mellitus: type 1, type 2, and gestational diabetes.

T2DM represents approximately 85-90% of cases of diabetes. It is a progressive condition of relative insulin deficiency caused by a loss of pancreatic beta-cell insulin secretion, and insulin resistance whereby the body becomes resistant to the effects of insulin. T2DM is associated with modifiable risk factors and disease progression can be prevented or delayed with lifestyle modification and adequate glycaemic control.

## Pharmacology

### GLP-1 RAs

GLP-1 RAs (PBS listed: dulaglutide, exenatide, semaglutide) bind to and activate the GLP-1 receptor. GLP-1 RAs stimulate receptors in the pancreas to increase insulin secretion and lower glucagon secretion in a glucose-dependent manner, lowering blood glucose. They also bind to receptors in the brain to reduce appetite which results in reductions in body weight. Some are used for weight management in adults with obesity, or overweight patients with a weight-related comorbidity. GLP-1 receptors are also present in the heart, vasculature, immune system, and kidney and these may mediate the cardiovascular (CV) and microvascular effects of GLP-1 RAs. CV outcome trials have demonstrated CV benefits of GLP-1 RAs, which are independent of reductions in glycaemia.[[1]](#footnote-1),[[2]](#footnote-2)

Adverse reactions associated with the use of GLP-1 RAs include gastrointestinal effects, acute pancreatitis, hypoglycaemia (when used with insulin or SU) and increased heart rate. The GLP-1 RAs listed on the PBS are administered by daily or weekly subcutaneous injections.

### SGLT2 inhibitors

SGLT2 inhibitors (PBS listed: dapagliflozin, empagliflozin, ertugliflozin) inhibit reabsorption of glucose from the proximal convoluted tubule in the kidney, increasing glucose excretion in the urine. SGLT2 inhibitors are weak diuretics which contribute to blood pressure reduction, and owing to their effect on glucose excretion, cause modest weight loss. As their glycaemic efficacy is dependent on renal function, they are not effective for glycaemic control in patients with impaired kidney function. However, SGLT2 inhibitors have CV and renal benefits that are independent of their effects on blood glucose.[[3]](#footnote-3),[[4]](#footnote-4) SGLT2 inhibitors are administered as oral tablets.

### DPP4 inhibitors

DPP4 inhibitors (PBS listed: sitagliptin, linagliptin, alogliptin, saxagliptin, vildagliptin) inhibit the enzyme DPP4, which is involved in the inactivation of the hormones GLP-1 and glucose-dependent insulinotrophic polypeptide (GIP). These hormones increase insulin secretion following a meal and reduce the production of glucagon by the liver, helping to regulate blood glucose levels. DPP4 inhibitors are weight neutral and are not associated with hypoglycaemia. Adverse effects associated with DPP4 inhibitors include hypertension, upper respiratory tract infections, and increased risk of pancreatitis.[[5]](#footnote-5),[[6]](#footnote-6) DPP4 inhibitors are administered as oral tablets.

## Therapeutic Goods Administration (TGA) approved indications

Table 1 provides a summary of the TGA approved indications for PBS-listed GLP-1 RAs, SGLT2 inhibitors and DPP4 inhibitors. For further information on TGA indications for other medicines included in this analysis please refer to the [Australian Register of Therapeutic Goods](https://www.tga.gov.au/australian-register-therapeutic-goods).

Table 1: TGA approved indications for PBS-listed GLP-1 RAs, SGLT2 inhibitors and DPP4 inhibitors (at August 2022)

1. SGLT2 inhibitors

| **Medicine** | **TGA approved indication/s** |
| --- | --- |
| Dapagliflozin | Glycaemic control in adults with T2DM:   * as monotherapy (with diet and exercise) where metformin is otherwise indicated but was not tolerated; * as initial combination therapy with metformin (with diet and exercise) where metformin monotherapy is unlikely to provide adequate glycaemic control (e.g. high initial HbA1c levels); * in combination with other anti-hyperglycaemic agents to improve glycaemic control, when these together with diet and exercise, do not provide adequate glycaemic control.   Prevention of hospitalisation for heart failure (HF):   * indicated in adults with T2DM and established cardiovascular disease (CVD) or risk factors for CVD to reduce the risk of hospitalization for HF.   Heart failure (HF):   * indicated in adults for the treatment of symptomatic HF with reduced ejection fraction, as an adjunct to standard of care therapy.   Chronic kidney disease:   * indicated in adults to reduce the risk of progressive decline in kidney function in adults with proteinuric chronic kidney disease (CKD Stage 2,3 or 4 and urine ACR greater than or equal to 30mg/g). |
| Empagliflozin | Glycaemic control in adults with T2DM:   * as monotherapy (with diet and exercise where metformin is not tolerated; * as add-on combination therapy with other glucose–lowering agents including insulin, when these together with diet and exercise, do not provide adequate glycaemic control.   Prevention of cardiovascular death:   * indicated in patients with T2DM and established CVD to reduce the risk of CV death. JARDIANCE should be used in conjunction with current standard of care to reduce CV risk.   Heart failure:   * indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as adjunct to standard of care therapy. |
| Ertugliflozin | Glycaemic control in adults with T2DM:   * monotherapy (with diet and exercise) when metformin not tolerated; * in combination with other anti-hyperglycaemic agents |
| Dapagliflozin + metformin | Glycaemic control in adults with T2DM as an adjunct to diet and exercise when treatment with both dapagliflozin and metformin is appropriate.  Prevention of hospitalisation for heart failure (HF) in adults with T2DM and established CVD or risk factors for CVD. |
| Empagliflozin + metformin | Glycaemic control in adults with T2DM as an adjunct to diet and exercise when treatment with both empagliflozin and metformin is appropriate.  Empagliflozin is indicated in adults with T2DM and established CVD to reduce the risk of cardiovascular death and should be used in conjunction with the current standard of care to reduce CV risk. |
| Ertugliflozin + metformin | Glycaemic control in adults with T2DM as an adjunct to diet and exercise when treatment with both ertugliflozin and metformin is appropriate. |

1. GLP-1 RAs

| **Medicine** | **TGA approved indication/s** |
| --- | --- |
| Exenatide BD | Adjunctive therapy to improve glycaemic control in patients with T2DM who are taking metformin, SU, metformin + SU, or metformin + basal insulin, but are not achieving adequate glycaemic control. |
| Exenatide QW | Treatment of T2DM to improve glycaemic control in combination with other glucose-lowering medicinal products when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control. |
| Dulaglutide | Adjunct to diet and exercise to improve glycaemic control in adults with T2DM as:   * monotherapy * combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.   Adjunct to standard of care therapy to reduce the risk of major adverse CV events in adults with T2DM who have established CVD or multiple CV risk factors. |
| Semaglutide | Treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise:   * as monotherapy when metformin is not tolerated or contraindicated. * in addition to other medicinal products for T2DM. |

1. DPP4 inhibitors

| **Medicine** | **TGA approved indication/s** |
| --- | --- |
| Linagliptin | Treatment of T2DM in adult patients to improve glycaemic control in conjunction with diet and exercise as:   * monotherapy when metformin and sulfonylureas are not tolerated, or are contraindicated, or, * as an add on to metformin, sulfonylureas or metformin plus sulfonylureas, or to insulin (with or without metformin) or,   as an add on to metformin plus SGLT2 inhibitors |
| Saxagliptin | Treatment of T2DM in adult patients to improve glycaemic control in combination with other glucose lowering medicines, when these together with diet and exercise, do not provide adequate glycaemic control:  for use as initial combination therapy with metformin, when dual saxagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects for response to monotherapy). |
| Alogliptin | Treatment of T2DM in adult patients to improve glycaemic control in, when diet and exercise do not provide adequate glycaemic control:   * as add on to metformin, a sulfonylurea, a thiazolidinedione, insulin (with or without metformin), or, * in combination with metformin and a thiazolidinedione when dual therapy does not provide adequate glycaemic control. |
| Sitagliptin | Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM as:   * monotherapy when metformin is considered inappropriate due to intolerance; or,   in combination with other anti-hyperglycaemic agents, including insulin |
| Vildagliptin | Treatment of T2DM in adults, as an adjunct to diet and exercise to improve glycaemic control:   * As monotherapy when metformin is inappropriate due to contraindications or intolerance. * In dual combination with one of metformin, a sulfonylurea or pioglitazone when a single agent does not result in adequate glycaemic control. * In triple combination with a sulfonylurea and metformin when dual therapy with these agents does not provide adequate glycaemic control.   In combination with insulin (with or without metformin) when a stable dose of insulin does not result in adequate glycaemic control. |
| Linagliptin + metformin | Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM:   * when treatment with both linagliptin and metformin is appropriate, * in patients inadequately controlled on metformin alone, or those already being treated and well controlled with the free combination of linagliptin and metformin. * in triple combination therapy with a sulfonylurea in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.   in triple combination therapy with an SGLT2 inhibitor in patients inadequately controlled on their maximum tolerated dose of metformin and an SGLT2 inhibitor. as add-on to insulin when insulin and metformin alone do not provide adequate glycaemic control. |
| Saxagliptin + metformin | Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate. |
| Alogliptin with metformin | Indicated to improve glycaemic control in adult patients with T2DM when diet and exercise do not provide adequate glycaemic control and:   * treatment with both alogliptin and metformin is appropriate when treatment with metformin alone does not provide adequate control; or * in combination with a thiazolidinedione or with insulin when dual therapy does not provide adequate control.   can also be used to replace separate tablets of alogliptin and metformin in patients already being treated with this combination. |
| Sitagliptin + metformin | Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both sitagliptin and metformin is appropriate. |
| Vildagliptin + metformin | Indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with T2DM not adequately controlled on metformin hydrochloride alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. Treatment should not be initiated with this fixed-dose combination:   * Indicated in triple combination therapy with a sulfonylurea in patients inadequately controlled with metformin and a sulfonylurea.   Indicated as add-on to insulin in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control. |

1. SGLT2 inhibitors + DPP4 inhibitors

| **Medicine** | **TGA approved indication/s** |
| --- | --- |
| Saxagliptin + dapagliflozin | Indicated as an adjunct to diet and exercise, in combination with metformin, to improve glycaemic control in adults with T2DM when treatment with both saxagliptin and dapagliflozin is appropriate. |
| Empagliflozin + linagliptin | Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both empagliflozin and linagliptin is appropriate. |
| Ertugliflozin + sitagliptin | Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM as:   * monotherapy when metformin is considered inappropriate due to intolerance; or * in combination with other anti-hyperglycaemic agents |

## Dosage and administration

The list of medicines included in this report is available in Appendix A, Table A.1. For information on dosage and administration of these medicines, please refer to the current Product Information (PI) and Consumer Medicine Information (CMI), available from the [TGA (Product Information)](http://tga.gov.au/hp/information-medicines-pi.htm) and the [TGA (Consumer Medicines Information)](http://www.tga.gov.au/consumers/information-medicines-cmi.htm).

## PBS listing details (at August 2022)

### PBS Restrictions (Abridged)

Metformin, sulfonylureas, acarbose and most insulins have unrestricted PBS listings. Insulin detemir has a restricted benefit listing for type 1 diabetes and was excluded from this analysis.

DPP4 inhibitors, SGLT2 inhibitors, GLP-1 RAs and pioglitazone have Authority Required (STREAMLINED) listings for patients meeting certain criteria and for use in combination with specified medicines. Table 2 provides an overview of the current PBS restrictions for the Authority Required diabetes medicines. None of these classes of medicines are currently PBS subsidised for use as monotherapy.

Initiation on any of these medicines requires patients to have, or have had, a HbA1c measurement greater than 7% despite treatment with specified medicines; OR if HbA1c measurement is clinically inappropriate, blood glucose levels above 10 mmol per L in more than 20% of tests over a 2-week period despite treatment with specified medicines.

GLP-1 RAs are not PBS-subsidised for use in combination with a DPP4 inhibitor, pioglitazone, or an SGLT2 inhibitor. The PBS restrictions for GLP-1 RAs differ from SGLT2 and DPP4 inhibitors in that dual therapy with metformin or a SU requires contraindication/intolerance to a combination of metformin and a SU. The PBS restrictions for SGLT2 and DPP4 inhibitors also previously required contraindication/intolerance to a combination of metformin and a SU. However, in 2013, as a result of the 2012/13 DUSC ‘Analysis of drugs for type 2 diabetes’, the PBAC recommended that the restrictions for DPP4 inhibitors be amended to remove this requirement contingent on a price reduction to account for the likely amount of non-cost-effective use. The PBAC recommended that approximately 40% of use should be cost-minimised to the price of the average daily dose of a SU. In 2014, the PBAC recommended alignment of the restrictions and prices for SGLT2 inhibitors with DPP4 inhibitors.

Table 2: Abridged PBS restrictions for Authority Required (Streamlined) T2DM medicines for T2DM indications (at 1 August 2022)

| **Class** | **Drug** | **Dual therapy with met/SU** | **Triple therapy with met + SU** | **With insulin(+/- met)** | **Triple therapy with met +** |
| --- | --- | --- | --- | --- | --- |
| DPP4 inhibitors (Gliptins) | Alogliptin2 | 🗸 | X | X | X |
| DPP4 inhibitors (Gliptins) | Linagliptin2,5 | 🗸 | 🗸 | 🗸3 | SGLT2i |
| DPP4 inhibitors (Gliptins) | Saxagliptin2,5 | 🗸 | 🗸 | X | SGLT2i |
| DPP4 inhibitors (Gliptins) | Sitagliptin2,5 | 🗸 | 🗸 | 🗸3 | SGLT2i |
| DPP4 inhibitors (Gliptins) | Vildagliptin2 | 🗸 | 🗸 | 🗸3 | X |
| SGLT2 inhibitors (Flozins) | Dapagliflozin2 | 🗸 | 🗸 | 🗸3 | DPP4i |
| SGLT2 inhibitors (Flozins) | Empagliflozin2,4 | 🗸 | 🗸 | 🗸3 | DPP4i |
| SGLT2 inhibitors (Flozins) | Ertugliflozin2,4 | 🗸 | X | X | DPP4i |
| Thiazolidinediones (TZD) | Pioglitazone | 🗸1 | 🗸 | 🗸3 | X |
| GLP-1 RAs | Exenatide | 🗸1 | 🗸 | 🗸7 | X |
| GLP-1 RAs | Dulaglutide8 | 🗸1,6 | 🗸 | 🗸7 | X |
| GLP-1 RAs | Semaglutide8 | 🗸1 | 🗸 | 🗸7 | X |

Source: the [PBS website](http://www.pbs.gov.au/pbs/home).

Abbreviations: DPP4i: dipeptidyl-peptidase-4 inhibitor; Met: metformin; SGLT2i: sodium-glucose cotransporter 2 inhibitor; SU: sulfonylurea.

Notes:

1. Only if the patient is contraindicated or intolerant to metformin and a sulfonylurea.
2. Fixed dose combination products with metformin are also available for these medicines and listed for the same indications. FDCs are not subsidised for initial therapy.
3. Despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.
4. FDC with DPP4 inhibitor available.
5. FDC with SGLT2 inhibitor available.
6. Restricted to use in combination with metformin, not sulfonylurea.
7. Treatment must be in combination with metformin unless contraindicated or not tolerated.
8. Special Pricing Arrangements apply.

For details of the current PBS listing refer to the [PBS website](file:///\\central.health\DFSGroupData\Sites\CO1\CO\PBD\PEB\EVAL\DUSC\DUSC%20Documents\Predicted%20vs%20actual%20usage\pbs.gov.au).

### Changes to listings

PBAC recommendations and PBS listings for diabetes medicines since the DUSC review in 2017 are summarised by medicine class in Table 3.

Major changes to T2DM medicines since the DUSC review in 2017 include:

* The listing of two GLP-1 RAs, dulaglutide in June 2018 and semaglutide in July 2020, for use as dual therapy with metformin (or a SU for semaglutide) or triple therapy with metformin and a SU, and extensions to these listings in 2021 to allow concomitant use with insulin and metformin (or insulin alone where metformin is contraindicated or not tolerated).
* FDCs of SGLT2 inhibitors with DPP4 inhibitors were listed and the listings for these medicines were extended to allow use in triple therapy with metformin.
* The listing of an additional SGLT2 inhibitor, ertugliflozin in December 2018, including in FDCs with metformin and sitagliptin.
* Extension of the listing for vildagliptin to include use with insulin and metformin, or insulin alone where metformin is contraindicated.
* Rosiglitazone was delisted in July 2019.
* Exenatide once-weekly formulation was delisted in February 2022.

The basis for the listing of diabetes medicines during this period was cost-minimisation with alternative therapies.

For details of the current PBS listing refer to the [PBS website](file:///\\central.health\DFSGroupData\Sites\CO1\CO\PBD\PEB\EVAL\DUSC\DUSC%20Documents\Predicted%20vs%20actual%20usage\pbs.gov.au).

Dapagliflozin was PBS listed for the treatment of chronic heart failure (CHF) on 1 January 2022 and chronic kidney disease (CKD) on 1 September 2022. Empagliflozin was PBS listed for the treatment of CKD on 1 April 2022.

Table 3: Recent major PBS listings changes for T2DM medicines and PBAC consideration.

| Class  Summarised restriction | Drug, Date of listing/change  Relevant aspects of PBAC consideration1 |
| --- | --- |
| **SGLT2i + DPP4i**  Triple therapy: with met | Empagliflozin + linagliptin, 1 April 2018  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 than cost-minimisation against insulin glargine or exenatide.  For use in combination with metformin, the PBAC advised empagliflozin + linagliptin should be treated as interchangeable on an individual patient basis with dapagliflozin + saxagliptin. The equi-effective doses were empagliflozin 10 mg or 25 mg plus linagliptin 5 mg compared to dapagliflozin 10 mg plus saxagliptin 5 mg. |
| Dapagliflozin + saxagliptin, 1 April 2018  Cost-minimisation compared with empagliflozin + linagliptin. The equi-effective doses were empagliflozin 10 mg and 25 mg to dapagliflozin 10 mg, and linagliptin 5 mg to saxagliptin 5 mg. |
| Ertugliflozin + sitagliptin, 1 December 2018  Cost-minimisation basis compared with dapagliflozin + saxagliptin + metformin and empagliflozin + linagliptin + metformin. The equi-effective doses of the FDC products were considered equivalent to the same dose of individual components taken concomitantly: ertugliflozin 5 mg or 15 mg with sitagliptin 100 mg, dapagliflozin 10 mg with saxagliptin 5 mg and empagliflozin 10 mg or 25 mg with linagliptin 5 mg. |
| **DPP4i**  Triple therapy:  with ins2 + met | Vildagliptin, 1 April 2018  Cost-minimisation basis against sitagliptin and linagliptin. The estimated equi-effective doses: vildagliptin 100mg daily is equivalent to sitagliptin 100mg daily or linagliptin 5mg daily.  Vildagliptin with metformin 50/500mg, 50/850mg and 50/1000mg FDC bid is equivalent to the concomitant administration of vildagliptin 50mg bid and metformin hydrochloride 500/850/1000mg bid. |
| **GLP-1 RA**  Dual therapy: with met  Triple therapy: with met + SU | Dulaglutide, 1 June 2018  Cost-minimisation basis against once weekly and twice daily forms of exenatide (5mcg + 10mcg). The equi-effective doses, when used in combination with metformin (dual therapy), and combination with metformin and sulfonylurea (triple therapy) are dulaglutide 1.5mg once weekly is equal to exenatide 10µg twice daily. |
| **GLP-1 RA**  Dual therapy: with met/SU  Triple therapy: with met + SU | Semaglutide, 1 July 2020  Cost-minimisation basis against dulaglutide. Both exenatide and dulaglutide should be considered comparators to semaglutide. The equi-effective doses for the cost-minimisation to dulaglutide: when used in combination with metformin (dual therapy) and in combination with metformin plus a sulfonylurea (triple therapy) semaglutide 1.0 mg once weekly is equi-effective to dulaglutide 1.5 mg once weekly. |
| **GLP-1 RA**  Triple therapy: with ins2 + met | Dulaglutide, 1 March 2021  Cost-minimisation basis against exenatide 10mcg twice daily. |
| Semaglutide, 1 September 2021  Cost-minimisation basis against dulaglutide 1.5mg once weekly. |
| **GLP-1 RA**  Delist | Once weekly exenatide, 1 February 2022  Delisted |
| **TZD**  Delist | Rosiglitazone, 1 July 2019  Delisted |

Notes:

1. Further information on the PBAC consideration is available from the [Public Summary Documents by Product](https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product) on the PBS website.
2. Despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.

## Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

In July 2022, the PBAC recommended a review of the utilisation of T2DM medicines, considering the current treatment pathways and extent of use outside the PBS restrictions for DPP4 inhibitors, SGLT2 inhibitors and GLP‑1 RAs. This would include an estimation of the extend of use of GLP-1 RAs outside the PBS restrictions, such as use in monotherapy, and in dual therapy in patients not contraindicated/intolerant to a combination of metformin and a SU.

DUSC reviewed medicines for the treatment of T2DM in October 2012/February 2013,[[7]](#footnote-7) and for diabetes more broadly in February 2017.[[8]](#footnote-8)

Since the DUSC utilisation review in February 2017, the Department has contracted a project on the cost-effectiveness of T2DM medicines in stages. This project was recommended at the PBAC Executive meeting on 19 September 2019, in response to a request from a stakeholder for broader access to GLP-1 RAs and SGLT2 inhibitors for patients with cardiovascular disease (CVD) or high cardiovascular (CV) risk.

PBAC considered a report on the ‘Cost-effectiveness review of SGLT2 inhibitors for the treatment of T2DM’ (the SGLT2 inhibitor report) in November 2021 and March 2022. The report compared SGLT2 inhibitors to SUs for the treatment of T2DM as add-on therapy to metformin, using the UKPDS Outcomes Model Version 2 (UKPDS OM2) calibrated to the Australian setting by using Australian specific mortality, cost, and patient data. The report concluded that SGLT2 inhibitors decreased the risk of all-cause and CV-related mortality and reduced systolic blood pressure and weight when compared to SUs for the treatment of T2DM as add-on therapy to metformin. The report found that SGLT2 inhibitors were likely to improve life expectancy and quality-adjusted life expectancy (quality-adjusted life years, or QALYs) versus SUs, but were likely to lead to an overall increase in lifetime costs per patient.

In March 2022, PBAC recommended the listing of dapagliflozin and empagliflozin for the treatment of T2DM, as add-on therapy to metformin, in patients with established CVD or at high CV risk, without the requirement to have a specific unmet glycaemic target. The PBAC requested that the Department commence negotiations with sponsors to achieve a financial cap on the additional cost to the PBS over the forward estimates.[[9]](#footnote-9)

PBAC considered a similar report, ‘Clinical and cost utility analysis of GLP-1 RAs for the treatment of T2DM in the Australian setting’ (GLP-1 RA report) in July 2022, which compared GLP-1 RAs to SUs for the treatment of T2DM as add-on therapy to metformin. PBAC considered the clinical outcomes to be uncertain due to the paucity of trial data, resulting in low confidence in the results of the cost utility analysis. Noting the potentially high and uncertain estimates of cost-effectiveness, the PBAC did not recommend broadening the current PBS restrictions for GLP-1 RAs. The PBAC expressed concern over the price difference between GLP-1 RAs and SGLT2 inhibitors, noting that this difference was based on the requirement for patients initiating dual therapy with a GLP-1 RA to be contraindicated/intolerant to metformin and a SU. The PBAC noted that clinicians may have a broader interpretation of contraindication to SU in clinical practice than in the clinical trials and estimates of use that supported the PBS listing.[[10]](#footnote-10)

## Clinical guidelines

Several Australian clinical guidelines are available for the management of T2DM:

* Therapeutic Guidelines, ‘[Type 2 diabetes in Adults](https://tgldcdp.tg.org.au/viewTopic?topicfile=type-2-diabetes-in-adults)’ (Updated December 2020).
* Royal Australian College of General Practitioners, ‘[Management of type 2 diabetes: A handbook for general practice](https://www.racgp.org.au/getattachment/41fee8dc-7f97-4f87-9d90-b7af337af778/Management-of-type-2-diabetes-A-handbook-for-general-practice.aspx)’ (2020).
* Australian Diabetes Society, ‘[Australian Type 2 Diabetes Glycaemic Management Algorithm](https://diabetessociety.com.au/downloads/20210301%20T2D%20Management%20Algorithm%2001032021.pdf)’ (2021).
* Living Evidence for Diabetes Consortium, ‘[Australian Evidence-Based Guidelines for Diabetes](https://diabetessociety.com.au/20211104%20Guideline-Australian-Evidence-Based-Clinical-Guidelines-for-Diabetes.pdf)’ (2020).

These clinical guidance documents provide evidence-based algorithms to assist in the selection of medicines or combinations of medicines to manage blood glucose. Australian guidelines generally recommend a target HbA1c of ≤53 mmol/mol (7.0%) for most patients, noting that the treatment approach for T2DM, including HbA1c targets should be individualised based on patient-specific factors and the risk of hypoglycaemia. Some guidelines also advise or provide links for prescribers to consult the PBS schedule for restrictions and eligibility criteria.

## Previous reviews by DUSC

Medicines for the treatment of T2DM were reviewed by DUSC at its meetings in June and October 2012 and February 2013, and diabetes more broadly in February 2017. The February 2013 analysis results were used to inform the first and second terms of reference of the Post-market Review report on T2DM medicines.[[11]](#footnote-11) An analysis of predicted versus actual utilisation of exenatide was also considered in October 2014.[[12]](#footnote-12)

# Methods

Data extracted from the PBS claims database maintained by the Department of Health and Aged Care, and processed by Services Australia, were used for the analyses. Prescription data were extracted from 1 January 2015 up to and including 30 June 2022. Data were extracted on 11 August 2022.

As these analyses use date of supply prescription data, there may be small differences compared with publicly available Services Australia Medicare date of processing data.[[13]](#footnote-13) The publicly available Medicare data only includes subsidised R/PBS prescriptions, with prescriptions priced under the patient co-payment not included. The Medicare data used in this report includes under co-payment prescriptions from 1 April 2012.

Patients who were only supplied insulin in the 7.5-year study period were excluded as likely having type 1 diabetes.

R/PBS benefits paid is based on the published list prices. Special pricing arrangements are in place for some GLP-1 RAs (semaglutide and dulaglutide).

Diabetes medicines listed on the PBS that were included in the analysis are listed in Appendix A. Item codes related to the CHF and/or CKD listings for dapagliflozin and empagliflozin were excluded from analysis.

Data analysis was undertaken using SAS.

### Prior use of metformin, SU and/or insulin in patients initiating a GLP-1 RA

A two-year lookback (2015 and 2016) was used to identify patients initiating a GLP‑1 RA from 1 January 2017 onwards. Patients initiating a GLP-1 RA were then examined to determine if they had been supplied metformin (alone or in an FDC), SU, and/or insulin prior to supply of the GLP-1 RA. Prior use included same day supply.

### Combination use of GLP-1 RAs with GLP-1 RAs, DPP4 inhibitors or SGLT2 inhibitors

This analysis considered patients supplied a GLP-1 RA between January 2021 and December 2021, inclusive. Due to supply issues associated with some GLP-1 RAs in 2022,[[14]](#footnote-14) data from 2021 were used instead. SGLT2 inhibitors (dapagliflozin and empagliflozin) were not listed for the treatment of CHF and/or CKD until 2022.

Combination treatment was defined as receiving a supply of one drug, drug A (e.g., GLP‑1 RA), with supply of another drug within 30 days, drug B (e.g., an alternative GLP‑1 RA, DPP4 inhibitor or SGLT2 inhibitor), and then a supply of drug A again within a subsequent 30 days (e.g., a GLP-1 RA) (i.e., A🡪B🡪A). Same day supply of a GLP-1 RA with another GLP-1 RA, a DPP4 inhibitor or an SGLT2 inhibitor was also considered combination use.

Supplies of insulin, metformin, SUs, thiazolidinediones (TZDs) and acarbose were not considered in this analysis. FDCs of DPP4 inhibitors and SGLT2 inhibitors were included. Gaps in supply of more than 30 days were considered to represent a switch in use.

### Use of GLP-1 RAs, DPP4 inhibitors and SGLT2 inhibitors without metformin, SU or insulin

This analysis aimed to identify the proportion of patients supplied a GLP-1 RA, DPP4 inhibitor or SGLT2 inhibitor that were not also on concomitant therapy with metformin, a SU or insulin. The analysis considered patients supplied a GLP-1 RA, SGLT2 inhibitor or DPP4 inhibitor between January 2021 and December 2021, inclusive. Data from 2020 was used to check if the patient was supplied metformin, SU or insulin prior to 2021. Supplies of TZDs and acarbose were not considered in this analysis.

The number of supplies of GLP-1 RA, SGLT2 inhibitor or DPP4 inhibitor in a row, without supplies of metformin, SU or insulin, were counted for each patient. Patients with three or more supplies of a GLP-1 RA, SGLT2 inhibitor or DPP4 inhibitor in a row following initiation, or a supply of metformin or SU, and patients with five or more supplies of a GLP‑1 RA, SGLT2 inhibitor or DPP4 inhibitor in a row following a supply of insulin were considered to be using the GLP-1 RA, SGLT2 inhibitor or DPP4 inhibitor without concomitant therapy.

### Differences from previous reports

This report covers use of medicines for people with T2DM. The previous February 2017 DUSC analysis covered the use of medicines for people with type 1 and type 2 diabetes mellitus.

The Standard Coverage Days (SCDs), or median time to re-supply, by drug group were considered unlikely to have changed appreciably since the 2017 DUSC diabetes report. Table A.2 in Appendix A shows the SCDs estimated during the 2017 and 2012/13 DUSC diabetes analyses. The SCDs for most medicines were around 30 days, except for insulin, which was around 90 days.

The 2017 DUSC diabetes report used a more complex methodology to determine patient drug regimens. This report uses simpler methods focussed on estimating the proportion of use of GLP-1 RAs, DPP4 inhibitors and SGLT2 inhibitors outside the PBS restrictions.

# Results

The number of people receiving PBS medicines for the treatment of T2DM has increased gradually reaching approximately 1.22 million people in Q2 2022 (Figure 1). As patients who were supplied only insulin during 2015 to mid-2022 were excluded (in order to remove patients with likely type 1 or gestational diabetes from the analysis), a small number of T2DM patients managed on insulin monotherapy may have been excluded from this analysis.

**Figure 1: Number of patients estimated to be on a T2DM medicine by quarter (Q1 2017 to Q2 2022).**

The data in Figure 1 represent the point prevalence by quarter of patients treated with T2DM medicines through the PBS.The estimated prevalence of T2DM in Australia in 2017‑2018 based onself-reported data from the Australian Bureau of Statistics (ABS) 2017‑18 National Health Survey was around 1 million or 5.3% of those aged 18 and over,[[15]](#footnote-15) which matches closely to the prevalence estimate based on patients treated with T2DM medicines through the PBS during 2017-2018 per quarter of around 960,000.

Alternative measures of prevalence can provide different results. For example, a count of patients dispensed at least one PBS medicine in a calendar year will give a higher estimate because patients commencing or ceasing treatment (including due to patient death) partway through a year are counted in addition to patients treated for the whole year. In 2021, the total number of patients supplied a medicine for the treatment of T2DM was around 1.43 million (data not shown) (excluding patients supplied only insulin).

In Q2 2022, biguanides (metformin) were the most supplied class of medicines for the treatment of T2DM, followed by (in order of most supplied), DPP4 inhibitor + metformin FDCs, GLP-1 RAs, SUs, and SGLT2 inhibitors (Figure 2).

**Figure 2: R/PBS prescriptions supplied of T2DM medicines by class (Q1 2017 to Q2 2022)**

Abbreviations: AGI = acarbose; MET = metformin; SULF = sulfonylurea; TZD = thiazolidinediones.

Total expenditure on T2DM medicines has increased from around $516 million in 2017-2018 to around $756 million in 2021-22 (Table 4). Until the end of 2011, expenditure on T2DM medicines by class was highest on insulins (Figure 3). However, GLP‑1 RAs are now the highest expenditure class of medicines on the PBS for the treatment of T2DM representing 26% of expenditure in 2021-22 ($194 million) (noting that special pricing arrangements are in place for dulaglutide and semaglutide), followed by insulin at 23% ($177 million), DPP4 inhibitors (including metformin FDCs but excluding SGLT2 inhibitor FDCs) at 21% ($159 million), and SGLT2 inhibitors (including metformin FDCs but excluding DPP4 inhibitor FDCs) at 19% ($142 million) (Figure 3 and Table 4).

Table 4: R/PBS benefits paid by class of T2DM medicine for 2017-18 and 2021-22

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Financial Year** | **2017-18** | **2017-18 % of total** | **2021-22** | **2021-22 % of total** |
| **TZD** | $1,507,235 | 0.30% | $796,579 | 0.10% |
| **AGI** | $1,118,383 | 0.20% | $707,822 | 0.01% |
| **DPP4i1** | $129,127,536 | 24.50% | $159,060,615 | 20.5% |
| **GLP-1 RA2** | $37,553,823 | 7% | $193,508,927 | 26% |
| **SGLT2i1** | $70,721,194 | 14% | $141,575,846 | 19% |
| **SGLT2i + DPP4i3** | $410,513 | 0.01% | $19,393,171 | 3% |
| **INSULIN** | $220,147,361 | 43% | $176,722,930 | 23% |
| **MET** | $34,333,818 | 7% | $42,248,089 | 5.5% |
| **SULF** | $20,676,836 | 4% | $22,041,382 | 3% |
| **TOTAL** | **$515,596,699** | **100%** | **$756,055,361** | **100%** |

Notes:

1. DPP4 inhibitor and SGLT2 inhibitor include benefits paid for FDCs with metformin.
2. R/PBS benefits paid based on published list prices. Special pricing arrangements are in place for dulaglutideand semaglutide.
3. First FDC of SGLT2 inhibitor + DPP4 inhibitor not listed until the third quarter of 2018.

**Figure 3: R/PBS benefits paid for T2DM medicines by class by quarter (Q1 2017 to Q2 2022)**

Note: R/PBS benefits paid based on published list prices. Special pricing arrangements are in place for dulaglutide and semaglutide.

Figure 4 and Table 5 show the R/PBS prescriptions supplied for GLP-1 RAs, DPP4 inhibitors and SGLT2 inhibitors by quarter (Q1 2017 to Q2 2022 inclusive), and by year, respectively. Between 2017 and 2021, R/PBS prescriptions for these three classes of medicines increased almost 88%. Since 2020, there has been a rapid increase in the use of GLP-1 RAs. Use of SGLT2 inhibitor + DPP4 inhibitor FDCs appears relatively low and stable, representing around 3% of R/PBS prescriptions supplied for medicines in these three classes between 2019 and 2022.

**Figure 4: R/PBS prescriptions supplied of GLP1-RAs, DPP4 inhibitors and SGLT2 inhibitors and FDCs including these classes of medicine (Q1 2017 to Q2 2022)**

Table 5: R/PBS prescriptions for GLP1-RAs, DPP4 inhibitors, SGLT2 inhibitors and DPP4 inhibitor + SGLT2 inhibitor FDCs and percentage of total (2017 to 2022)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Year** | **DPP4i1** | **GLP-1 RA** | **SGLT2i1** | **SGLT2i+DPP4i2** | **TOTAL** |
| **2017** | 2,761,649 | 372,336 | 1,357,938 | NA | 4,491,923 |
| **% of total** | 62% | 8% | 30% | NA | 100% |
| **2018** | 3,060,872 | 450,622 | 1,844,335 | 49,393 | 5,405,222 |
| **% of total** | 57% | 8% | 34% | 1% | 100% |
| **2019** | 3,349,031 | 592,045 | 2,212,140 | 159,300 | 6,312,516 |
| **% of total** | 53% | 9% | 35% | 3% | 100% |
| **2020** | 3,636,223 | 787,589 | 2,688,282 | 222,183 | 7,334,277 |
| **% of total** | 49.5% | 10.5% | 37% | 3% | 100% |
| **2021** | 3,731,790 | 1,290,283 | 3,110,585 | 293,477 | 8,426,135 |
| **% of total** | 44% | 15% | 37% | 4% | 100% |
| **20223** | 1,771,236 | 934,227 | 1,624,113 | 148,575 | 4,478,151 |
| **% of total** | 39% | 21% | 37% | 3% | 100% |

Notes:

1. DPP4 inhibitor and SGLT2 inhibitor include numbers for FDCs with metformin.
2. First FDC of SGLT2 inhibitor + DPP4 inhibitor not listed until the third quarter of 2018.
3. Data from 2022 only available until end of June.

Figure 5 shows the number of patients initiating T2DM therapy by medicine class between Q1 2017 and Q2 2022, excluding metformin, which was the most common medicine for therapy initiation throughout the entire period (at around 35,000 patients per quarter in 2022). A two-year lookback period (2015-2016) was used to identify patients initiating T2DM therapy. Until 2021, excluding metformin, patients most commonly initiated T2DM therapy with a SU, insulin or DPP4 inhibitor + metformin FDC. In 2022, excluding metformin, patients most commonly initiated T2DM therapy with an SGLT2 inhibitor or a GLP-1 RA.

**Figure 5: Number of initiating patients (excluding metformin) for T2DM medicines by class (Q1 2017 to Q2 2022)**

In 2022, the most commonly supplied GLP-1 RA was semaglutide (Figure 6). Use of exenatide has declined since 2018 and in 2022 represented only 1% of R/PBS expenditure on GLP-1 RAs (Table 6). The once-weekly formulation of exenatide was delisted from the PBS in February 2022.

The most commonly supplied SGLT2 inhibitor in 2022 was empagliflozin, and the most commonly supplied DPP4 inhibitors were sitagliptin, followed by linagliptin (including FDCs with metformin) (data not shown).

**Figure 6: R/PBS prescriptions supplied for GLP-1 RAs by drug (Q1 2017 to Q2 2022)**

Table 6: R/PBS benefits paid for GLP-1 RAs by drug for T2DM from 2017 to 20221

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **Exenatide** | **Dulaglutide2** | **Semaglutide3** | **Total** |
| **2017** | $33,419,834 | NA | NA | $33,419,834 |
| **% of total** | 100% | NA | NA | 100% |
| **2018** | $37,679,542 | $5,899,547 | NA | $43,579,089 |
| **% of total** | 86% | 14% | NA | 100% |
| **2019** | $29,490,485 | $31,596,521 | NA | $61,087,006 |
| **% of total** | 48% | 52% | NA | 100% |
| **2020** | $38,859,747 | $55,404,070 | $5,427,159 | $99,690,976 |
| **% of total** | 39% | 56% | 5% | 100% |
| **2021** | $12,486,294 | $77,015,502 | $56,235,487 | $145,737,283 |
| **% of total** | 9% | 52% | 39% | 100% |
| **20221** | $1,439,995 | $44,731,317 | $58,002,301 | $104,173,613 |
| **% of total** | 1% | 43% | 56% | 100% |

Notes:

R/PBS benefits paid based on published list prices.

1. Data from 2022 only until end of June.
2. Dulaglutide first listed June 2018. Special pricing arrangements in place.
3. Semaglutide first listed 1 July 2020. Special pricing arrangements in place.

### Prior use of metformin, SU and/or insulin in patients initiating a GLP-1 RA

The PBS restrictions for GLP-1 RAs allow use in the following circumstances:

* Dual therapy with metformin (or SU for exenatide and semaglutide): Patient is contraindicated/intolerant to a combination of metformin + SU.
* Dual therapy with insulin: Patient is contraindicated/intolerant to metformin.
* Triple therapy with metformin + SU, or metformin + insulin.

Therefore, most patients initiating therapy with a GLP-1 RA should have been supplied metformin and a SU, or metformin and insulin, prior to initiating a GLP-1 RA. In a small number of cases patients contraindicated to treatment with metformin may have initiated treatment with insulin or a SU only prior to GLP-1 RA therapy, or patients contraindicated to a SU may have initiated therapy with metformin alone.

This analysis considered patients initiating a GLP‑1 RA from 1 January 2017 to 30 June 2022 inclusive and used a two-year lookback (2015 and 2016) to identify initiating patients. Patients initiating a GLP-1 RA were then examined to determine if they had been supplied metformin (alone or in an FDC), SU, and/or insulin prior to supply of the GLP-1 RA. Prior supply of medicines other than metformin, SU or insulin were not considered. Although the PBS restrictions require patients to be stabilised on therapy with insulin and other oral agents prior to commencing GLP-1 RA therapy, prior use included same-day supply in this analysis.

From 2017 to mid-2022, only 26% of patients had been supplied metformin and SU (15%), metformin and insulin (8%), or metformin, SU and insulin (3%), prior to initiating a GLP‑1 RA, as required by the PBS restrictions (Table 7). Eighteen per cent of patients supplied a GLP‑1 RA during this period, were not supplied metformin, SU or insulin prior to initiation, indicating clear use outside of the PBS restrictions. Further, 57% were supplied only insulin (1%), a SU (1%), or metformin (55%) prior to initiation of a GLP-1 RA, indicating possible use outside of the PBS restrictions.

These results indicate that contraindication to a SU may be being interpreted more broadly in clinical practice than was intended at the time of PBS listing of GLP-1 RAs. Contraindications for gliclazide, the most used SU in Australia, include hypersensitivity to sulfonamides; severe renal or hepatic insufficiency; acidosis, ketosis or coma, or repeated episodes of ketoacidosis or coma; pregnancy; lactation; and treatment with miconazole. Some endocrine disorders, alcoholism, and malnutrition/fasting/irregular or skipped meals may increase sensitivity to SUs and risk of hypoglycaemia.[[16]](#footnote-16)

In March 2017, when considering the listing of empagliflozin + linagliptin FDC, the PBAC noted that the requested listing for T2DM in patients intolerant or with contraindication to a SU 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.[[17]](#footnote-17)

The contraindication rate to metformin among all people with T2DM has been reported as 6.4%.[[18]](#footnote-18) In contrast, between 2017 to mid-2022, 20% of people had not trialled metformin prior to initiating therapy with a GLP-1 RA, using a minimum two-year lookback period. Regarding intolerance to metformin, a review of four trials and two observational studies concluded that between 1.2% to 5% of people receiving metformin discontinued it because of a metformin-associated adverse events.[[19]](#footnote-19)

Table 7: Prior therapy for patients initiating a GLP-1 RA between 2017 and mid-2022

|  |  |  |
| --- | --- | --- |
| **Type of prior therapy** | **Number of initiating patients** | **Percentage** |
| No prior met, sulf or insulin | 12,729 | 18% |
| Prior insulin only | 524 | 1% |
| Prior sulf only | 458 | 1% |
| Prior sulf and insulin only | 104 | 0% |
| Prior met only | 39,583 | 55% |
| Prior met and insulin only | 5,616 | 8% |
| Prior met and sulf only | 10,401 | 15% |
| Prior met, sulf and insulin | 2,215 | 3% |
| **Total** | **71,630** | **100%** |

### Combination use of GLP-1 RAs with GLP-1 RAs, DPP4 inhibitors or SGLT2 inhibitors

The PBS restrictions state that GLP-1 RAs are not subsidised for use with another GLP-1 RA, a DPP4 inhibitor or an SGLT2 inhibitor. This analysis aimed to quantify the amount of combination use of GLP-1 RAs with other newer classes of T2DM medicines. Due to low utilisation of pioglitazone its use was excluded from this analysis, although use of pioglitazone with GLP-1 RAs is also prohibited in the PBS restrictions.

The analysis considered patients supplied a GLP-1 RA in 2021. Of the approximately 1.43 million people supplied a medicine for the treatment of T2DM in 2021, around 12% (172,051) were supplied a GLP-1 RA. Of these, 42% were supplied a GLP-1 RA in combination with either another GLP‑1 RA (0.6%), a DPP4 inhibitor (10%), an SGLT2 inhibitor (24%), or a DPP4 inhibitor and an SGLT2 inhibitor (8%). When only considering patients supplied these medicines on the same day, 35% of patients supplied a GLP-1 RA were supplied this medicine in combination with another GLP‑1 RA, a DPP4 inhibitor, an SGLT2 inhibitor, or a combination of these medicines.

In 2021, 14% of people supplied an SGLT2 inhibitor and 7% of people supplied a DPP4 inhibitor were supplied these medicines in combination with a GLP-1 RA, outside of the PBS restrictions.

### Use of GLP-1 RAs, DPP4 inhibitors and SGLT2 inhibitors without metformin, SU or insulin

The PBS restrictions for GLP-1 RAs, DPP4 inhibitors and SGLT2 inhibitors require use to be concomitant with at least insulin, metformin or a SU. This analysis considered patients supplied a GLP-1 RA, SGLT2 inhibitor or DPP4 inhibitor in 2021. The number of supplies of GLP-1 RA, SGLT2 inhibitor or DPP4 inhibitor in a row, without supplies of metformin, SU or insulin, were counted for each patient. Patients with three or more supplies of a GLP-1 RA, SGLT2 inhibitor or DPP4 inhibitor in a row were considered to be using the medicine without metformin or SU, and patients with five or more supplies of a GLP‑1 RA, SGLT2 inhibitor or DPP4 inhibitor in a row were considered to be using the medicine without concomitant insulin.

The percentage of patients supplied a DPP4 inhibitor, SGLT2 inhibitor or GLP-1 RA without concomitant metformin, SU or insulin was:

* GLP-1 RAs: 27% (47,113 out of 172,051)
* SGLT2 inhibitors: 15% (58,934 out of 383,153)
* DPP4 inhibitors: 16% (69,821 out of 424,906).

As some patients may be using these newer classes of T2DM medicines in combination, e.g., an SGLT2 inhibitor with a GLP-1 RA, some patients may be counted twice in this analysis. When combined with the previous analysis, 9.5% (16,384) of patients using a GLP-1 RA in 2021 were using this medicine in combination with another GLP-1 RA, an SGLT2 inhibitor, a DPP4 inhibitor, or a combination of these, and without metformin, a SU or insulin.

The SCD or median time to resupply for GLP‑1 RAs, SGLT2 inhibitors, DPP4 inhibitors, metformin and SUs is approximately 30 days, while for insulins it is approximately 90 days (refer to Appendix A, Table A.2). Therefore, three supplies in a row of a GLP‑1 RA, SGLT2 inhibitor or DPP4 inhibitor would be approximately 60 days (30 days more than the SCD for metformin and SU), and five supplies in a row would be approximately 120 days (30 days more than the SCD for insulin). There may be some patients who are using concomitant insulin at very low doses, without metformin, who are misclassified in this analysis.

# Discussion

* In 2021, the total number of people supplied a medicine for the treatment of T2DM through the PBS was around 1.42 million, of which around 12% were supplied a GLP‑1 RA.
* Total R/PBS expenditure on T2DM medicines based on the published list prices has increased from around $516 million in 2017‑2018 to around $756 million in 2021-22. GLP‑1 RAs are now the highest expenditure class of medicines for the treatment of T2DM representing 26% of expenditure in 2021-22 ($194 million) (Table 4).
* While most patients initiate T2DM therapy with metformin, there has been a recent increase in the number of patients initiating therapy with a GLP-1 RA or an SGLT2 inhibitor (Figure 5).
* An analysis of medicines used prior to initiating GLP-1 RA therapy found that from 2017 to mid-2022, 18% of people initiating a GLP-1 RA were not supplied metformin, a SU or insulin prior to or at initiation, indicating clear use outside of the PBS restrictions. A further 57% were supplied only insulin, a SU, or metformin prior to or at initiation of a GLP-1 RA, indicating possible use outside of the PBS restrictions.
* In 2021, almost 60% of people supplied a GLP-1 RA received this medicine in a regimen that is inconsistent with the PBS restrictions either: in combination with another GLP‑1 RA, a DPP4 inhibitor, an SGLT2 inhibitor or a combination of these medicines (32%); without concomitant use of metformin, SU or insulin (17%); or both (9.5%).
* In 2021, of people supplied an SGLT2 inhibitor around 15% received this medicine without concomitant use of metformin, SU or insulin, and 14% received the medicine in combination with a GLP‑1 RA, regimens that are inconsistent with the PBS restrictions. It should be noted that these are not mutually exclusive categories.
* In 2021, of people supplied a DPP4 inhibitor, around 16% received this medicine without concomitant use of metformin, SU or insulin, and around 7% received the medicine in combination with a GLP‑1 RA, regimens that are inconsistent with the PBS restrictions.

# DUSC consideration

DUSC noted that there are several within-class inconsistencies in the PBS restrictions for T2DM medicines, particularly for DPP4 and SGLT2 inhibitors. DUSC considered that this may create complexity for prescribers and noted that the inability to view numerous and complex restrictions in prescriber software has been an ongoing concern.

DUSC noted that in mid-2022, biguanides (metformin) were the most supplied class of medicines for the treatment of T2DM, followed by (in order of most supplied), DPP4 inhibitor + metformin FDCs, GLP-1 RAs, SUs, and SGLT2 inhibitors (refer to Figure 2). However, DUSC noted that SGLT2 and DPP4 inhibitors were more commonly supplied than GLP-1 RAs when the components of the classes were considered, due to the availability of FDCs of SGLT2 and DPP4 inhibitors. DUSC noted that in Q2 2022, there were around 984,000 prescriptions supplied that included a DPP4 inhibitor; 920,000 prescriptions supplied that included an SGLT2 inhibitor; and 498,000 prescriptions supplied for GLP-1 RAs.

DUSC noted that clinical guidelines generally recommend GLP-1 RAs as a first-line agent in dual therapy. DUSC noted the recent changes to the Australian Type 2 Diabetes Glycaemic Management Algorithm (August 2022)[[20]](#footnote-20), which now contain a conditional recommendation against the use of SUs in dual therapy for T2DM management due to the risk of severe hypoglycaemia. DUSC considered that the PBS restrictions for GLP-1 RAs are not consistent with their place in therapy in T2DM clinical guidelines but noted that clinical guidelines do not consider cost-effectiveness.

DUSC noted that the February 2017 DUSC ‘Analysis of diabetes medicines’ indicated that there were around 900,000 patients supplied medicines for the treatment of diabetes in 2016 (based on the monthly point prevalence), and that the rate of growth between 2012 to 2016 appeared slow and stable. DUSC noted that the number of people receiving PBS medicines for the treatment of T2DM has increased from around 900,000 in Quarter 1 (Q1) 2017 to around 1.22 million people in Q2 2022. DUSC noted that over 1.26 million patients with T2DM were currently registered with the National Diabetes Services Scheme (NDSS), and that as NDSS registration is voluntary, this would be an underestimate of the prevalence of T2DM in Australia.

DUSC noted that the analysis of medications for T2DM therapy initiation between 2017 and mid-2022 showed that patients most commonly commenced therapy with metformin as recommended in clinical guidelines, but that in 2022 there was a marked increase in the number of patients initiating T2DM therapy with an SGLT2 inhibitor or a GLP-1 RA, outside of the PBS restrictions. DUSC considered that there was an increase in the rate of growth of the prevalent T2DM population from March 2020 based on prescription data, coinciding with an increase in prescriptions dispensed for GLP-1 RAs, particularly semaglutide. DUSC noted that there also appeared to be an increase in metformin prescriptions from 2020. DUSC considered that the listing of semaglutide on the PBS may have grown the T2DM market. DUSC considered that some of the growth may represent patients previously managed on diet and exercise therapy commencing pharmacotherapy due to the availability of medications with weight loss benefits and different side effect profiles. DUSC considered that an analysis of the time from commencing metformin therapy to commencement of GLP-1 RA therapy may be informative. DUSC considered that some of the growth in the T2DM market may also be a result of changing management of T2DM patients with a greater focus in recent years on patient-centred care, including individualised glycaemic targets and improved management of comorbidities, such as cardiovascular and renal risks.

DUSC noted that the analysis of patients initiating therapy with a GLP-1 RA between 2017 and mid-2022 indicated that 18% of patients were not previously, or at the time of initiation, supplied metformin, a SU or insulin, as required by the PBS restrictions. DUSC considered that this could represent use of GLP‑1 RAs and SGLT2 inhibitors outside of the T2DM indication, including use for the management of chronic kidney disease (CKD), heart failure (HF), weight loss and pre-diabetes. DUSC noted that some SGLT2 inhibitors were PBS-listed for CKD and HF indications in 2022, but that the relevant item codes were removed from the analysis. Alternatively, patients initiating therapy with an SGLT2 inhibitor or a GLP‑1 RA could represent use within the T2DM indication by patients not using recommended first-line monotherapies (e.g., metformin, SU, insulin or acarbose) due to contraindication/intolerance or the lack of weight loss benefits.

DUSC noted that the analysis of patients initiating therapy with a GLP-1 RA between 2017 and mid-2022 further showed that 57% of patients were supplied only one of metformin, a SU or insulin, with 55% supplied only metformin, prior to commencing GLP-1 RA therapy, indicating possible use outside of the PBS restrictions. DUSC considered that prescribers may be unaware of the PBS restrictions due to the lack of information provided in clinical guidelines or may have a wider interpretation of contraindication to SU than anticipated.

DUSC noted the analysis of combination use of GLP-1 RAs, SGLT2 inhibitors and DPP4 inhibitors based on data from 2021, which showed that 42% of patients supplied a GLP-1 RA were supplied this medicine in combination with another GLP-1 RA, an SGLT2 inhibitor, a DPP4 inhibitor or a combination of these, outside of the PBS restrictions. DUSC considered that these results were unlikely to be due to misclassification due to switching, as the analysis of same-day dispensing showed 35% of supply was concomitant. DUSC noted that concomitant use of GLP-1 RA with a DPP4 inhibitor, SGLT2 inhibitor, or both, has not been assessed for cost-effectiveness. DUSC noted that some of the use outside of the PBS restrictions is in accordance with clinical guideline recommendations (e.g., use of a GLP-1 RA with an SGLT2 inhibitor), while other use may represent a quality use of medicines issue (e.g., use of a GLP-1 RA with another GLP-1 RA).

DUSC noted the analysis indicated that 27% of patients supplied a GLP-1 RA were not supplied this medicine in combination with metformin, SU or insulin in 2021, and that overall, almost 60% of patients supplied a GLP-1 RA in 2021 were supplied this medicine in a regimen inconsistent with the PBS restrictions. DUSC considered that the analysis indicated that there was extensive use of GLP‑1 RAs outside of the PBS restrictions. DUSC commented that there were several options that PBAC could consider to restore cost-effective use of GLP-1 RAs, including:

* Increasing the restriction level to an online authority.
* Restricting use to the third-line setting, by adding the requirement for contraindication/intolerance to an SGLT2 inhibitor to the restriction for dual therapy use.
* Aligning the restrictions and prices with DPP4 and SGLT2 inhibitors by removing the requirement for contraindication/intolerance to a combination of metformin and a SU.
* Writing to Australian T2DM clinical guideline developers to ensure that guidelines accurately reflect the PBS restrictions.

DUSC noted that the analysis also demonstrated use of SGLT2 inhibitors and DPP4 inhibitors that is inconsistent with the PBS restrictions, including that in 2021, around 15% of people supplied these medicines received them without concomitant metformin, SU or insulin. DUSC also noted that around 14% of people supplied an SGLT2 inhibitor and 7% of people supplied a DPP4 inhibitor in 2021, received these medicines in combination with a GLP‑1 RA. DUSC commented that some of the options to restore cost-effective use of GLP-1 RAs could also be considered by PBAC to restore cost-effective use of SGLT2 and DPP4 inhibitors, including:

* Increasing the restriction level to an online authority.
* Cost-minimising the proportion of use of SGLT2 and DPP4 inhibitors without metformin, SU or insulin to the cost of metformin or a SU (noting that patients using these medicines in combination with insulin alone would be contraindicated/intolerant to at least metformin).
* Cost-minimising the proportion of use of SGLT2 and DPP4 inhibitors with a GLP-1 RA to the cost of a SU or insulin, as the most likely medicines to have been substituted in these regimens.
* Writing to Australian T2DM clinical guideline developers to ensure that guidelines accurately reflect the PBS restrictions.

DUSC noted that 71,630 was the GLP-1 RA initiating cohort between 2017 and mid-2022, while 172,051 was the number of patients supplied a GLP-1 RA in 2021. DUSC considered that the results may indicate that a large proportion of the patients supplied a GLP-1 RA in 2021 may have commenced or trialled GLP-1 RA therapy with exenatide prior to 2017. DUSC recalled that the February 2017 DUSC ‘Analysis of diabetes medicines’ indicated that by July 2016 there were around 24,000 patients on a regimen including exenatide (twice-daily formulation) and that the exenatide once-daily formulation was PBS-listed in September 2016.

# DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

# Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits, and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

# Sponsors’ comments

### Boehringer Ingelheim Pty Ltd

Boehringer Ingelheim notes the DUSC feedback particularly on the current PBS restrictions for the SGLT2 and DPP-4 inhibitors which are complex and could create confusion for prescribers. Therefore, we support simplification of the PBS restrictions and an educational program for prescribers to address any perceived inappropriate use of Type 2 diabetes medicines. The review into type 2 diabetes medicines should follow the post market review framework.

### Eli Lilly Pty Ltd

Eli Lilly notes that any growth in the T2DM market needs to be contextualised within a changing management of patients with T2DM with a greater focus on a holistic patient-centred treatment approach. The DUSC report highlights that the majority of diabetes medicines are prescribed in accordance with clinical guidelines recommendations, demonstrating the importance of individualised clinical decision making in the management of chronic illnesses. Eli Lilly remains concerned about whether this DUSC analysis provides an accurate or representative assessment of the utilisation of T2DM medicines as Eli Lilly considers that some methodological limitations have not been adequately considered.

### Sponsors with no comment

No comments were received from the following sponsors: Apotex Pty Ltd, Alphapharm Pty Ltd, Arrotex Pharmaceuticals Pty Ltd, Arrow Pharma Pty Ltd, Amneal Pty Ltd, AstraZeneca Pty Ltd, Avallon Pty Ltd, Celltrion Healthcare Pty Ltd, Generic Health Pty Ltd, Merck Sharp & Dohme Pty Ltd, Novartis Pharmacueticals Pty Ltd, Novo Nordisk Pty Ltd, Pfizer Pty Ltd, Pharmacor Pty Ltd, Sanofi-aventis Pty Ltd, Sandoz Pty Ltd, Servier Laboratories Pty Ltd, Strides Pharma Pty Ltd, Sun Pharma Pty Ltd, Takeda Pharmaceuticals Pty Ltd.

# Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health and Aged Care (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

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# Appendix A

Table A.1: ATC codes of included T2DM medicines

|  |  |
| --- | --- |
| **Medicine** | **ATC Code** |
| **Sulfonylureas (SUs)** | |
| Glibenclamide | A10BB01 |
| Gliclazide | A10BB09 |
| Glimepiride | A10BB12 |
| Glipizide | A10BB07 |
| **Biguanides** | |
| Metformin | A10BA02 |
| **Metformin + SU FDC** | |
| Metformin with glibenclamide | A10BD02 |
| **Alpha glucosidase inhibitors** | |
| Acarbose | A10BF01 |
| **Insulins** | |
| Insulin aspart | A10ABO5 |
| Insulin lispro | A10AB04 |
| Insulin glulisine | A10ABO6 |
| Neutral insulin | A10AD01 |
| Isophane insulin | A10AC |
| Insulin glargine | A10AE04 |
| Neutral insulin with isophane | A10AD |
| Insulin aspart with aspart protamine | A10AD |
| Insulin lispro with lispro protamine | A10AD |
| Insulin aspart with degludec | A10AD06 |
| **DPP4 inhibitors** | |
| Sitagliptin | A10BH01 |
| Saxagliptin | A10BH03 |
| Linagliptin | A10BH05 |
| Alogliptin | A10BH04 |
| Vildagliptin | A10BH02 |
| **DPP4 inhibitor + metformin FDCs** |  |
| Linagliptin with metformin | A10BD11 |
| Saxagliptin with metformin | A10BD10 |
| Sitagliptin with metformin | A10BD07 |
| Vildagliptin with metformin | A10BD08 |
| Alogliptin with metformin | A10BD13 |
| **DPP4 inhibitor + SGLT2 inhibitor FDCs** | |
| Saxagliptin with dapagliflozin | A10BD21 |
| Empagliflozin with linagliptin | A10BD19 |
| Ertugliflozin with sitagliptin | A10BD24 |
| **SGLT2 inhibitors** | |
| Dapagliflozin\* | A10BK01 |
| Ertugliflozin | A10BK04 |
| Empagliflozin# | A10BK03 |
| **SGLT2 inhibitor + metformin FDCs** | |
| Dapagliflozin with metformin | A10BD15 |
| Empagliflozin with metformin | A10BD20 |
| Ertugliflozin with metformin | A10BD23 |
| **DPP4 inhibitors** | |
| Dulaglutide | A10BJ05 |
| Exenatide | A10BJ01 |
| Semaglutide | A10BJ06 |
| **Thiazolidinediones (TZDs)** | |
| Rosiglitazone | A10BG02 |
| Pioglitazone | A10BG03 |

Notes: \* Excludes item codes 12823X for CHF and 13106T for CKD.

# Excludes item code 12918X for CHF.

Table A.2: Standard Coverage Days for Drug Groups

| **Drug Group** | **Standard Coverage Days (i.e. Median time to re-supply by any item of the same drug group)** | **Standard Coverage Days**  used in DUSC February 2013 analysis for prescriptions supplied from July 2010 to July 2011 (allowing re-supply up to July 2012) for the “concessional only” cohort |
| --- | --- | --- |
| Metformin | 37 | 35 |
| Sulfonylurea | 33 | 32 |
| Met + DPP4i FDC | 30 | 29 |
| Insulin | 92 | 88 |
| Gliptin | 29 | 30 |
| Pioglitazone | 28 | 28 |
| Exenatide | 32 | 31 |
| SGLT2 | 29 | NA |
| Met + Sulf FDC | 30 | 29 |
| Acarbose | 31 | 31 |
| Met + Rosiglitazone FDC | 29 | 29 |
| Rosiglitazone | 28 | 28 |
| Met+ SGLT2 FDC | 29 | NA |

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