

Medicines for the treatment of diabetes

Drug utilisation sub-committee (DUSC)

February 2017

Abstract

Purpose

To review the utilisation of medicines for the treatment of diabetes.

Background

There have been a number of new medicines and extensions to PBS listings since the last DUSC review in February 2013.

Key changes have included the listing of sodium-glucose co-transporter 2 inhibitors (flozins), extensions to listings for the dipeptidyl peptidase-4 inhibitors (gliptins) and the glucagon-like peptide-1 (GLP-1) analogue, and the availability of additional fixed dose combination products. Further details are provided in Table 1 of this report.

Current PBS restrictions (abridged)

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

The gliptins, flozins, exenatide (GLP-1 analogue) and pioglitazone have Authority Required (STREAMLINED) listings for patients meeting certain criteria and for use in combination with specified medicines.

Rosiglitazone has an Authority Required (telephone) listing for patients meeting certain criteria and in combination with other specified medicines.

For further details see Table 2 of this report or pbs.gov.au

Data Source / methodology

Data were extracted from the Department of Human Services (DHS) prescription database for prescriptions supplied from July 2011 to September 2016. Drug regimens were estimated on a weekly basis.

Key Findings

- In mid-2016, 3.85%¹ of the Australian population (928,561 people) were estimated to be receiving diabetes medicines, compared with 3.57%² (811,009 people) in mid-2012.
- At the end of July 2016, about half of all people receiving medicines for diabetes were estimated to be on monotherapy and half were on two or more medicines.
- The top five most common regimens (starting with the most common) were metformin monotherapy, insulin monotherapy, gliptin + metformin, metformin + sulfonylurea and insulin + metformin (See Figure 3).
- The regimens that had the largest growth over the last four years were gliptin + metformin, gliptin + metformin + sulfonylurea and flozin + metformin (See Figure 4).
- There are several examples of apparent use outside the PBS restriction. These are the use of flozins and gliptins together (See Figure 6) and the use of a flozin, gliptin or exenatide as monotherapy (See Figures 6, 8 and 13).

Abbreviations/Glossary

FDC	Fixed dose combination
Flozin	Sodium-glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin and empagliflozin)
Gliptin	Dipeptidyl peptidase 4 (DPP-4) inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin and alogliptin)
GLP-1 analogue	Glucagon-like-peptide-1 analogue (exenatide)
Regimen	PBS subsidised medicines that are deemed to be used concurrently by a patient at a point in time
SCD	Standard Coverage Days
Sulf, SU	Sulfonylurea (glimepiride, gliclazide, glibenclamide and glipizide)
TZD	Thiazolidinediones (pioglitazone and rosiglitazone)

¹ ABS Estimated residential population (ERP) as at 30 June 2016, using ABS Population Clock

² ABS ERP as at 30 June 2012, using ABS.Stat beta

Purpose of analysis

To review the utilisation of medicines for the treatment of diabetes.

Background

At its June 2016 meeting the DUSC requested that a comprehensive review of utilisation of diabetes medicines be undertaken. DUSC noted that the utilisation of medicines for diabetes was last reviewed in February 2013 and since this time there have been a large number of changes and additional listings including the listing of flozins and the broadening of restrictions for gliptins.

The post-market review of products used in the management of diabetes was also completed over this period. Part 3 of this review focussed on Type 2 diabetes medicines and was considered by the Pharmaceutical Benefits Advisory Committee (PBAC) in November 2014. When summarising the outcomes of the post-market review, the PBAC noted that while most dual therapy combinations are PBS subsidised, at that time there were limited options for subsidised triple therapy. However, a number of triple therapy combinations were being used in practice. The PBAC considered there was limited evidence of benefit in reduction of HbA1c, reduced rates of hypoglycaemia or weight loss associated with most combinations that were not subsidised in 2014. The exception was metformin + sulfonylurea + SGLT2 inhibitor (flozin). The PBAC welcomed submissions for this combination. *Submissions for dapagliflozin and empagliflozin in triple therapy with metformin + sulfonylurea have since been received, recommended by the PBAC and listed on the PBS.*

Additional background material on PBS medicines for diabetes is available from Post-Market Review of Products Used in the Management of Diabetes, Part 3: Type 2 Diabetes Medicines, Final Report, October 2014.

Additions/Changes to PBS listings and relevant aspects of PBAC consideration

PBAC recommendations and PBS listings for diabetes medicines since the previous DUSC review are summarised by medicine class in Table 1. Extensions to listings have occurred on a drug by drug and restriction by restriction basis resulting in a large number of changes.

Major changes have included the expansion of the gliptin and flozin restrictions to include use as dual oral therapy (without requirement for patients to be contraindicated or intolerant to metformin and a sulfonylurea); use of the flozins and most gliptins as triple oral therapy with metformin and sulfonylurea; and use of exenatide, flozins or gliptins (only sitagliptin or linagliptin) with insulin. Full wording of the restrictions, including notes, can be found at www.pbs.gov.au

Table 1. Recent PBS listings and relevant aspects of PBAC consideration

Summarised restriction	Date of listing/change	Relevant aspects of PBAC consideration [^]
Flozins		
<i>Dual oral therapy</i> with either metformin or a sulfonylurea where patient is intolerant or contraindicated to metformin and a sulfonylurea	1 Dec 2013 (dapagliflozin & canagliflozin [#])	Cost-minimisation basis with sitagliptin. Equi-effective doses: canagliflozin 300 mg or dapagliflozin 10mg to sitagliptin 100 mg. The PBAC recommended that cost-offsets be applied to canagliflozin and dapagliflozin to account for an increased rate of adverse events such as genital mycotic infections compared with sitagliptin. These offsets would include the cost of monitoring these events which would include additional visits to doctor, treatment with antifungals.
	1 Jan 2015 (empagliflozin)	Cost-minimised against dapagliflozin and canagliflozin in terms of effectiveness, and dapagliflozin in terms of safety.
<i>Dual oral therapy</i> with either metformin or a sulfonylurea	1 Dec 2014 (dapagliflozin ⁺)	Previously, dapagliflozin could be added to either metformin or a sulphonylurea only if the patient was contraindicated to, or intolerant of, the combination of metformin and a sulfonylurea. This was recommended at the July 2014 PBAC meeting to align the dapagliflozin restriction with the restriction for the gliptins.
	1 Apr 2015 (empagliflozin)	Cost-minimised against dapagliflozin
<i>Use with insulin</i>	1 Apr 2015 (dapagliflozin ⁺)	Cost-minimisation and cost-analysis derived from the costs of insulin up-titration avoided.
	1 Mar 2016 (empagliflozin)	Cost-minimisation with dapagliflozin. The equi-effective doses are empagliflozin 10mg or 25mg and dapagliflozin 10mg.
<i>Triple oral therapy</i> with metformin and a sulfonylurea when dual oral therapy is inadequate	1 Jul 2015 (dapagliflozin ⁺)	Cost analysis compared with insulin (including drug acquisition costs and costs of healthcare resource consumption). The equi-effective doses are dapagliflozin 10mg (oral) and insulin glargine 24 IU/day (subcutaneous).
	1 Mar 2016 (empagliflozin)	Cost-minimisation with dapagliflozin. The equi-effective doses are empagliflozin 10mg or 25mg and dapagliflozin 10mg.
Gliptins		
<i>Dual oral therapy</i> with either metformin or a sulfonylurea	1 Dec 2013 (alogliptin ⁺) 1 April 2014 (linagliptin, saxagliptin, sitagliptin ⁺ , vildagliptin)	Previously, a gliptin could be added to either metformin or a sulfonylurea only if the patient was contraindicated to, or intolerant of, the combination of metformin and a sulfonylurea. A DUSC report found that there was extensive use of gliptins in patients who had not trialled metformin and a sulfonylurea. The PBAC (April 2013) recommended listing at a reduced price, where the likely proportion of use in patients who have not trialled a sulfonylurea was cost-minimised to the average daily dose of a sulfonylurea in combination with metformin.

Summarised restriction	Date of listing/change	Relevant aspects of PBAC consideration [^]
<i>Gliptins (continued)</i>		
<i>Triple oral therapy</i> – when dual oral therapy is inadequate	1 Dec 2015 (sitagliptin ⁺ , saxagliptin ⁺)	Cost minimisation analysis compared with dapagliflozin in combination with MET and a SU. The equi-effective doses are sitagliptin 100mg or saxagliptin 5mg/day and dapagliflozin 10mg.
	1 Sept 2016 (vildagliptin ⁺)	Cost-minimisation with dapagliflozin. The equi-effective doses were dapagliflozin 10mg/day and vildagliptin 100mg/day (given as two 50mg doses)
	1 Sept 2016 (linagliptin ⁺)	Cost-minimisation with sitagliptin. The equi-effective doses were linagliptin 5mg and sitagliptin 100mg.
<i>Use with insulin*</i>	1 Oct 2016 (sitagliptin ⁺ , linagliptin)	Cost-minimisation basis with dapagliflozin in combination with insulin. The equi-effective doses were sitagliptin 100mg or linagliptin 5mg and dapagliflozin 10mg.
<i>GLP-1 analogues</i>		
<i>Triple therapy with insulin*</i>	1 Oct 2015 (exenatide)	Cost analysis basis compared with intensification of insulin therapy to the full basal-bolus regimen
<i>Once weekly exenatide</i>	1 Sep 2016	Cost-minimisation with a partial cost offset for reduced needle use and a further small price advantage for exenatide 2 mg once weekly on the basis of potential health benefits from likely improved adherence by a small number of high clinical need populations.

[^] Further information on the PBAC consideration is available from Public Summary Documents by Product.

⁺ Indicates the change also applied to the fixed dose combination formulation containing metformin. Listing dates: alogliptin with metformin FDC (1 Feb 2014); saxagliptin or linagliptin with metformin FDCs (1 March 2014), dapagliflozin with metformin FDC (1 Oct 2015 -dual oral) and 1 Dec 2015-(triple oral and with insulin); empagliflozin with metformin FDC (1 March 2016).

[#] Delisted 1 August 2013

* despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.

The basis for the listing of most diabetes medicines during this period was cost-minimisation with alternative therapies. Generally the listings were expected to be essentially cost-neutral or cost-saving to the PBS. The exception was an increase in net cost to the PBS with the listing of the exenatide once weekly formulation, for which the cost to government was partially offset by a reduction in needle use.

Part 5 of the PMR report³ (PBS listing of Type 2 Diabetes Medicines) gives details of changes to the listings in the period before that covered in Table 1. It also includes information about TGA indications and a history of PBAC recommended submissions for dual and triple therapy.

Full wording of the restrictions, including notes, can be found at www.pbs.gov.au

³ [Post-Market Review of Products Used in the Management of Diabetes, Part 3: Type 2 Diabetes Medicines, Final Report, October 2014](#)

Current PBS restrictions (abridged)

Metformin, sulfonylureas, acarbose and most insulins and analogues have unrestricted PBS listings.

Insulin detemir has a restricted benefit listing for type 1 diabetes. Bovine insulins are Authority Required for diabetes mellitus where the patient is intolerant to human insulin.

The gliptins, flozins, GLP-1 analogues and pioglitazone have Authority Required (STREAMLINED) listings for patients meeting certain criteria and for use in combination with specified medicines. Rosiglitazone has an Authority Required (telephone) listing for patients meeting certain criteria and in combination with other specified medicines because of safety concerns. 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. Full details of the PBS eligibility criteria are available from www.pbs.gov.au

Table 2 provides an overview of the current PBS restrictions for the Authority Required diabetes medicines (as at 1 November 2016).

Table 2: PBS restrictions (abridged) for Authority required (streamlined or telephone)^ medicines, excluding bovine insulin.

	Dual oral with met or SU	Triple therapy with met + SU	With insulin [#]
<i>Gliptins</i>			
Alogliptin ⁺	✓	X	X
Linagliptin ⁺	✓	✓	✓
Saxagliptin ⁺	✓	✓	X
Sitagliptin ⁺	✓	✓	✓
Vildagliptin ⁺	✓	✓	X
<i>Flozins</i>			
Dapagliflozin ⁺	✓	✓	✓
Empagliflozin ⁺	✓	✓	✓
<i>Thiozolidioines</i>			
Pioglitazone	✓*	✓	✓
Rosiglitazone ⁺	✓*	X	X
<i>GLP-1 analogues</i>			
Exenatide	✓*	✓	✓

[^] All are Authority required (streamlined) except rosiglitazone (telephone).

^{*} Only if the patient is contraindicated or intolerant to metformin and a sulfonylurea.

⁺ 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.

[#] despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.

None of the above four classes of medicines are currently PBS subsidised for use in combination with one another. Nor are they available for use as monotherapy. An alternative presentation of the restrictions, outlining all of the combinations of medicines that are eligible for PBS subsidy, is provided in Appendix A.

Clinical Guidelines

Several clinical guidance and position statements are available for both type 1 and type 2 diabetes, including:

- National Evidence-Based Clinical Care Guidelines for Type 1 Diabetes for Children, Adolescents and Adults developed by the Australasian Paediatric Endocrine Group and the Australian Diabetes Society. These guidelines are approved by the National Health and Medical Research Council (NHMRC).
- A new blood glucose management algorithm for type 2 diabetes: a position statement of the Australian Diabetes Society. This algorithm has been incorporated into General practice management of type 2 diabetes: 2016–18.
- Therapeutic Guidelines (eTG): endocrinology.

These clinical guidance documents provide evidence-based algorithms to assist in the selection of medicines or combinations of medicines to manage blood glucose. The guidelines also highlight that patient-centred treatment may mean that deviations from the algorithm need to be considered on a case-by-case basis.

The guidelines also advise or provide links for prescribers to consult the PBS schedule for restrictions and eligibility criteria.

Approach taken to estimate utilisation

Dapagliflozin – dual oral therapy (July 2013 PBAC, listed December 2013)

The utilisation estimates were based on a market share approach. The DPP-4 and TZD markets were projected from 2012 prescription utilisation data using the average growth rate of each market over the previous 3 years.

DUSC considered an earlier submission to the March 2012 PBAC for the same indication. The advice it provided to the PBAC was that there was potential for utilisation to be greater than anticipated in the submission. In response, the estimates in the July 2013 submission were higher. Table 3 shows these estimates and also the final estimates agreed with the sponsor.

Table 3: Dapagliflozin prescription estimates

	2012	2013	2014	2015	2016	2017
July 2013 submission						
Final agreed estimates						

Canagliflozin – dual oral therapy (July 2013 PBAC, listed December 2013)

The canagliflozin submission for dual oral therapy was recommended at the July 2013 PBAC, the same meeting as dapagliflozin. Thus in the final agreed estimates both drugs

were estimated to have 50% of the SGLT2 inhibitor market. The prescription numbers for canagliflozin were slightly lower as it has a pack size of 30 tablets, compared to 28 tablets for dapagliflozin.

Table 4: Prescription estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Note: Year 1 is December 2013 to November 2014.

There was a Risk Share Agreement (RSA) put in place for the SGLT2 inhibitor market. However, this lapsed in December 2014 when the price and restriction of dapagliflozin were changed.

Empagliflozin - dual oral therapy (July 2014 PBAC, listed January 2015)

The estimates were based on a market share approach. The submission stated, "Given that empagliflozin is a pharmacological analogue of the two other SGLT2 inhibitors that are currently available on the PBS (dapagliflozin and canagliflozin), empagliflozin would substitute prescriptions that would have otherwise been attributed to canagliflozin or dapagliflozin, with no increase in the overall SGLT2 inhibitor market size as a consequence of listing". The final agreed estimates (September 2014) were 30% less than those in the July 2014 submission (see Table 5).

Table 5: Prescription estimates

	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Dapagliflozin – therapy with insulin (November 2014 PBAC, listed April 2015)

The submission for triple therapy with insulin was based on a market share approach. The estimates were based on the pack volumes in the SGLT2 inhibitor market caps in the RSA. The estimated additional dapagliflozin prescriptions are shown in Table 6. The November 2014 submission estimates and the final agreed estimates were the same.

Table 6: Additional dapagliflozin prescription estimates

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

Dapagliflozin – triple oral therapy (March 2015 PBAC, listed July 2015)

The estimates were based on a market share approach.

Table 7: Additional dapagliflozin prescription estimates

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

Empagliflozin – therapy with insulin & triple oral therapy (November 2015 PBAC, listed March 2016)

As these two indications were already approved for dapagliflozin, it was assumed that this listing would not grow the flozin market.

Flozin combination products

The listings of dapagliflozin with metformin FDC in October 2015 and of empagliflozin with metformin FDC in March 2016, were not expected to impact the size of the SGLT2 inhibitor market.

Previous reviews by DUSC

Medicines for the treatment of diabetes were reviewed by DUSC at its meetings in June and October 2012 and February 2013. The February 2013 analysis results were used in the first and second terms of reference of the Diabetes PMR report.

Methods

Patient drug regimens were estimated from prescriptions extracted from the Department of Human Services (DHS) PBS prescription claim database for prescriptions supplied from July 2011 to September 2016, inclusive.

Prior to April 2012 under co-payment prescriptions were missing from these data. These missing prescriptions are estimated in the DUSC database, but are not used in this analysis as they do not have a patient ID for each script and so cannot be used for patient level analysis (eg. estimating drug regimens).

The prescriptions were supplied from July 2011 to September 2016. However the resulting drug regimens are only estimated from September 2012 to the end of July 2016. This is because the estimates from July 2011 to August 2012 are inaccurate because;

- the data prior to April 2012 is missing patient level under co-payment scripts, and
- drug regimens require a “run in” period to stabilise because some prescriptions are infrequent and the true drug regimen is only evident after prescriptions of all the drugs in the regimen have been supplied.

Also the estimated drug regimens were inaccurate near the end of the data period (ie. August and September 2016) because there is greater uncertainty in this period whether or not patient treatment is on-going after their last script.

For more details on the method used to estimate patient drug regimens see Appendix B.

Diabetes medicines listed on the PBS were defined as all PBS items with a WHO or PBS ATC code starting with A10 (Drugs used in diabetes).

Data analysis was undertaken using SAS.

Differences from previous reports:

- This report covers use of medicines for people with Type 1 and Type 2 diabetes. People taking insulin monotherapy are included in medicine regimen analyses. The February 2013 DUSC diabetes medicines analysis also included these patients but focussed on Type 2 diabetes medicines. The aim of Analysis 1 in that report was “Assessing the extent that gliptins, glitazones and exenatide supplied through the PBS meet the restrictions with regard to the co-administration of other medicines for type 2 diabetes”. This analysis included all drugs used in diabetes (ie. ATC=A10) and so regimens for Type 1 diabetes patients were also included in Figures 7.4.3 to 7.4.6. However Analysis 1 Figures 7.4.7 to 7.4.13 included only regimens which contained gliptins, glitazones and exenatide which are applicable to Type 2 diabetes only. The aim of Analysis 2 in the February 2013 analysis was “To determine the proportion of patients who receive a supply of metformin and a sulfonylurea prior to initiating therapy with a gliptin, glitazone or exenatide”. Thus this analysis only included Type 2 diabetes patients.

- The method used to estimate regimens (and thereby differentiate add on, switch, cessation of a medicine) has been updated since the 2013 report. The key differences are:
 - The 2013 report only included “concessional only” patients because of the possibility of missing under co-payment scripts (eg. metformin) for general patients. This analysis includes all patients as there are now sufficient data since the collection of under co-payment prescription data (which started in April 2012) to estimate 4 years’ worth of drug regimens for PBS supplied medicines for all patients.
 - Using drug specific Standard Coverage Days (SCDs) to distinguish between an add and a switch (see point 2 in Appendix B). In the 2013 report a drug coverage overlap of less than 5 weeks was deemed to be a switch (ie. there was no real drug overlap). In this report the 5 week period was replaced by the drug specific SCD of the prior drug. That is, if the apparent drug overlap does not last longer than the SCD of the prior drug, then the prior drug most likely ceased when the new drug was added (ie. it was a switch). This is an improvement in the method as insulins have much longer SCDs than the other diabetes drugs so switches are more accurately inferred when the drug specific SCD is used.
- The SCDs for drug groups in this analysis have not changed appreciably since the 2013 report. See Table B.2 in Appendix B.

Results

The number of people receiving PBS medicines for the treatment of diabetes has increased gradually reaching approximately 930,000 people in mid-2016 (Figure 1).

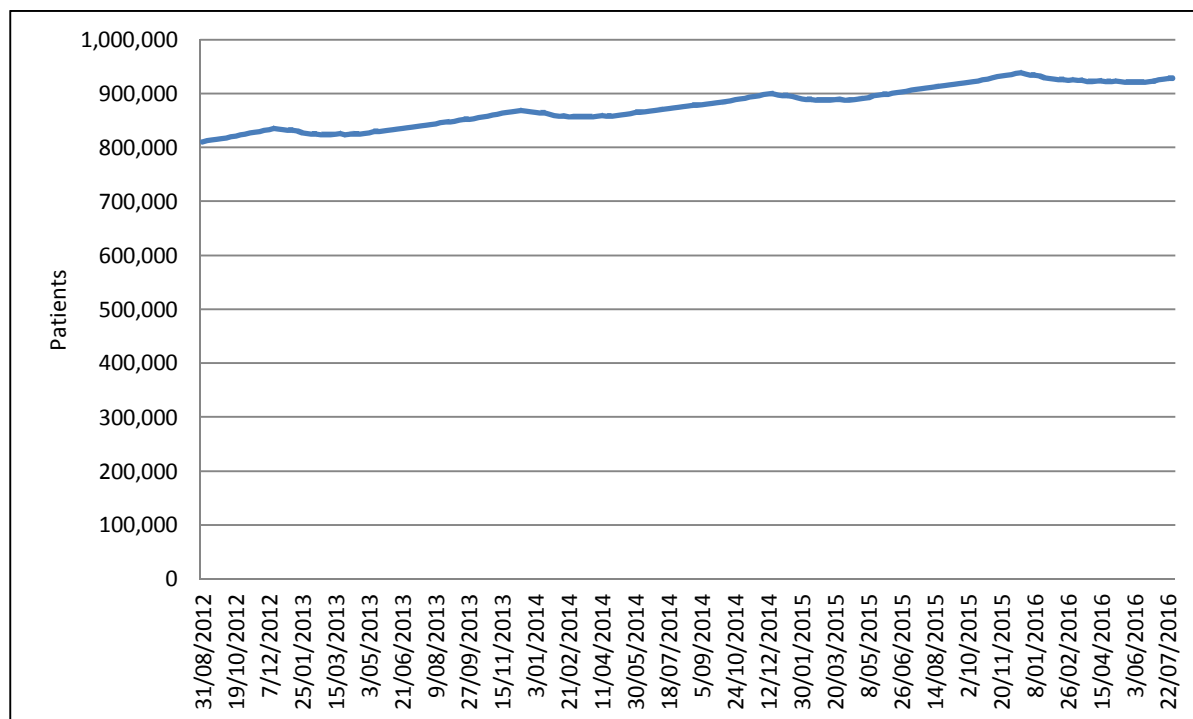


Figure 1: Number of patients estimated to be on a diabetes medicine by week

Note: The x axis shows starting date of week

The data in Figure 1 represent the point prevalence of patients treated with diabetes medicines through the PBS. In mid-2016, 3.85%⁴ of the Australian population (928,561 people) were estimated to be receiving diabetes medicines, compared with 3.57%⁵ (811,009 people) in mid-2012.

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 (see Appendix C).
- the prevalence of diabetes reported in the Australian Health Survey 2014-15 represents all patients who reported having been told by a doctor or nurse that they had diabetes, irrespective of whether the person considered their diabetes to be current or long-term. It was estimated that in 2014-15, 5.1% of the Australian population (1.2 million people) had some type of diabetes, an increase from 4.5% in 2011-12. Data on the proportion of these people using medicines to treat their diabetes was not reported.

⁴ ABS Estimated residential population (ERP) as at 30 June 2016, using ABS Population Clock

⁵ ABS ERP as at 30 June 2012, using ABS.Stat beta

Some patients receiving treatment for diabetes require multiple medicines. Figure 2 shows the number of medicines used for patients represented in Figure 1.

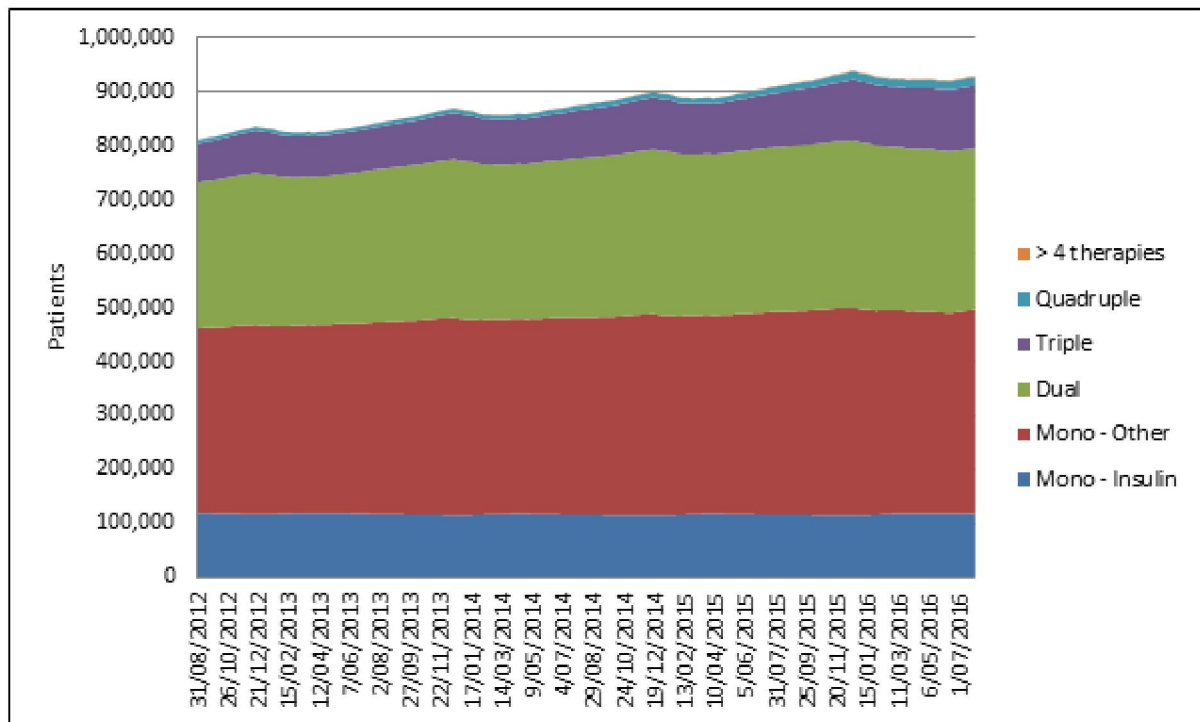


Figure 2: Number of diabetes therapies used together

Figure 2 shows that in mid-2016 about half of all patients received monotherapy. Of these, 24.1% used insulin monotherapy; the majority of these patients are likely to have type 1 diabetes. The remaining patients would mostly comprise those with type 2 diabetes. Of these patients, about half (46.5%) were treated with a single medicine, about a third (36.8%) with dual therapy, and a smaller proportion on three or more medicines (16.7%).

There has been growth in the number of patients treated with single and multiple therapies, but most of the growth across the period has been mainly in triple and quadruple therapy (Table 8).

Table 8: Patients by number of diabetes therapies used together

Calendar week	Mono - Insulin	Mono - Other	Dual	Triple	Quadruple	More than 4 therapies	Total
31/08/2012	119,718	341,829	270,625	72,469	6,028	340	811,009
29/07/2016	119,234	376,411	297,976	116,738	16,705	1,497	928,561
% patients							
31/08/2012	14.76%	42.15%	33.37%	8.94%	0.74%	0.04%	100%
29/07/2016	12.84%	40.54%	32.09%	12.57%	1.80%	0.16%	100%

Figure 3 shows the 10 most common diabetes medicine regimens for patients represented in Figures 1 and 2.

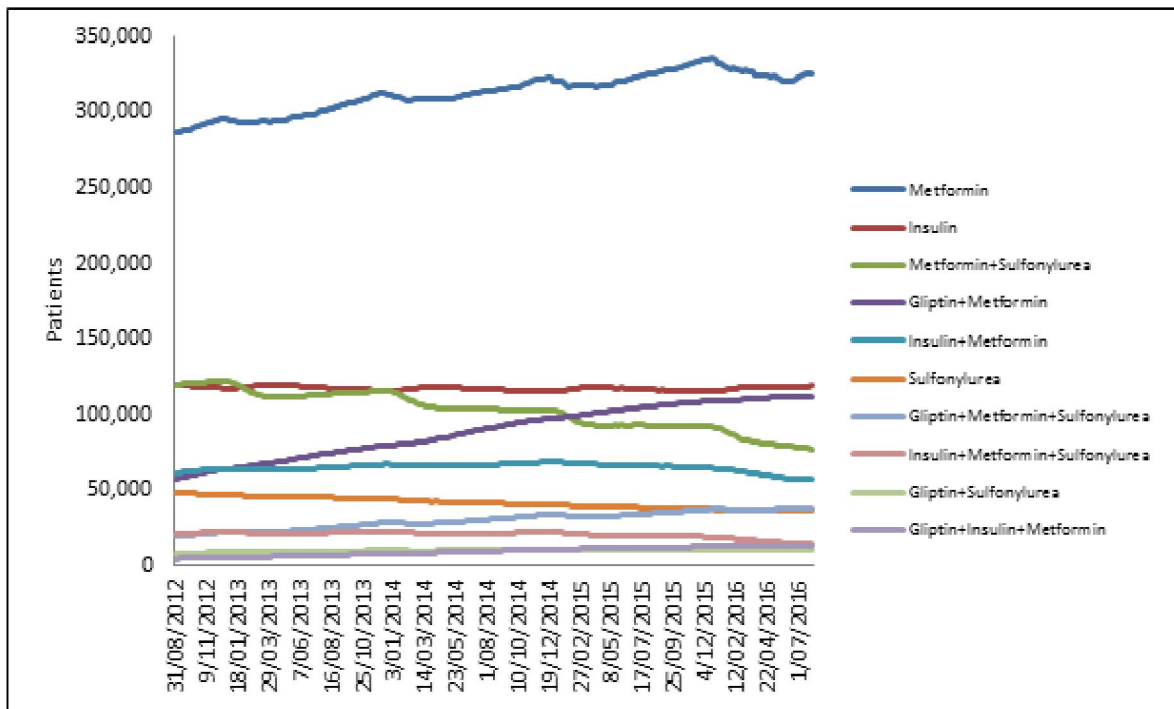


Figure 3: Top 10 drug regimens for patients supplied a diabetes medicine by week

Note: The x axis shows starting date of week. Combination products are shown as plain constituents

The top three regimens over the period were metformin monotherapy, insulin monotherapy and metformin + sulfonylurea, respectively. The number of patients using metformin monotherapy has gradually increased, insulin monotherapy was constant and the number of people using metformin + sulfonylurea declined. By the end of the period the gliptin + metformin (including in FDC form) regimen became the third most common regimen. To enable examination of trends in the remaining regimens, the top 3 were removed and the results are shown in Figure 4.

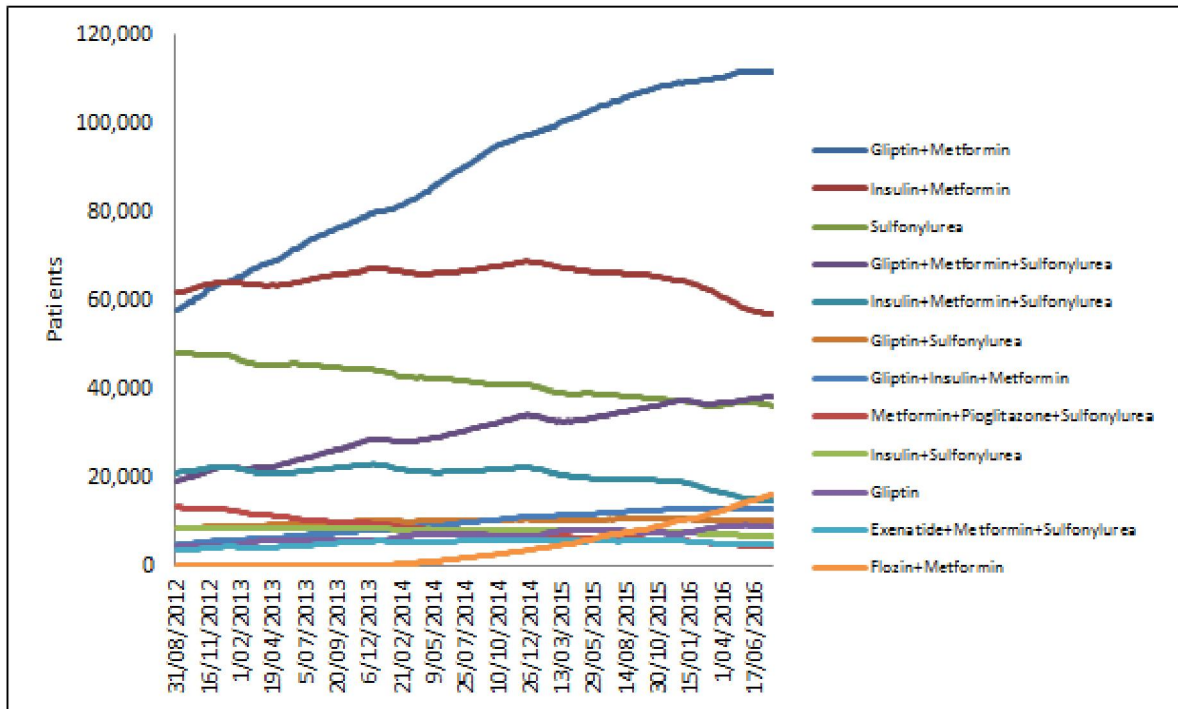


Figure 4: Drug regimens ranked from 4 to 14 (ie. excluding the top 3) by week

Note: x axis shows starting date of week. Combination products are shown as plain constituents

Figure 4 shows that the gliptin + metformin, gliptin + metformin + sulfonylurea, gliptin + insulin + metformin, gliptin monotherapy and flozin + metformin regimens increased over the period. Other regimens were either steady or decreased across the period. Insulin + metformin increased up until the end of 2014 and has been decreasing since.

The majority of additions, extensions and changes to listing for diabetes medicines since the previous DUSC review in 2013 have involved gliptins, flozins and GLP-1 agonists. The following sections focus on changes in the use of these medicine groups, including prescription volume and the medicine regimens.

Flozins

Figure 5 shows the number of patients with a drug regimen containing a flozin, in plain or FDC form, since the listing of dapagliflozin and canagliflozin in December 2013. Overall, about 65,000 persons had a drug regimen than included a flozin by July 2016.

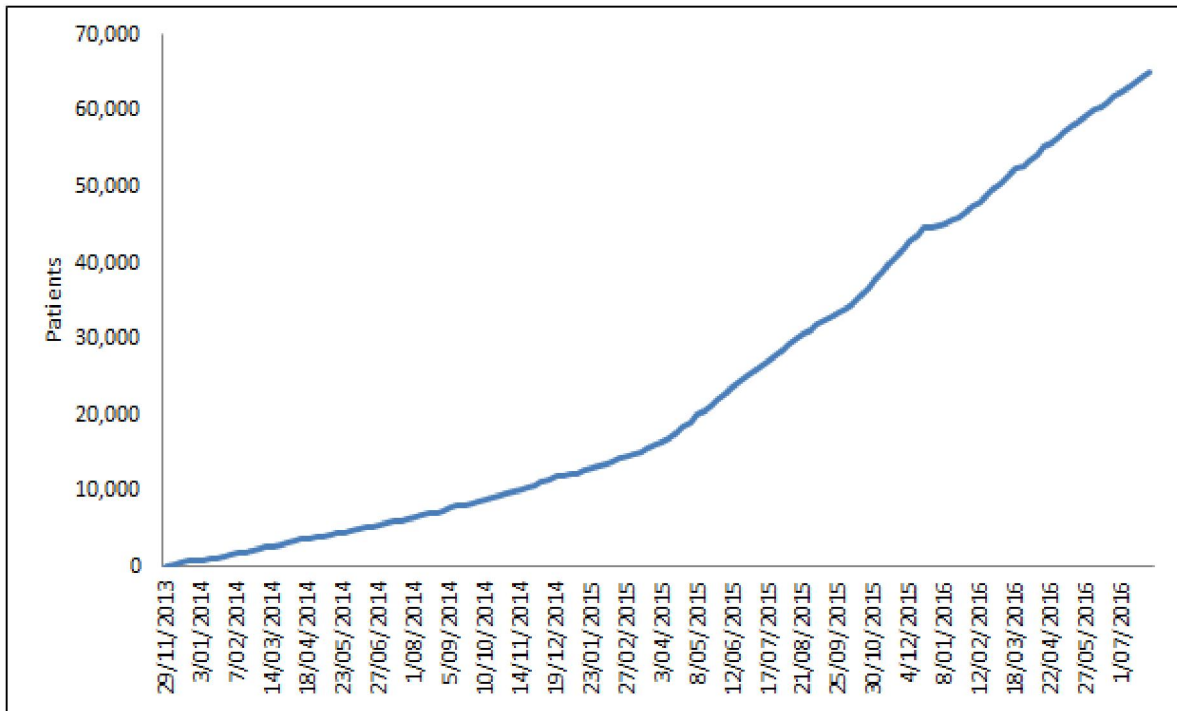


Figure 5: Number of patients with a drug regimen containing a flozin (plain or in a FDC)

Initial uptake of was gradual and there was a noticeable increase in the rate of growth around April 2015. There were several expansions to the listing of flozins around this time (see Table 1).

Figure 6 shows the ten most common diabetes medicines regimens containing a flozin.

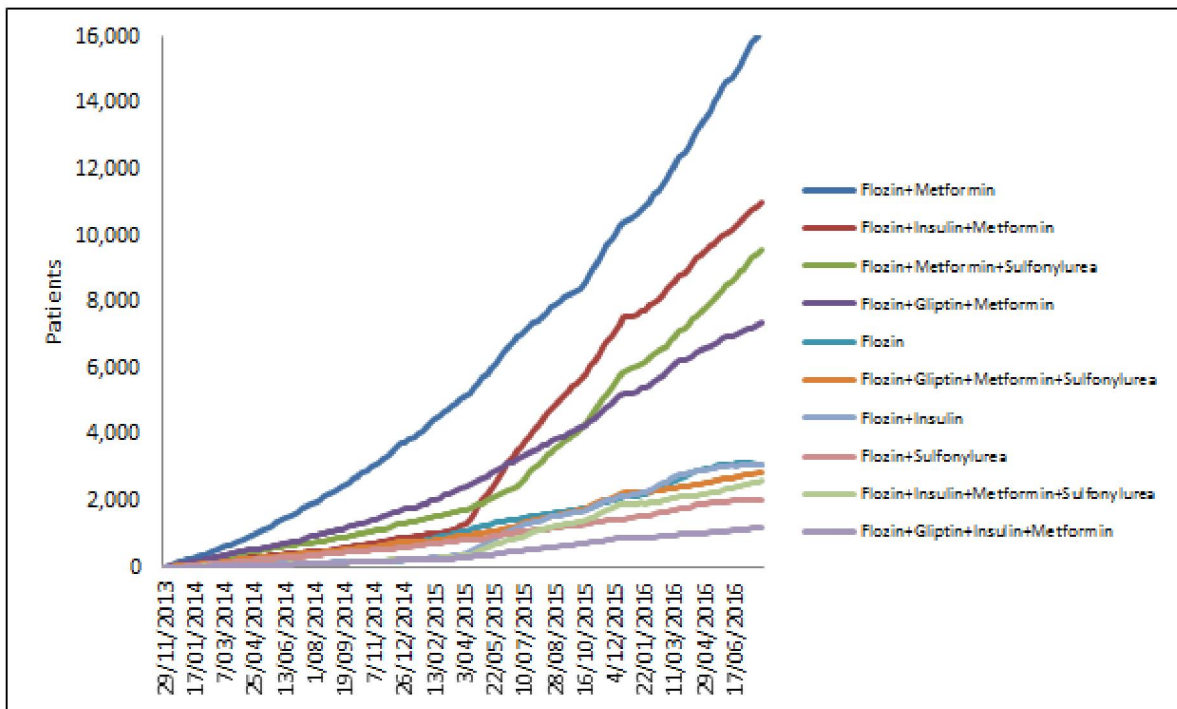


Figure 6: Top 10 drug regimens containing a flozin medicine

Figure 6 shows:

- A sharp increase in the number of patients on regimens containing insulin and a flozin (ie. flozin + insulin + metformin, flozin + insulin and flozin + insulin + metformin + sulfonylurea) began soon after April 2015 when the dapagliflozin restriction was changed to allow therapy with insulin (see Table 1).
- A sharp increase in the number of patients on regimens containing triple oral therapy (ie. flozin + metformin + sulfonylurea) began in about July 2015 when the dapagliflozin restriction was changed to allow triple oral therapy (see Table 1).
- There appears to be a growing number of patients on regimens that include both a flozin and a gliptin (ie. flozin + gliptin + metformin and flozin + gliptin + metformin + sulfonylurea), which is not allowed under current restrictions.
- There does not appear to have been a noticeable change in the rising rate of flozin dual oral therapy regimens with metformin or sulfonylurea at the time the dapagliflozin restriction was changed in December 2014 (see Table 1) to allow dual oral therapy with metformin or sulfonylurea without the requirement that “the condition must not be able to be adequately controlled by treatment with metformin **and** a sulfonylurea”. This same restriction change was made to empagliflozin from April 2015, but again there does not appear to have been a noticeable change in the rising rate of flozin dual oral therapy regimens with metformin or sulfonylurea at that time.
- There is an increasing number of patients supplied flozin monotherapy which is outside the PBS restriction.

Gliptins

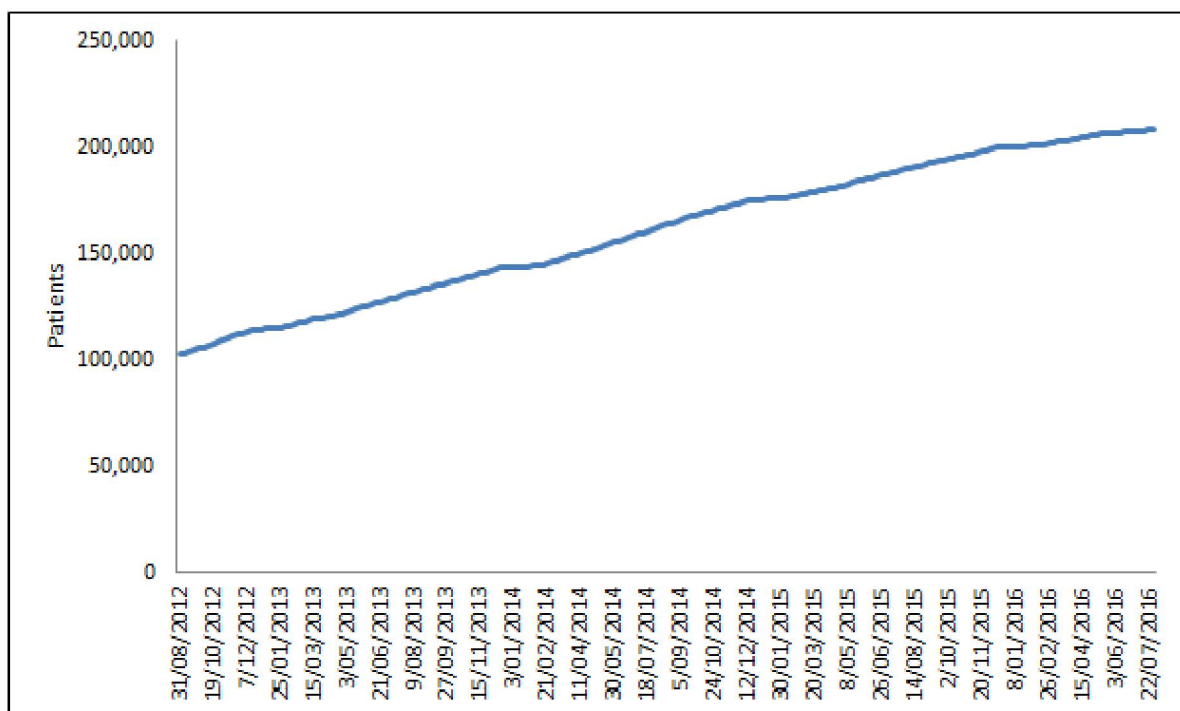


Figure 7: Number of patients with a drug regimen containing a gliptin (plain or in a FDC)

Figure 7 shows that the number of patients with a drug regimen containing a gliptin, in plain or FDC form, has increased steadily over the 4 year period. Overall, about 208,000 persons had a drug regimen containing a gliptin by July 2016.

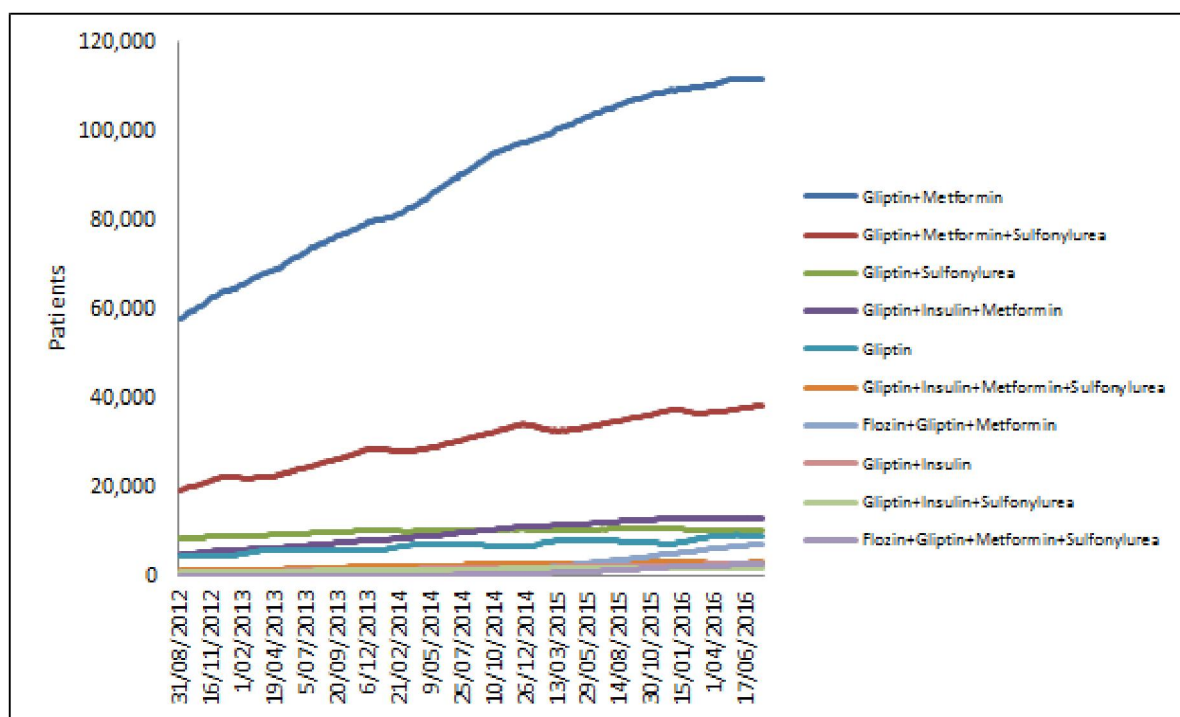


Figure 8: Top 10 drug regimens containing a gliptin (plain or in a FDC)

Figure 8 shows that the gliptin + metformin, gliptin + metformin + sulfonylurea, insulin + gliptin + metformin, gliptin monotherapy and flozin + gliptin + metformin regimens are the ones that have contributed to the increase in gliptin containing regimens. The latter two of these are outside the PBS restriction. In the November 2014 PBAC minutes regarding the Post-Market Review of type 2 diabetes medicines⁶, the PBAC noted that *“there were limited treatment options for patients on dialysis. The PBAC noted that there is anecdotal evidence of off-label use of low dose DPP-4 inhibitors for this indication. It was considered that this may partly explain the DPP-4 inhibitor monotherapy use seen in the DUSC analysis of type 2 diabetes medicines utilisation.”*

There does not appear to be a noticeable change in dual oral therapy with metformin or sulfonylurea regimens (ie. gliptin + metformin or gliptin + sulfonylurea) at the time the alogliptin restriction was changed in December 2013 to allow dual oral therapy with metformin or sulfonylurea without the requirement that “patients in whom combination therapy with metformin and a sulfonylurea is contraindicated or not tolerated.”

Figure 9 below shows the gliptin + metformin regimen by whether or not it included an FDC product.

⁶ <http://www.pbs.gov.au/reviews/diabetes-files/pbac-minutes-for-type-2-diabetes-medicines.pdf>

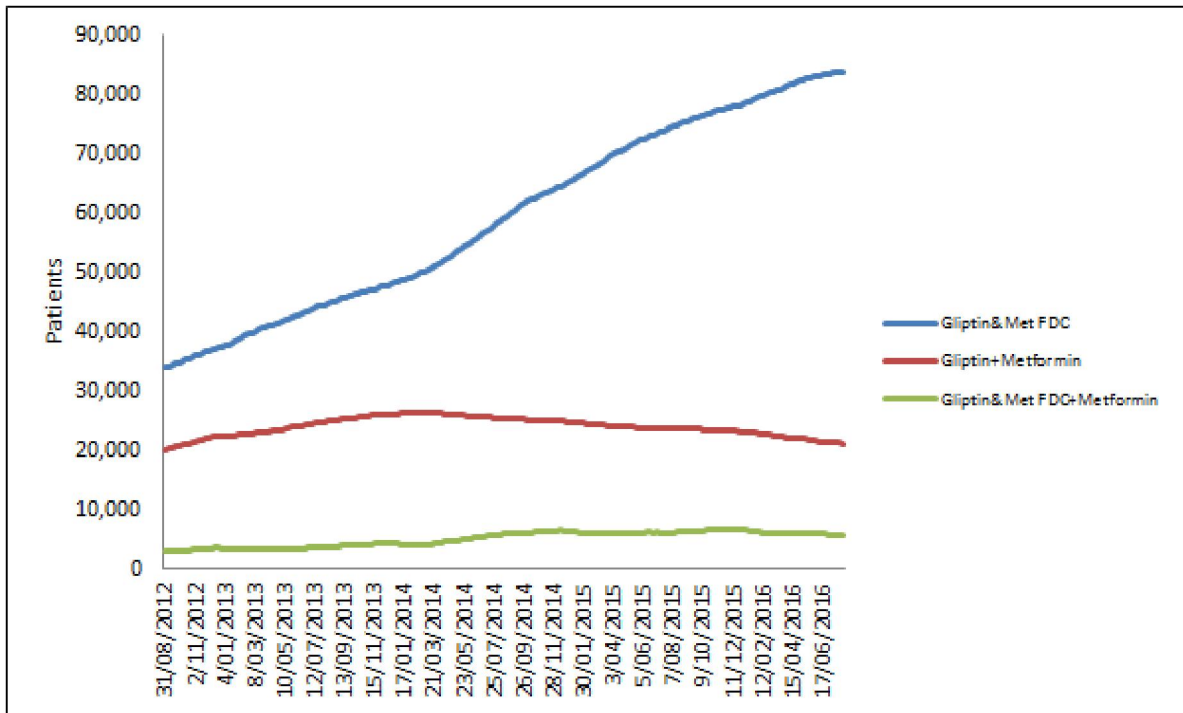


Figure 9: Combination products used in the gliptin dual therapy with metformin regimen

There appears to be a noticeable change in dual oral therapy with metformin regimens (ie. Gliptin&Met FDC and gliptin + metformin) at the time the alogliptin restriction was changed in December 2013 to allow dual oral therapy with metformin or sulfonylurea without the requirement that “patients in whom combination therapy with metformin and a sulfonylurea is contraindicated or not tolerated.” This restriction change was applied to all other gliptins in April 2014. The effect on these regimens is in opposite directions with the Gliptin&Met FDC regimen increasing at a faster rate and gliptin + metformin decreasing.

The Gliptin&Met FDC + metformin regimen may be appropriate for a patient to reach optimal metformin dosage.

Effect of December 2013 gliptin restriction change on utilisation prior to initiating a gliptin

The alogliptin restriction was changed in December 2013 to allow dual oral therapy with metformin or sulfonylurea without the requirement “patients in whom combination therapy with metformin and a sulfonylurea is contraindicated or not tolerated.” This restriction change was applied to all other gliptins in April 2014. To assess the effect of this change, drug regimens in the 12 months prior to initiation of a gliptin were examined for two gliptin initiating cohorts. The “Prior” cohort was patients initiating from September to the end of November 2013, prior to the restriction change. Drug regimens for these patients were assessed back to 12 months prior to their individual gliptin initiation dates. It was not possible to look back any further for this cohort as the drug regimens were reliably estimated only from September 2012, due to the fact that under co-payment prescription data began in April 2012. A similar analysis was undertaken in the February 2013 DUSC diabetes analysis, and in that case it was possible to look back for 2 years prior to initiation, but this was because general patients were excluded from the analysis.

In this analysis, the “Post” cohort was patients initiating from May to the end of July 2016, post the restriction change and as recent as possible. Even though it was possible to have a longer look back period for this cohort, the same look back period used for the “Prior” cohort (ie. 12 months) was used for the “Post” cohort to make the results comparable.

Patients were classified based on their drug regimen history into the following groups;

1. metformin only supplied
2. sulfonylurea only supplied
3. neither metformin nor sulfonylurea supplied
4. metformin and sulfonylurea deemed to be co-administered for a period
5. metformin and sulfonylurea supplied but not deemed to be co-administered at any time.

The analysis also had regard to whether or not the gliptin initiation was with an FDC (ie. gliptin & metformin, there are no FDC products on the PBS containing a gliptin & sulfonylurea) or single component product.

Table 9: Treatment regimens in the 12 months prior to initiation of a gliptin classified by whether initiation was with the single component (SC) or FDC.

Patients	Gliptin initiated from Sept to end of Nov 2013			Gliptin initiated from May to end of July 2016		
	Initiating gliptin product was					
Pre-initiation treatment regimen summary	SC	FDC	Total	SC	FDC	Total
1. metformin only supplied	2,972	3,800	6,772	2,267	5,328	7,595
2. sulfonylurea only supplied	710	134	844	533	137	670
3. neither metformin nor sulfonylurea supplied	585	869	1,454	685	1,313	1,998
<i>Total regimen summaries histories not containing both metformin and a sulfonylurea</i>	4,267	4,803	9,070	3,485	6,778	10,263
4. metformin and sulfonylurea deemed to be co-administered for a period	2,961	2,482	5,443	1,755	2,495	4,250
5. metformin and sulfonylurea supplied but not deemed to be co-administered at any time	164	74	238	116	75	191
<i>Total regimen summaries histories containing both metformin and a sulfonylurea</i>	3,125	2,556	5,681	1,871	2,570	4,441
Total	7,392	7,359	14,751	5,356	9,348	14,704

Table 10: Results from table above presented as percentage of patients initiating

Patients	Gliptin initiated from Sept to end of Nov 2013			Gliptin initiated from May to end of July 2016		
	Initiating gliptin product was					
Pre-initiation treatment regimen summary	SC	FDC	Total	SC	FDC	Total
1. metformin only supplied	40.2%	51.6%	45.9%	42.3%	57.0%	51.7%
2. sulfonylurea only supplied	9.6%	1.8%	5.7%	10.0%	1.5%	4.6%
3. neither metformin nor sulfonylurea supplied	7.9%	11.8%	9.9%	12.8%	14.0%	13.6%
<i>Total regimen summaries histories not containing both metformin and a sulfonylurea</i>	57.7%	65.3%	61.5%	65.1%	72.5%	69.8%
4. metformin and sulfonylurea deemed to be co-administered for a period	40.1%	33.7%	36.9%	32.8%	26.7%	28.9%
5. metformin and sulfonylurea supplied but not deemed to be co-administered at any time	2.2%	1.0%	1.6%	2.2%	0.8%	1.3%
<i>Total regimen summaries histories containing both metformin and a sulfonylurea</i>	42.3%	34.7%	38.5%	34.9%	27.5%	30.2%
Total	100%	100%	100%	100%	100%	100%

Table 10 shows that dual oral therapy with metformin and sulfonylurea pre-initiation to a gliptin decreased between the Prior and Post cohorts (ie. from 36.9% to 28.9%). This percentage is lower for patients who initiated on a gliptin & metformin FDC (ie. from 33.7% to 26.7%). This trend is what would be expected from the change in restriction which meant that trialling of combination therapy with metformin and a sulfonylurea was no longer required.

Insulin

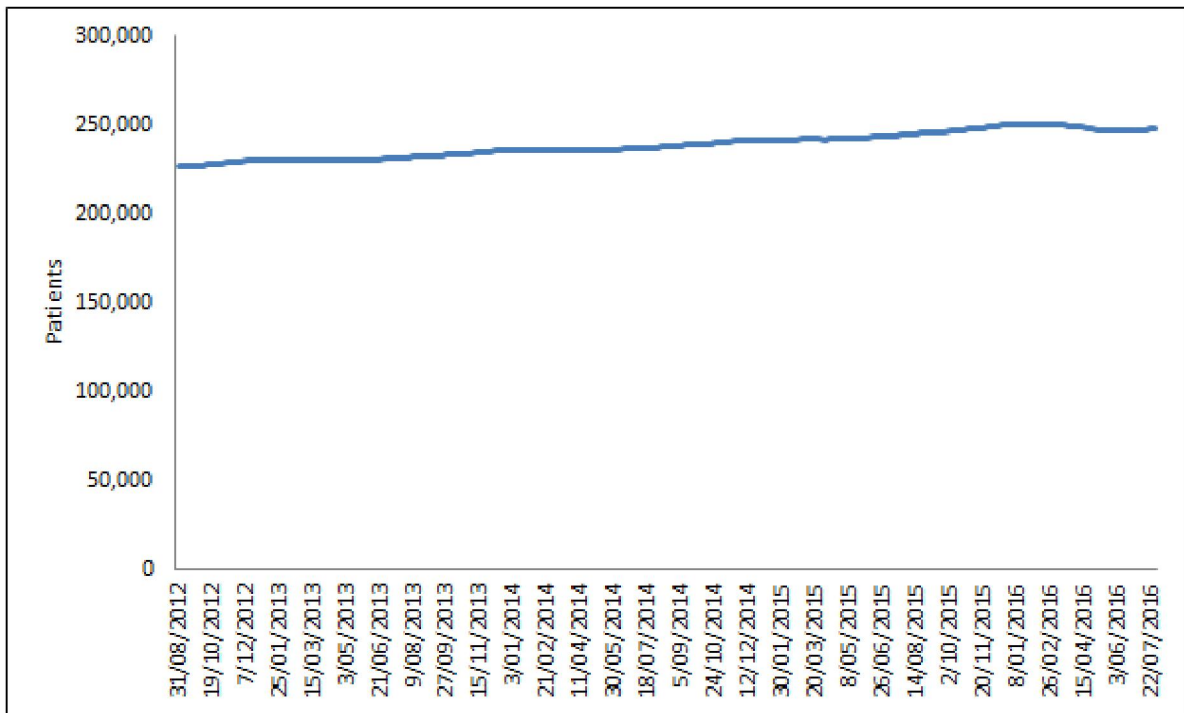


Figure 10: Number of patients with a drug regimen containing insulin

Figure 10 shows that the number of patients on a regimen containing insulin has been increasing steadily, but appears to have plateaued in 2016, with approximately 248,000 persons on a regimen containing insulin at July 2016.

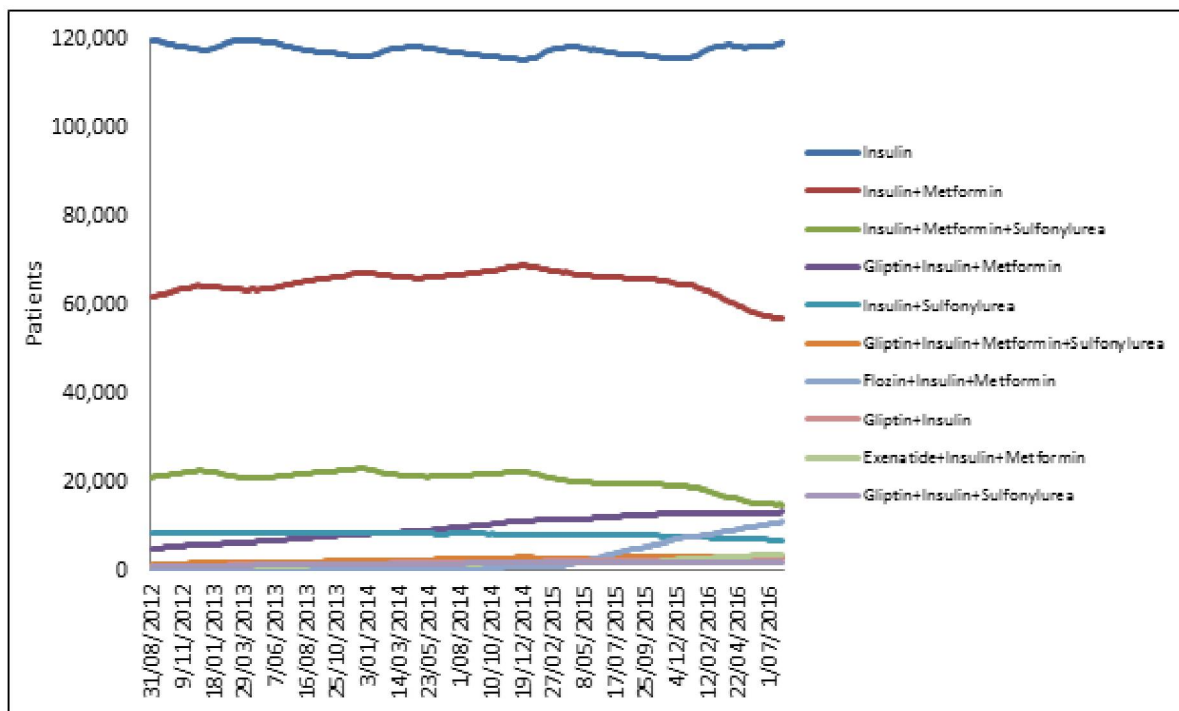


Figure 11: Top 10 drug regimens containing insulin

There has been a recent decrease in the number of patients on the insulin + metformin and insulin + metformin + sulfonylurea regimens. These decreases have been offset by increases in:

- flozin + insulin + metformin since about April 2015 when the restriction for dapagliflozin was changed to allow therapy with insulin.
- insulin + gliptin + metformin across the whole period. This triple therapy was not allowed under the gliptin restrictions for the period shown but has been approved from October 2016 for sitagliptin and linagliptin.
- exenatide + insulin + metformin since about October 2015 when the restriction for exenatide was changed to allow triple therapy with insulin.

Glucagon-like peptide-1 receptor agonists (GLP-1RA)

The only GLP-1RA listed on the PBS is exenatide, with about 24,000 patients with a drug regimen including exenatide by July 2016.

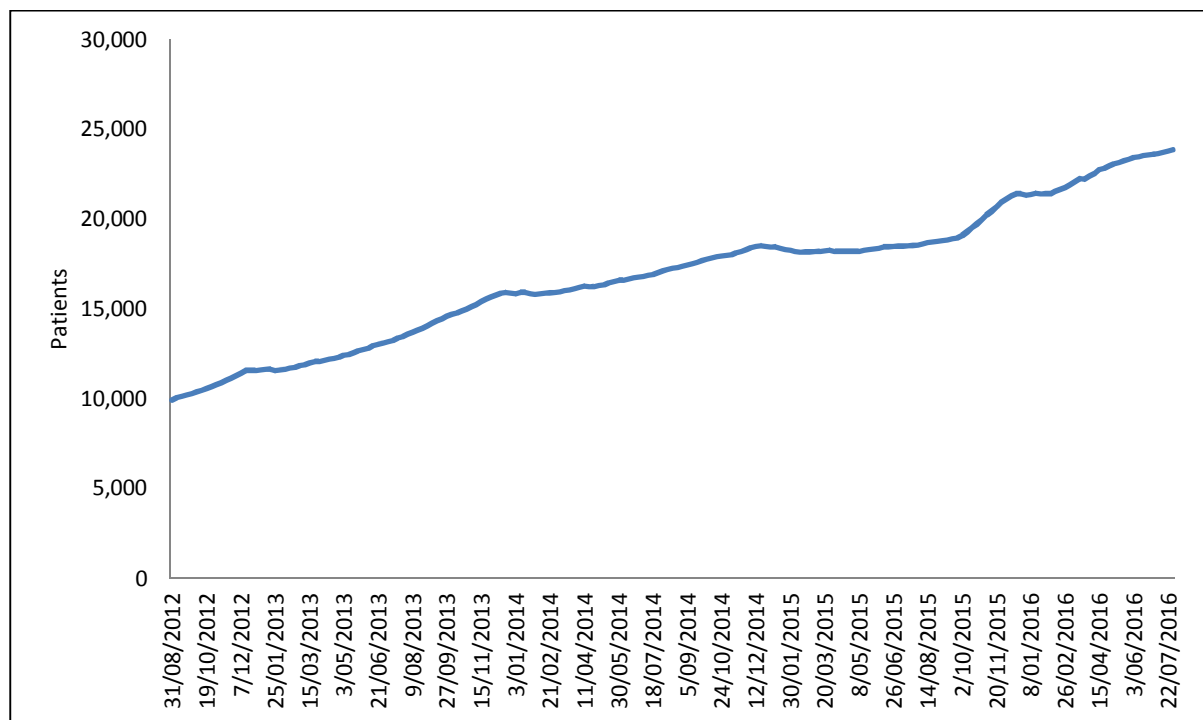


Figure 12: Number of patients with a drug regimen containing exenatide

Figure 12 shows that the number of patients on a regimen containing exenatide steadily increased across the period.

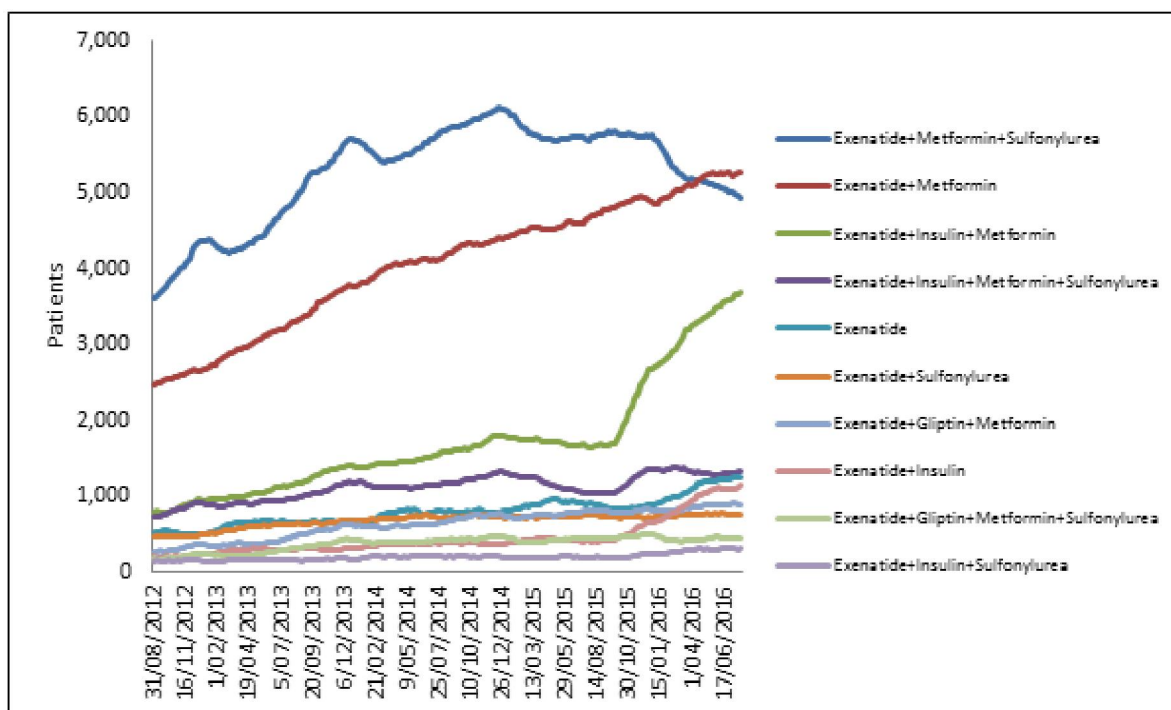


Figure 13: Top 10 drug regimens containing exenatide

Figure 13 shows that there was a marked increase in the exenatide + insulin + metformin regimen from October 2015 when the PBS listing for exenatide was expanded to include triple therapy with insulin and metformin. There was an increasing number of patients supplied exenatide monotherapy which is outside the PBS restriction. There was also an increase in exenatide dual therapy with insulin (exenatide + insulin). This regimen is only allowed under the restriction if the patient is contradicted or intolerant to metformin.

Thiazolidinediones (TZD ie. pioglitazone and rosiglitazone)

A separate analysis of regimens containing pioglitazone or rosiglitazone is not presented because the number of prescriptions for these is low and declining (see Figure 14).

Use of FDCs with plain metformin

There were some regimens that included a fixed dose combination product (all of which contain metformin) and a plain metformin product. In the week beginning 29/7/2016 it was estimated that 161,387 patients had a regimen including a combination product. Of these, 15,035 patients (9.3%) had regimens that also included a plain metformin product. Some patients may require the addition of plain metformin to an FDC to optimise management or there may be some inadvertent use of the FDC and plain form together.

Other regimens of interest

In the November 2014 PBAC minutes regarding the Post-Market Review of Type 2 diabetes medicines⁷, the PBAC recommended that the following combinations (see Table 11) should

⁷ <http://www.pbs.gov.au/reviews/diabetes-files/pbac-minutes-for-type-2-diabetes-medicines.pdf>

not be PBS-subsidised on the basis that no trial data demonstrating efficacy was available at that time.

Table 11: Patients estimated to be in regimen groups not recommended for PBS subsidy

Regimen group	Outside PBS restriction? (as at 1 November 2016)	Patients as at 29/7/2016
metformin + gliptin + TZD	Yes	1,211
metformin + gliptin + flozin	Yes	12,218
metformin + gliptin + exenatide	Yes	2,109
metformin + gliptin + insulin	No*	18,530
sulfonylurea + gliptin + flozin	Yes	3,978
sulfonylurea + gliptin + exenatide	Yes	780
sulfonylurea + gliptin + insulin	No*	5,563
metformin + flozin + exenatide	Yes	2,320
sulfonylurea + flozin + exenatide	Yes	968
Any triple therapy combination of the following medicines: gliptin, TZD, flozin, insulin, and exenatide.	Yes	3,805
Any combination of insulin with three oral therapies.	No^	8,826

* the restrictions for sitagliptin and linagliptin were expanded to include use with insulin on 1 October 2016

^ see "Other combinations" category in Appendix A

Note: Some regimens are classified into more than one regimen group. For example, the regimen metformin + gliptin + insulin + sulfonylurea is counted in both metformin + gliptin + insulin and sulfonylurea + gliptin + insulin regimen groups.

At least 51,000 patients had regimens outside the PBS restrictions in July 2016. However only about half would have been outside the PBS restrictions after the 1 October 2016 expansion of listings for gliptins with insulin.

The regimen group with the highest number of patients was metformin + gliptin + insulin, which was PBS subsidised from 1 November 2016. The next most common group was metformin + gliptin + flozin.

Prescriptions

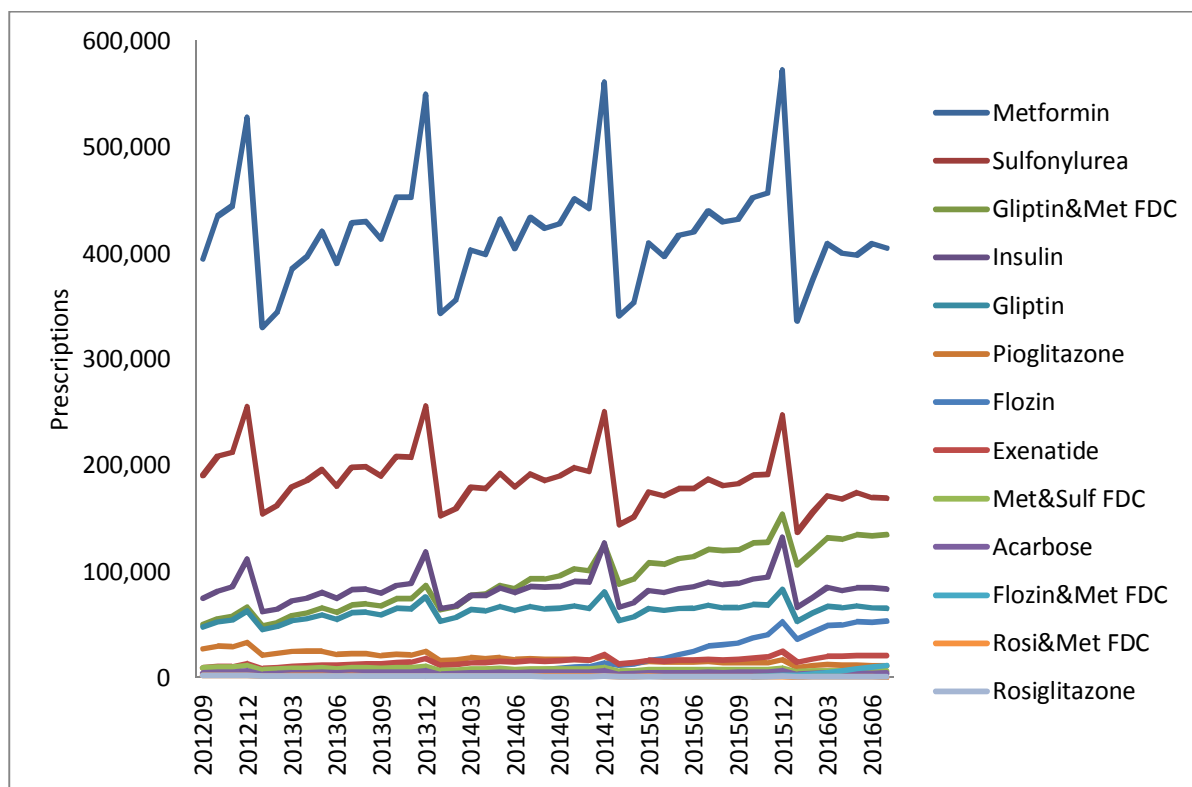


Figure 14: Diabetes medicines (ATC = A10) by month of supply

Figure 14 shows the prescriptions for diabetes medicines by month of supply over the same period as for the patient level analyses. It shows that stockpiling related to the PBS Safety Net is occurring. Whilst this phenomenon is taken into account in the method used to estimate drug regimens (see Appendix B for details), residual effects can still be seen in some drug regimen time series (e.g. Metformin and Metformin+Sulfonylurea in Figure 2).

Expenditure

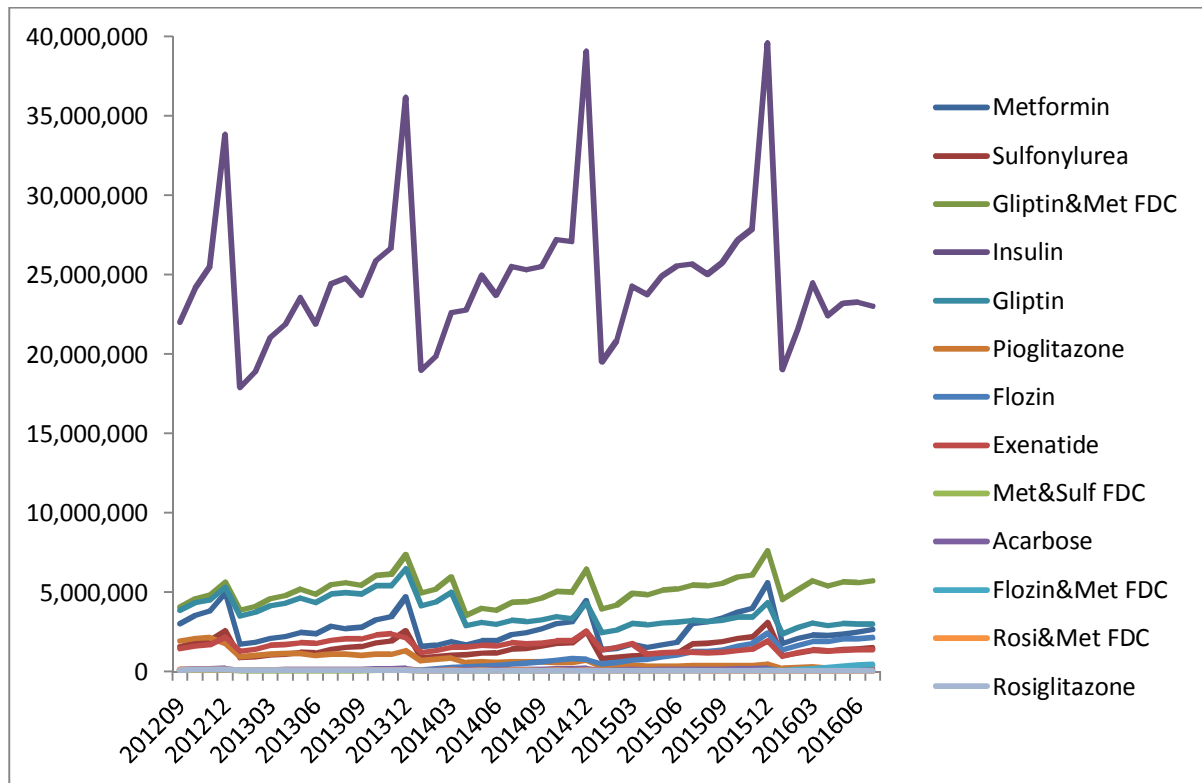


Figure 15: R/PBS expenditure on diabetes medicines by month of supply

Note: Special pricing arrangements apply for exenatide, insulin glargine and insulin detemir.

Comparing Figure 14 and Figure 15 shows that expenditure on insulin is proportionally much greater than prescriptions for insulin.

It also shows that expenditure on gliptins and gliptin & metformin FDCs declined after the restriction change and price reduction in April 2014. There was also a price reduction for flozins in December 2014.

Table 12: R/PBS expenditure on diabetes medicines by financial year of supply

Drug / Drug Group	2012-13	2013-14	2014-15	2015-16
Insulin	\$276,238,655	\$294,716,181	\$308,772,492	\$305,286,354
Gliptin&Met FDC	\$54,897,160	\$63,792,500	\$58,290,440	\$68,423,837
Gliptin	\$50,700,905	\$54,667,145	\$38,182,636	\$38,169,854
Metformin	\$33,959,345	\$30,702,246	\$27,923,906	\$36,341,446
Exenatide	\$19,519,943	\$22,007,309	\$20,061,374	\$15,905,349
Sulfonylurea	\$17,480,860	\$17,299,231	\$16,753,924	\$20,615,823
Pioglitazone	\$18,533,474	\$10,873,297	\$5,936,428	\$3,831,276
Flozin		\$1,635,888	\$8,637,712	\$20,764,866
Acarbose	\$1,693,056	\$1,693,714	\$1,672,700	\$1,525,426
Rosi&Met FDC	\$1,476,896	\$1,081,150	\$787,641	\$291,222
Rosiglitazone	\$1,256,996	\$913,884	\$673,482	\$597,994
Met&Sulf FDC	\$934,347	\$824,434	\$740,373	\$875,483
Flozin&Met FDC				\$1,525,099
Total	\$476,691,637	\$500,206,978	\$488,433,108	\$514,154,027

Note: Special pricing arrangements apply for exenatide, insulin glargine and insulin detemir.

Table 12 shows that total expenditure dipped in 2014-15 after the gliptin and flozin price cuts, however it has resumed growth in 2015-16.

Table 13 does not contain a PVA analysis for R/PBS expenditure because even though the submissions and Final Agreed estimates used to create Tables 3 to 7 contain estimates of the size of the flozin market in prescriptions, they do not contain expenditure estimates of this whole market.

Discussion

- Expansion of the PBS listing of dapagliflozin in April 2015 to include therapy with insulin resulted in sharp increases in the number of people supplied the regimens flozin + insulin + metformin, flozin + insulin and flozin + insulin + metformin + sulfonylurea. The triple therapy market had the largest increase followed by the dual and then the quadruple therapy (see Figure 6).
- The expansion of PBS listing of dapagliflozin in July 2015 to include triple oral therapy with metformin and sulfonylurea resulted in a sharp increase in the number of patients on flozin + metformin + sulfonylurea (see Figure 6).
- There appears to be a growing number of patients on regimens that include both a flozin and a gliptin (ie. flozin + gliptin + metformin and flozin + gliptin + metformin + sulfonylurea, see Figure 6). These regimens are not allowed under current PBS restrictions.
- There was no noticeable change in the number of people on flozin dual oral therapy regimens (ie. flozin + metformin and flozin + sulfonylurea) at the time the dapagliflozin restriction was changed (December 2014) to allow dual oral therapy with metformin or sulfonylurea without the requirement that “the condition must not be able to be adequately controlled by treatment with metformin and a sulfonylurea” (see Figure 6).
- There was a noticeable change in the number of people deemed to be on gliptin dual oral therapy with metformin regimens (ie. Gliptin&Met FDC and gliptin + metformin) at the time the alogliptin restriction was changed (December 2013) to allow dual oral therapy with metformin or sulfonylurea without the requirement that “patients in whom combination therapy with metformin and a sulfonylurea is contraindicated or not tolerated” (see Figure 9). This restriction change was applied to all other gliptins in April 2014. The effect of the restriction change on these regimens was in opposite directions, with the Gliptin&Met FDC regimen increasing at a faster rate and gliptin + metformin decreasing. However, these two effects cancel each other out, so there was no impact on the gliptin with metformin dual therapy market overall (see Figure 8). The restriction change does not appear to have affected the growth rate of gliptin dual therapy with sulfonylurea (see Figure 8).
- There was growing use of a flozin, gliptin or exenatide as monotherapy (see Figures 6, 8 and 13), which is outside the current PBS restriction.

DUSC consideration

DUSC considered that:

- The increase in the number of people receiving medicines for the treatment of diabetes is consistent with the increase in prevalence of the condition.⁸
- Metformin alone remains the most common regimen. This is consistent with guidelines.
- Sulfonylureas alone and in combination with metformin have decreased. This may be related to concerns about hypoglycaemia and weight gain.
- There was large increase in the number of patients receiving flozins or gliptins in combination with metformin. The majority of the gliptin and metformin regimens use an FDC product. There has been a reduction in use of sulfonylureas with metformin prior to patients initiating gliptin. This is consistent with the PBS restriction change in December 2013.
- The segments of the market that grew the fastest (in terms of market share between August 2012 and July 2016) were patients receiving triple and quadruple therapy. The percentage of patients on more than 4 therapies also grew rapidly, but from a very low base. DUSC considered that the growth of multi drug regimens raises questions about quality use of medicines (QUM). These being the increasing difficulty for the patient to be compliant to the regimen the more complex it becomes, and the increased likelihood of drug interactions with drugs being used to treat comorbid conditions.
- GPs tend to only escalate treatment to triple therapy and after this refer to a specialist if the patient's condition is still not adequately controlled.
- The Predicted vs Actual analysis indicated that the overall flozin market size was consistent with predictions.
- The use of regimens outside of PBS restrictions is a concern. This includes monotherapy with a flozin ($\approx 3,000$ patients, Figure 6), gliptin ($\approx 8,000$ patients, Figure 8) and exenatide ($\approx 1,200$ patients, Figure 13). The use of flozin, gliptin and/or GLP-1 analogues in combination each other ($\approx 27,389$ instances of regimens containing 2 or more of these drug groups. This is calculated by adding patients in regimen groups in Table 11, but excluding the groups "metformin + gliptin + insulin", "sulfonylurea + gliptin + insulin" and "Any combination of insulin with three oral therapies").
- It was possible that some of the apparent monotherapy with a flozin, gliptin or exenatide is actually dual therapy with metformin, where the metformin has been supplied on a private script and so not part of the PBS prescription data.
- There has been a global shortage of some metformin extended release tablet products. This was first reported by the TGA on 17 June 2016. This shortage is unlikely to have significantly affected this analysis as drug regimen results are only reported up until the end of July 2016 (based on date of supply). This shortage may need to be taken into account in future analyses of diabetes medicines.
- Some patients were on metformin in an FDC product as well as in a plain product (e.g. see Figure 10, approximately 10% of patients on gliptin and metformin dual therapy were in this category). It is not possible to tell the proportion of these that were

⁸ <http://www.aihw.gov.au/how-common-is-diabetes/>

intentional (to achieve the required metformin dose) or unintentional (i.e. an error of not ceasing the plain form when the FDC was added).

DUSC noted that NPS MedicineWise diabetes program was launched July 2016. This was a multifaceted program with face-to-face visiting, print publications, online case studies and clinical audits. It focussed on the place of non-insulin blood glucose-lowering medicines, and in particular on second and third line therapy options. To date 9,788 GPs, 1,211 nurses and 1,922 pharmacists have participated in an activity.

DUSC noted that:

- Six sponsors provided feedback on the DUSC analysis, many highlighting that the majority of use is consistent with PBS restrictions. Reasons proposed by Sponsors for use outside of restrictions were;
 - Complexity of the PBS restrictions. One Sponsor suggested that the DUSC and PBAC may wish to consider simplification of the PBS restrictions for diabetes medicines, which could lead to a greater understanding by prescribers of PBS-listed treatment regimens. DUSC agreed that the restrictions were complex and recalled that this issue was raised during the Post-Market Review of Products Used in the Management of Diabetes. A suggestion at that time was the development of a flow chart of the PBS restrictions for type 2 diabetes medicines, similar to the General Statement for lipid lowering drugs, to reduce confusion. However, the establishment of a general statement is challenging because not all medicines in the same class have the same PBS listed indications. For example, not all gliptins are listed for triple therapy with metformin and a sulfonylurea, or for use with insulin.
 - That the Standard Coverage Days (SCDs) method used to distinguish between an add and a switch may overestimate use outside of restrictions. DUSC commented that the method used in the analysis to distinguish adds and switches requires that an apparent medication overlap period be chosen such that that the opposite errors of imputing an overlap in treatment when there was none (ie. the patient actually switched) and not imputing is a period of overlapping treatment when there was one (ie. the patient actually added a medication for a period of time) are approximately equal. Logic and experience has shown that an overlap period of less than one SCD of the prior drug (to define a switch) minimises and balances these errors and gives the least biased estimate.
 - Concern that some double counting may also lead to an overestimate. The report acknowledges in the footnote to Table 11 that “Some regimens are classified into more than one regimen group”. Thus if regimen groups are combined then the resulting measure is more accurately described as “instances of regimens being outside the PBS restrictions” rather than patients.
 - Use of regimens that do not meet the PBS criteria demonstrate an unmet clinical need.
 - Patients unable to use metformin or sulfonylurea may be using gliptins, flozins or exenatide as monotherapy. For example, dialysis patients with diabetes taking gliptin monotherapy. DUSC noted that while this use may be clinically reasonable in these specific circumstances, this indication has not been considered by the PBAC for listing on the PBS.

- FDCs for empagliflozin with linagliptin and dapagliflozin with saxagliptin recently received TGA approval, and there is a submission to the March 2017 PBAC meeting for the listing of empagliflozin with linagliptin. DUSC considered that there may be sound clinical reasons for the use of a gliptin and flozin in combination but this combination is not currently subsidised through the PBS.
- A Sponsor requested further data analysis to explore the details of the outside restriction regimens (ie. patient demographics and comorbidities, prescriber type, level of kidney disease by linking to MBS items, temporal sequence for drugs in the regimens) before referral of report to the PBAC. DUSC did not consider any additional analyses to be necessary at the current time.
- A Sponsor indicated they are willing to collaborate to provide education of prescribers

Conclusion

Multiple changes have occurred since last DUSC review and the use of diabetes medicines continues to grow. DUSC considered the high use of metformin monotherapy to be reassuring and reflects its place in guidelines as first line therapy. The use of flozins and gliptins are increasing. Overall use of diabetes medicines appears generally within PBS restrictions. There is some concern about use outside of restrictions, such as possible use of flozins, gliptins or exenatide as monotherapy and regimens containing combinations of flozins, gliptins and/or exenatide. An application to list the combination of empagliflozin and linagliptin on the PBS will be considered by the PBAC at the March 2017 meeting. If successful this may partly address the latter concern.

DUSC actions

A copy of this report was provided to the sponsors of diabetes medicines.

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

AstraZeneca: The DUSC report highlights that the majority of diabetes medicines are prescribed in accordance with their PBS listings. A small number of patient are receiving apparent off-restriction usage (e.g. flozins and gliptins together). This indicates a strong clinical need.

Other sponsors: no comments received.

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 (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.

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Appendix A:

PBS-subsidised combinations of diabetes medicines (at 1 Oct 2016).

Use	Oral only	Injections ± oral
Monotherapy	Metformin SU Acarbose	Insulin
Dual combination therapy	Metformin + SU Metformin + acarbose SU + acarbose DPP-4 + metformin TZD + metformin SGLT2 + metformin DPP-4 + SU TZD + SU SGLT2 + SU	Metformin + insulin SU + insulin Acarbose + insulin Pioglitazone + insulin Exenatide + metformin Exenatide + SU DPP-4 (sitagliptin and linagliptin only) + insulin (sita Oct16, lina Oct16)* SGLT2 + insulin (dapa Apr15, empag Mar16)
Triple combination therapy	Metformin + acarbose + SU Pioglitazone + metformin + SU DPP-4 (excluding alogliptin) + metformin + SU (sita Dec15, vilda Sep16, saxa Dec15, lina Sep16) SGLT2 + metformin + SU (dapa Jul15, empag Mar16)	Metformin + SU + insulin Metformin + acarbose + insulin SU + acarbose + insulin Exenatide + metformin + SU Pioglitazone + metformin + insulin Pioglitazone + SU + insulin Pioglitazone + acarbose + insulin Exenatide + insulin + metformin (Oct 15) DPP-4 (sitagliptin and linagliptin only) + insulin + metformin (sita Oct16, lina Oct16) DPP-4 (sitagliptin and linagliptin only) + insulin + SU (sita Oct16, lina Oct16) DPP-4 (sitagliptin and linagliptin only) + insulin + acarbose (sita Oct16, lina Oct16) SGLT2 + insulin + metformin (dapa Apr15, empag Mar16) SGLT2 + insulin + SU (dapa Apr15, empag Mar16) SGLT2 + insulin + arcarbose (dapa Apr15, empag Mar16)

Use	Oral only	Injections ± oral
Other combinations	<p data-bbox="424 719 823 842">DPP-4 (excluding alogliptin) + metformin + SU + acarbose (sita Dec15, vilda Sep16, saxa Dec15, lina Sep16)</p> <p data-bbox="424 875 815 936">SGLT2 + metformin + SU + acarbose (dapa Jul15, empag Mar16)</p>	<p data-bbox="839 259 1238 286">Metformin + acarbose + SU + insulin</p> <p data-bbox="839 320 1273 347">Pioglitazone + metformin + SU + insulin</p> <p data-bbox="839 380 1342 407">Pioglitazone + metformin + acarbose + insulin</p> <p data-bbox="839 441 1254 468">Pioglitazone + SU + acarbose + insulin</p> <p data-bbox="839 501 1398 528">Pioglitazone + metformin + SU + acarbose + insulin</p> <p data-bbox="839 562 1342 589">Exenatide + insulin + metformin + SU (Oct 15)</p> <p data-bbox="839 622 1410 649">Exenatide + insulin + metformin + acarbose (Oct 15)</p> <p data-bbox="839 683 1466 710">Exenatide + insulin + metformin + SU + acarbose (Oct 15)</p> <p data-bbox="839 743 1490 804">DPP-4 (sitagliptin and linagliptin only) + insulin + metformin + SU (sita Oct16, lina Oct16)</p> <p data-bbox="839 837 1490 893">DPP-4 (sitagliptin and linagliptin only) + insulin + metformin + acarbose (sita Oct16, lina Oct16)</p> <p data-bbox="839 927 1490 983">DPP-4 (sitagliptin and linagliptin only) + insulin + acarbose + SU (sita Oct16, lina Oct16)</p> <p data-bbox="839 1016 1490 1077">DPP-4 (sitagliptin and linagliptin only) + insulin + metformin + SU + acarbose (sita Oct16, lina Oct16)</p> <p data-bbox="839 1111 1434 1171">SGLT2 + insulin + metformin + SU (dapa Apr15, empag Mar16)</p> <p data-bbox="839 1205 1430 1265">SGLT2 + insulin + metformin + acarbose (dapa Apr15, empag Mar16)</p> <p data-bbox="839 1299 1501 1326">SGLT2 + insulin + SU + acarbose (dapa Apr15, empag Mar16)</p> <p data-bbox="839 1359 1474 1420">SGLT2 + insulin + metformin + SU + acarbose(dapa Apr15, empag Mar16)</p>

Abbreviations: DPP-4 = DPP-4 inhibitor; SGLT2 = SGLT2 inhibitor; and SU = sulfonylurea.

Notes:

* the information in brackets refers to individual drugs and PBS listing dates within the drug group. **Bolded** medications represent the newer agents with restrictions. TZDs include pioglitazone and rosiglitazone. DPP-4 inhibitors include linagliptin, saxagliptin, sitagliptin, vildagliptin and alogliptin. SGLT2 inhibitors include dapagliflozin and empagliflozin.

It is assumed that unrestricted PBS medications can be used in possible combinations which reflect clinical practice/individual physician therapeutic decisions; the PBS neither explicitly restricts nor mandates such combination use. Some of these possible combinations may not reflect best practice or likely combinations seen in practice.

Appendix B

Detailed methodology to estimate drug regimens and regimen transitions

Drug treatment regimens are estimated from prescription supply dates

The prescription data contains date of supply of each prescription, but no information on whether or not medicines should be (or were) co-administered. Thus co-administration was estimated from the data in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode of treatment for each drug or drug group.

Step 2:

Determine the estimated medication coverage days across all drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Similar methods have been used for assessing medicine use in Australian populations.^{9,10} Hallas¹¹ describes the method and provides references to early variants.

Figure A.1 illustrates the method specified above. It addresses the scenario where the research question is concerned with the drug regimens before and after initiation to a third line agent (Drug C in this example). However the method of determining a patient's drug regimen at any point in time is the same for other scenarios (eg. when the regimens are estimated in each calendar weeks rather than in weeks relative to an initiation event). The standard coverage days (SCD) for each drug A, B & C have been shortened to 5 days to enable the figure to fit on one page. The Step 1 process results in the production of the episodes (pink bars) and the Step 2 process results in the production of the treatment regimen (blue bar). The days in this illustration are days from initiation (applicable to an incident patient analysis) but they can also be calendar days (applicable to a prevalent patient analysis).

In this illustration, a break in treatment is defined as a coverage gap of 2 or more SCDs (i.e. the patient has not received re-supply at two consecutive expected refill dates. The first

⁹ Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P 2011 "Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: a self-controlled case-series analysis in an Australian health care claims database" *Drug Saf.* 34(7):567-75. doi: 10.2165/11588470-000000000-00000.

¹⁰ Vitry AI, Roughead EE, Preiss AK, Ryan P, Ramsay EN, Gilbert AL, Caughey GE, Shakib S, Esterman A, Zhang Y, McDermott RA 2010 "Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study" *PLoS One.* 5(11):e14024. doi: 10.1371/journal.pone.0014024.

¹¹ Hallas J. 2005 "Drug utilization statistics for individual-level pharmacy dispensing data" *Pharmacoepidemiol Drug Saf.* 14:455-463. doi: 10.1002/pds.1063.

gap in drug A coverage (from days -39 to -35) is not deemed to be a break in the drug A Episode 1 as the estimated gap in coverage is only 1 x SCD. The second gap in drug A coverage from days -29 to -20 is deemed to be a break in treatment and the end of Episode 1 because the gap in estimated coverage is 2 x SCD.

The two prescriptions for drug B supplied on day -9 are interpreted as dose escalation of drug B, if each prescription is for a different strength. The two prescriptions are deemed to be necessary to supply one SCD period and not used to extend the drug coverage period. If each prescription of drug B were for the same strength then this would be interpreted as “stockpiling” and assumed to extend the drug coverage period (see Details of Methodology below for details)

Drug C is a third line agent and initiated on day 0 (by definition). The basic method imputes a short period of B+C, but a refinement of the method includes the calculation of an adjusted treatment regimen which removes short periods of overlap when it is likely that a switch has occurred before prior medicine is deemed to be fully used.

The final method for estimating the drug treatment regimen includes several refinements which are explained in below. Briefly they are:

1. Calculation of the treatment regimen on a weekly rather than daily basis.
2. Calculation of drug treatment regimen transitions – including an adjustment to allow for switching when the prior medication is not fully used.
3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days.
4. Change in the rules for prescriptions whose coverage spans the initiation data;
- removal of the stockpiling rule
5. Estimating if a patient is continuing or stopping treatment after their last script

Details of Methodology

1. Calculation of the treatment regimen

Drug treatment regimens are estimated from prescription supply dates in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Step 2 above was modified so that the treatment regimen was estimated on a weekly rather than daily basis. This modification was deemed necessary to keep the data volume at a manageable level. This modification means that if the a medication coverage start date falls in a particular calendar week (for prevalent patient analysis) or week since initiation (for initiation analysis) then the medication is deemed to cover that week. The same rule was applied to the medication coverage end date.

2. Drug regimen transitions - including an adjustment to allow for switching when the prior medication is not fully used

Once estimated drug regimens have been determined for every week, then transitions can be computed.

These are useful for determining patient behaviour upon initiation of a drug; e.g. $A \rightarrow A+B$ (adding to existing therapy), $A \rightarrow B$ (switching) or $\text{None} \rightarrow A$ (starting therapy).

Every drug regimen transition is assessed as to whether or not it is likely to be a real change, or an apparent addition of a drug that is really a substitution of another drug (ie. a switch of drugs). An apparent addition occurs when a patient has not consumed all of the prior drug before starting a new drug. As the coverage of the prior drug is based on when the script was supplied and the SCD for that drug, there may be apparent overlap of coverage of the two drugs that does not occur in reality.

This is assessed by noting the composition and length of the current, prior and post drug regimens. For example, if the regimen being assessed is $A+B$ and the prior regimen is A , the post regimen is B and the length of the $A+B$ regimen is less than or equal to the SCD of prior regimen (ie. A) then the $A+B$ regimen is deemed to have not occurred and the regimen is changed to the post regimen (ie. B). Thus before adjustment the regimen sequence would

have been $A \rightarrow A+B \rightarrow B$ and after adjustment the sequence is $A \rightarrow B \rightarrow B$ which is the same as $A \rightarrow B$. In this way all apparent overlaps, which are really switches, are corrected for.

If the prior regimen contains multiple drugs (eg. $A+B+C$) then the minimum period overlap of regimens required for the transition to be deemed real, and not apparent, is equal to the longest SCD of the drugs in the prior regimen (eg. if A & B have a SCDs of 5 weeks and C has and SCD of 9 weeks then the overlap period needs to be 9 weeks).

Further criteria for defining a switch are;

- all drugs in the prior and post regimen are in the current regimen; and
- the prior and post regimens are different

3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days

The two step methodology outlined in point 1 and refined by logic in point 2 above did not take into account the phenomenon of stockpiling. This often occurs towards the end of the calendar year when a Safety Net card holder fills prescriptions more frequently than expected, so as to stockpile the medicine and avoid a higher co-payment in the next calendar year when they lose Safety Net eligibility. Stockpiling can also occur at other times of the year. Step 1 can impute higher rates of breaks in episodes around February. This is likely to be due to the stockpiling effect and not due to genuine breaks in treatment. Thus the rule to estimate the prescription coverage end date was modified to be the greater of;

- the predicted coverage end date of the previous prescription plus the standard coverage days (SCD); and,
- the actual supply date of the prescription plus the SCD.

This way of calculating the prescription coverage end date takes into account medication stockpiling (i.e. early supply). The logic of the break rule remained unchanged, that is;

- a break was where a prescription was supplied 2 x SCD or more after the coverage end date of the previous prescription for the same drug or drug group.

Application of this refinement results in the reduction of the extent of seasonality in the number of breaks in episodes.

If multiple prescriptions of the same drug (but not the same strength) or drug group are supplied on the same day, it was assumed that these were necessary for the prescribed dose for the SCD and not for an extension of coverage.

If multiple prescriptions of the same drug are supplied it is generally for two different strengths to enable the prescribed dose to be administered. If two prescriptions for the same strength (as opposed to increased quantity for a single script) are supplied, the method assumes this is similar to stockpiling (i.e. same day stockpiling) and the predicted coverage end date is extended to be the greater of;

- the predicted coverage end date of the previous prescription plus $n \times$ SCD; and,

- the actual supply date of the prescription plus $n \times \text{SCD}$ where n = number of prescriptions on the same day.

A special case of multiple prescriptions being supplied on the same day is Regulation 24 prescriptions.

If the original and repeat prescriptions were supplied under Regulation 24 on the same day, then this was assumed to extend the coverage period (i.e. coverage period = prescriptions \times SCD).

There is a danger that patients who consistently consume their medicine in less than the SCD period for a particular drug, will be deemed to be stockpiling (when they are not) and the coverage end date for a prescription will get unrealistically ahead of the supply date. To reduce this risk, the stockpiling rule was modified to limit the stockpiling to 3 extra SCD periods of coverage.

4. Change in the rules for prescriptions whose coverage spans an initiation date; - removal of stockpiling rule

It was found that the stockpiling rule could result in the script coverage end date getting considerably ahead of the script supply date. This is the intent of the rule, however when a new drug B was initiated the stockpiling rules was resulting in the imputation that the new drug B was being added to an existing drug A, when in all probability it was substituting drug A. To correct for this, the script coverage rule was changed so that if the script coverage period for a drug A script included the initiation date for drug B, then the stockpiling rule would not apply to the drug A script (i.e. its coverage would be from its supply date to the supply date + SCD). The rationale for this change is that even if patient has a lot of drug A on hand, the decision by the prescriber to initiate a new drug means that a switch could have occurred.

5. Estimating if a patient is continuing or stopping after their last script

If the last script in a patients script history is supplied within $2 \times \text{SCD}$ of the end of the data period then the treatment is estimated to be continuing at the end of the data period (i.e. the episode coverage end date is set to the end date of the data period). Otherwise the treatment episode is estimated to have stopped and the episode coverage end date is equal to If the last script in a patients script history plus $1 \times \text{SCD}$.

Table B.1: Standard Coverage Days used in this analysis

Drug	Standard Coverage Days (i.e. Median time to re-supply by any item of the same drug)
Metformin	37
Gliclazide	34
Sitagliptin + Metformin	29
Sitagliptin	28
Glimepiride	30
Pioglitazone	28
Insulin Glargine	137

Drug	Standard Coverage Days (i.e. Median time to re-supply by any item of the same drug)
Vildagliptin + Metformin	31
Insulin Aspart	122
Insulin Aspart + Insulin Aspart Protamine	88
Exenatide	32
Linagliptin	29
Dapagliflozin	29
Metformin + Glibenclamide	30
Saxagliptin	28
Glibenclamide	33
Insulin Isophane Human + Insulin Neutral Human	89
Vildagliptin	32
Acarbose	31
Glipizide	32
Insulin Lispro	120
Linagliptin + Metformin	31
Saxagliptin + Metformin	29
Insulin Detemir	143
Insulin Isophane Human	118
Insulin Lispro + Insulin Lispro Protamine	86
Insulin Neutral Human	122
Rosiglitazone + Metformin	29
Rosiglitazone	28
Empagliflozin	30
Insulin Glulisine	137
Alogliptin + Metformin	30
Dapagliflozin + Metformin	29
Alogliptin	28
Canagliflozin	30
Empagliflozin + Metformin	31
Insulin Isophane Bovine	90
Insulin Neutral Bovine	118
Sitagliptin + Simvastatin	29.5

Even though this analysis estimated drug group regimens, the SCD of the individual drugs within the group were used to calculate the coverage of each prescription. The table below show the SCDs for the drug groups as a whole (ie. combining some of the drugs), but these were not used in the estimation of the drug group regimens.

Table B.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
MetGlipCombo	30	29
Insulin	92	88
Gliptin	29	30
Pioglitazone	28	28
Exenatide	32	31
Flozin	29	NA
MetSulfCombo	30	29
Acarbose	31	31
MetRosiCombo	29	29
Rosiglitazone	28	28
MetFlozCombo	29	NA

If the drug regimens are display by calendar week instead of weeks relative to initiation, then towards the end of the data period there may be some obvious “end effect” artefacts in some of the regimen time series. This is because the true continuation rate may not be well estimated by the continuation logic described above (ie. If the last script is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period). If this is the case then there will be a trend change close to the end of the regimen time series plot. One solution to this problem is to not display approximately the last 2 x SCD portion of the time series.

Appendix C: Comparison of prevalence measures

Table C.1 below shows patient prevalence to script supply, which is the standard way that patients are counted in DUSC analyses. Prevalence is counted for supply in a year, half year and quarter for comparison with Figure 1 which shows the number of patients estimated to be on a diabetes drug regimen in each week (close to a point prevalence estimate of patients on treatment), regardless of prescription supply in that week or not.

Table C.1: Patients prevalent to supply of a diabetes medicine prescription for various periods

Year	prevalent to supply in year	6 months	prevalent to supply in 6 months	Quarter	prevalent to supply in Quarter	Week starting	estimated weekly (point) prevalence to therapy
		2013H2	933,945	2012Q3	807,066	31/8/2012	811,009
				2012Q4	834,111	5/10/2012	818,186
2013	1,058,798	2013H1	935,028	2013Q1	785,117	4/01/2013	832,292
				2013Q2	827,464	5/04/2013	824,889
		2013H2	978,210	2013Q3	848,011	5/07/2013	837,910
				2013Q4	871,385	4/10/2013	853,991
2014	1,103,872	2014H1	974,928	2014Q1	820,613	3/01/2014	865,786
% annual growth	4.3%			2014Q2	860,876	4/04/2014	858,374
		2014H2	1,016,916	2014Q3	880,691	4/07/2014	870,088
				2014Q4	904,987	3/10/2014	884,025
2015	1,153,550	2015H1	1,017,408	2015Q1	854,609	2/01/2015	896,631
% annual growth	4.5%			2015Q2	898,042	3/04/2015	887,744
		2015H2	1,062,821	2015Q3	921,075	3/07/2015	905,202
				2015Q4	946,378	2/10/2015	920,869
2016	NA	2016H1	1,058,314	2016Q1	894,885	1/01/2016	934,766
				2016Q2	928,599	1/04/2016	922,929
		2016H2	NA	2016Q3	930,205	29/07/2016	928,561

Table C.1 shows that the quarterly prevalence of prescription supply of a diabetes drug is approximately equal to the point prevalence estimate of patients on a diabetes drug regimen (See Figure 1 and final two columns of Table C.1). The difference between the two is that in prescription supply prevalence will include patients who had a supply early in the quarter but stopped therapy early in the quarter. This would make the quarterly prevalence greater than the point prevalence later in the quarter. On the other hand there will be patients on therapy, who stockpiled in the previous quarter but had no supply in the next quarter or had a supply of a drug which is normally supplied infrequently (eg. Insulin Aspart, which has a median time to resupply of 122 days, see Appendix B) in the previous quarter and no supply in the next quarter. This would make the quarterly prevalence less than the point prevalence (as the treatment is deemed to continue through the next

quarter). It looks like these two effects are approximately equal and cancel each other out at the quarterly level. At the half yearly and yearly level the former effect is bigger than the latter and so the half yearly and yearly prevalence to prescription supply is greater than the estimate of the weekly/point estimate of the number of patients on a diabetes drug regimen shown in Table C.1.