

Analysis of drugs for type 2 diabetes

Drug utilisation sub-committee (DUSC)

October 2012 and February 2013

Summary

The natural history of type 2 diabetes means that most patients need anti-diabetic drugs in order to optimise blood glucose control and achieve good long-term health outcomes.

Drugs considered for listing on the Pharmaceutical Benefits Scheme (PBS) are assessed for effectiveness, safety, and cost-effectiveness compared to the therapy they are most likely to replace. Expected use and financial implications are also considered.

In recent years there have been a number of changes to the listing of drugs for type 2 diabetes on the PBS. These have included amended restrictions on the criteria for subsidisation of already listed drugs, additional indications for existing drugs, as well as the listing of new drugs. In addition, some safety concerns have arisen.

As use outside the PBS restrictions can affect the cost-effectiveness of the drugs (i.e. their value for money), the Drug Utilisation Sub-committee (DUSC) examined the utilisation and patterns of treatment of drugs for type 2 diabetes, and compared this use with current PBS restrictions. Drugs considered were the oral anti-diabetic drugs, metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors (known as gliptins), thiazolidinediones (known as glitazones) and acarbose; and the injectable anti-diabetic drugs, insulin and exenatide.

Patients eligible for an oral anti-diabetic drug on the PBS must start therapy on metformin or a sulfonylurea before using any other anti-diabetic drug (apart from insulin or acarbose). If blood glucose control isn't achieved, a trial of metformin and a sulfonylurea in combination is required in most cases before any other therapies (apart from insulin) can be used. If glycaemic control is still not achieved, various criteria exist in relation to third line therapies. The gliptins, glitazones and exenatide are restricted PBS benefits and can only be prescribed in certain combinations to qualify for PBS subsidy (see full report for details).

The analysis presented in this report examined de-identified data from DUSC and the Department of Human Services (DHS) (Medicare) databases. The results show the use of drugs to manage type 2 diabetes is increasing: this is not surprising given the increasing prevalence of type 2 diabetes.

Metformin and the sulfonylureas were the most commonly prescribed oral anti-diabetic drugs. Metformin use has increased over time, as has use of fixed dose combination (FDC) products, basal insulin and the gliptins. Use of sulfonylureas overall has remained relatively

stable. Acarbose use, which is low, has also been reasonably stable, with a recent, slight decline. Although exenatide has a broader PBS listing compared to the gliptins, use of exenatide is lower than the gliptins. As exenatide was only listed on the PBS in 2010, it may not yet have an established market. Use of glitazones is declining: safety concerns may be contributing to low and declining use.

Metformin remains the most common first line therapy for patients with type 2 diabetes. Metformin was the drug of choice for initiation of therapy for 62% of patients in 2003-2004, increasing to 79% of patients in 2009-2010. The high proportion of first line use with metformin is expected, as clinical guidelines recommend metformin as first line therapy and metformin has an unrestricted PBS listing.

The use of drugs in the first 3.5 years after starting therapy was analysed. In that period, most patients with type 2 diabetes did not need a second or third line drug. The analysis showed a small amount of use beyond the PBS restrictions in this time period. This use generally involved the addition of a second drug without a trial of both metformin and a sulfonylurea.

After considering the overall use of anti-diabetic therapies and the likelihood of some use beyond the PBS restrictions, particularly as patients progress beyond the first 3.5 years of treatment, DUSC asked for an additional analysis to be undertaken on third line agents. The analysis aimed to determine the proportion of use outside the PBS restrictions.

The analysis showed that nearly half (49%) of all patients starting on gliptin therapy had not taken metformin and a sulfonylurea in the 2-year period prior. This figure increased to 55% for patients starting on a gliptin and metformin in a FDC product.

The apparent high use of a gliptin with metformin in lieu of a sulfonylurea with metformin is concerning. Gliptins cost a lot more than sulfonylureas and are not PBS listed as an alternative to those drugs unless there is a contraindication or intolerance. The prevalence of true intolerance to sulfonylureas is low. Use outside the criteria for subsidisation is occurring more frequently with FDC products.

Overall, 28% of prevalent patients prescribed a gliptin, a glitazone or exenatide are prescribed it in a regimen of co-prescribed therapies that does not comply with PBS subsidy criteria.

- Pioglitazone (13% of pioglitazone users) has the least use beyond the PBS restriction of the third line therapies: rosiglitazone the highest (48% of rosiglitazone users). However total utilisation of rosiglitazone is very low and continues to decline.
- The use of a gliptin with both metformin and a sulfonylurea contributes the most to use outside PBS restrictions in terms of co-prescribed therapies. Some use of gliptin monotherapy is also evident. Gliptins are being used in a number of ways that have either not been considered or accepted to be cost-effective by the Pharmaceutical Benefits Advisory Committee (PBAC). The long-term safety of this relatively new class of agents has not been established and gliptins are of

high cost compared to some of the therapies they are substituting in practice (such as sulfonylureas and pioglitazone).

- For exenatide, some use beyond PBS restrictions is apparent, mostly in combination with insulin. This indication has not been assessed as cost-effective by the PBAC.

The results of this analysis will be forwarded onto the Pharmaceutical Benefits Advisory Committee and the NPS MedicineWise for information.

This report was prepared by the Drug Utilisation Sub-committee (DUSC) of the PBAC.

Full report

Purpose of analysis

This analysis examined the utilisation of drugs for type 2 diabetes. The analysis was requested by DUSC as there have been a number of changes to anti-diabetic products listed on the Pharmaceutical Benefits Scheme (PBS) and safety concerns have arisen for some drugs. DUSC also noted that the PBS restrictions have become complex over time.

The specific objectives of the analysis were to:

- describe the utilisation and patterns of treatment of medicines for type 2 diabetes, including the sequence of therapies and agents administered concomitantly; and
- compare this use with current PBS restrictions.

Within that framework, this report covers four aspects of utilisation:

- part I: overall utilisation of PBS listed medicines for diabetes, including the number of prescriptions and expenditure
- part II: patterns of use when patients start drug therapy for type 2 diabetes
- part III: the extent to which the restricted benefit PBS medicines (gliptins, glitazones and exenatide) meet the restrictions regarding therapies that need to be tried prior to starting on these medicines
- part IV: the extent to which the restricted benefit PBS medicines meet the restrictions for co-administration with other medicines for type 2 diabetes.

This report brings together analyses from the October 2012 and February 2013 meetings of DUSC. Its scope includes all drugs listed on the PBS that are used to treat diabetes (Anatomical Therapeutic Chemical (ATC) classification A10).

Table 1: Glossary of terms

Term	Definition
Authority required benefits	Restricted benefits that require prior approval from the Department of Human Services or the Department of Veterans' Affairs
Authority required (streamlined) benefits	Restricted benefits that do not require prior approval from the Department of Human Services or the Department of Veterans' Affairs but require the recording of a streamlined authority code on the prescription
Co-administration	Assumed use (determined from prescriptions supplied) of two or more medicines at the same time
Compliant treatment regimen	Drug regimens meeting requirements for PBS subsidy
Copayment	A payment made by the user at the time of service as part of the total payment for that service and any associated product
Dual therapy	In this report, dual therapy means use of either metformin or a sulfonylurea in combination with another anti-diabetic therapy for the management of type 2 diabetes

Term	Definition
Gliptin	Dipeptidyl peptidase 4 (DPP-4) inhibitor – products included in this report were linagliptin, saxagliptin, sitagliptin and vildagliptin
Glitazone	Thiazolidinedione – products included in this report were pioglitazone and rosiglitazone
GLP-1 analogue	Glucagon-like peptide-1 analogue – products included in this report include exenatide
Government expenditure	Expenditure by the Australian Government, excluding out of pocket costs, including copayments, and private prescriptions
Initiating or starting treatment	<p>In part II of this report, refers to a patient with no prescription supplied for any anti-diabetic medicine in at least the previous 12 months. These patients are assumed to be starting drug treatment for their diabetes for the first time</p> <p>In part III and IV of this report, refers to a patient being supplied with a prescription for a certain drug for the first time. The patient may have been on other diabetes medicines in the past</p>
Monotherapy	In this report, refers to use of a single drug at any given time to manage type 2 diabetes
Non-compliant treatment regimen	Drug regimens not meeting requirements for PBS subsidy
Published price	The price of the drug as published in the Pharmaceutical Benefits Schedule
Regimen	A drug or combination of drugs deemed to be taken at the same time by a patient at a point in time
Restricted benefit	A restriction that means the relevant drug can be prescribed through the PBS only for specific therapeutic uses
Special pricing arrangement	A commercial-in-confidence arrangement between the Commonwealth and a pharmaceutical company that affects the actual price paid by the Commonwealth for supplied medicines
Switch	Changing from one subsidised therapy to another
Third line therapy or agent	In this report, refers to gliptins, glitazones and exenatide
Triple therapy	In this report triple therapy refers to use of metformin or a sulfonylurea in combination with two other anti-diabetic therapies to manage type 2 diabetes
Under-copayment	A PBS medicine that costs less than the general patient copayment

Table 2: Abbreviations of drugs

Abbreviation	Full term
Exen	Exenatide
FDC	Fixed dose combination
Glip	Gliptin (also known as dipeptidyl peptidase-4 inhibitors)
Glit	Glitazone (also known as thiazolidinedione)
Met	Metformin
GLP-1	Glucagon-like peptide-1
Insulin - fast	Short acting/ultra short acting insulin: insulin neutral, insulin glulisine, insulin lispro, insulin aspart
Insulin - intermediate or Insulin - mixed	Insulin isophane, insulin isophane and insulin neutral, insulin lispro and lispro protamine, insulin aspart and aspart protamine
Insulin - basal	Insulin glargine and insulin detemir
Pio	Pioglitazone
Rosi	Rosiglitazone
SCD	Standard coverage days
Sul	Sulfonylurea (glimepiride, gliclazide, glibenclamide, glipizide)

Background

Clinical situation

Type 2 diabetes is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, insufficient insulin secretion or both. Diet and lifestyle modifications are the first steps in managing the disease, followed by the addition of drug therapy with metformin. When diet, lifestyle modifications and metformin monotherapy is inadequate in controlling blood glucose levels, current treatment guidelines, based on PBS criteria,¹ recommend adding a sulfonylurea. If dual therapy with metformin and a sulfonylurea is unsuccessful, a range of other treatment options follow. The pharmacology of the anti-diabetic agents available to treat diabetes is described in the next section.

Pharmacology

Metformin reduces hepatic glucose production and increases peripheral utilisation of glucose.

The sulfonylureas increase pancreatic insulin secretion and may decrease insulin resistance.

The insulins increase or restore cells' ability to metabolise glucose by enhancing glucose uptake – they also inhibit endogenous glucose output and lipolysis.

The glitazones are agonists of peroxisome proliferator-activated receptor gamma, which regulates genes involved in lipid and glucose metabolism. They increase the sensitivity of peripheral tissues to insulin and decrease hepatic glucose output.

The gliptins inhibit dipeptidyl peptidase-4 (DPP-4), thereby increasing the concentration of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Glucose-dependent insulin secretion is increased and glucagon production is reduced.

Acarbose delays the intestinal absorption of carbohydrates by inhibiting alpha-glucosidase enzymes in the small intestine.

Exenatide is a synthetic analogue of glucagon-like peptide-1 (an incretin) – it enhances glucose-dependent insulin secretion and suppresses inappropriate glucagon secretion. It also delays gastric emptying, which reduces the rate of glucose absorption and decreases appetite.

TGA listings

The indications approved by the Therapeutic Goods Administration (TGA) and the PBS listings may or may not be the same. The alignment between PBS listings and TGA approved indications are shown for anti-diabetic drugs that became available through the PBS prior to 2002 (Table 3) and at various time points between 2003 and 2012 (Table 4). Cells shaded in grey indicate differences between TGA-approved indications and PBS listings.

Table 3: Medicines for diabetes PBS listed before 2002: TGA-approved indications versus PBS listings

		Mono-therapy	Dual therapy [+met or sul]	Dual therapy [+glit]	Triple therapy [+met+sul]	With insulin
Metformin	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glibenclamide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Gliclazide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glimepiride	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glipizide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Acarbose	TGA	✓	✓	✓ ^a	✓	✓
	PBS	✓	✓	✗	✓	✓

Source: Schedule of Pharmaceutical Benefits and Product Information (October 2012)

Notes: The references to mono-, dual and triple therapy are in relation to the active ingredient(s), not products. The (✓) indicates that the drug can be part of the regimen by virtue of not being specifically excluded. The (✗) indicates that the drug can't be part of the regimen. Cells in grey highlight differences between TGA/PBS indications.

^a Acarbose is TGA-approved as adjunct therapy. However, the glitazones are not TGA-approved for use with acarbose

Acarbose, metformin, sulfonylureas (glibenclamide, gliclazide, glipizide and glimepiride) and combinations such as metformin + glibenclamide are all unrestricted benefits in the General Schedule of the PBS, and there are no restrictions for prescribers in using these agents for monotherapy, dual or triple therapy or in combination with insulin for the management of type 2 diabetes.

Table 4: Medicines for diabetes listed between 2003 and 2012: TGA-approved indications versus PBS listings

		Mono-therapy	Dual therapy [+met or sul]	Dual therapy [+glip or glit]	Triple therapy [+met+sul]	With insulin
Glitazones						
Rosiglitazone	TGA	✓	✓	✗	✗	✗
	PBS	✗	✓	✗	✗	✗
Pioglitazone	TGA	✓	✓	✗	✓	✓ ^a
	PBS	✗	✓	✗	✓	✓ ^a
Gliptins						

		Mono-therapy	Dual therapy [+met or sul]	Dual therapy [+glip or glit]	Triple therapy [+met+sul]	With insulin
Sitagliptin	TGA	✗	✓	✓ ^b	✗	✗
	PBS	✗	✓	✗	✗	✗
Saxagliptin	TGA	✗	✓ ^e	✓ ^b	✗	✓
	PBS	✗	✓ ^e	✗	✗	✗
Vildagliptin	TGA	✗	✓	✓ ^{b,c}	✗	✗
	PBS	✗	✓	✗	✗	✗
Linagliptin	TGA	✗	✓	✗	✓	✗
	PBS	✗	✓	✗	✗	✗
Glucagon-like peptide-1 (GLP-1) analogues						
Exenatide BD	TGA	✗	✓	✗	✓	✓
	PBS	✗	✓	✗	✓	✗
Fixed dose combinations						
Metformin+ glibenclamide	TGA	✗	✓	✗	✓	✓
	PBS	✗	✓	✗	✓	✓
Rosiglitazone+ metformin	TGA	✗	✓	✓	✗	✗
	PBS	✗	✓ ^d	✓	✗	✗
Vildagliptin+ metformin	TGA	✗	✓	✗	✗	✗
	PBS	✗	✓ ^d	✗	✗	✗
Sitagliptin+ metformin	TGA	✗	✓	✗	✗	✗
	PBS	✗	✓ ^d	✗	✗	✗

Source: Schedule of Pharmaceutical Benefits and Product Information (October 2012)

Note: The references to mono-, dual and triple therapy are in relation to the active ingredient(s), not products. The (✓) indicates that the drug can be part of the regimen by virtue of not being specifically excluded. The (✗) indicates that the drug can't be part of the regimen. Cells in grey highlight differences between TGA/PBS indications

^a TGA-approved for dual therapy in combination with insulin. However, the PBS-listing does not specify the diabetes medicines to be used in combination with insulin and appears broader

^b TGA-approved for dual therapy in combination with glitazones. However, glitazones are not TGA-approved for use with gliptins

^c Pioglitazone only

^d Only dual therapy with metformin allowed

^e The TGA-approved indication is wider, and includes use as initial combination therapy when dual saxagliptin and metformin therapy is appropriate

Dosage and administration

The dosage and administration details of PBS listed drugs used in the treatment of type 2 diabetes are provided in Appendix 1.

PBS listing details (as at February 2013)

The PBS listing details of drugs used in the treatment of type 2 diabetes is provided in Appendix 2.

Restrictions

Metformin, sulfonylureas, acarbose and all insulins except for insulin detemir are unrestricted benefits on the Pharmaceutical Benefits Scheme (PBS). Insulin detemir is a restricted benefit for type 1 diabetes. Exenatide, pioglitazone and gliptins (as single agents and fixed dose combination (FDC) products) are authority required (streamlined) listings and can only be prescribed through the PBS for specific therapeutic uses. Rosiglitazone and rosiglitazone with metformin FDC are authority required listings due to safety concerns.

The PBS restrictions are presented as a flow chart in Figure 1. In practice, metformin is usually considered first line, with a sulfonylurea added on to metformin as a second line agent.

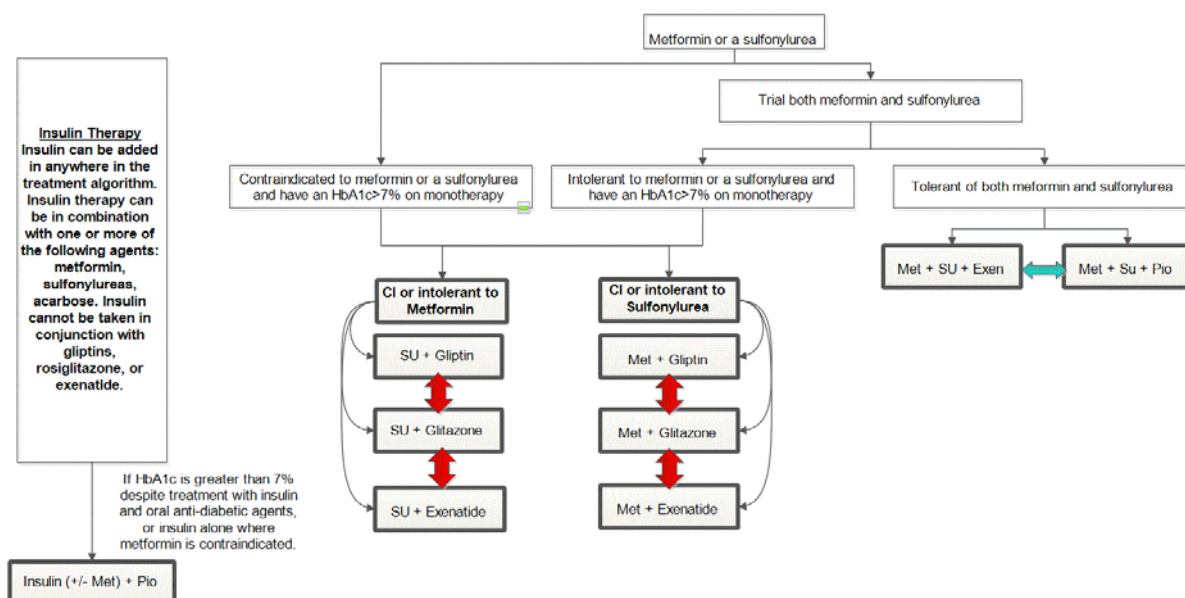


Figure 1: PBS restrictions for anti-diabetic drugs

Abbreviation: HbA1c, glycosylated haemoglobin

Note: The red and blue arrows indicate where switching between drugs is permitted without having to requalify with respect to HbA1c levels. Acarbose has an unrestricted listing and can be used at any point in therapy

Table 5: Full PBS restriction wording by restriction and drug

Restriction	Drug
Unrestricted	Metformin Glibenclamide Gliclazide Glimepiride Glipizide Acarbose Insulin aspart Insulin aspart and protamine suspension Insulin glargine Insulin glulisine Insulin lispro Insulin lispro and protamine suspension Insulin neutral Insulin neutral and insulin isophane (biphasic isophane) Metformin and glibenclamide FDC
Restricted benefit Type 1 diabetes	Insulin detemir
Authority required (streamlined) Dual oral combination therapy with metformin or a sulfonylurea Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c ^a is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.	Rosiglitazone (telephone Authority required) Pioglitazone Sitagliptin Saxagliptin Vildagliptin Linagliptin Exenatide
Authority required Type 2 diabetes in a patient whose HbA1c ^a is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with metformin and where a sulfonylurea is contraindicated or not tolerated.	Rosiglitazone and metformin
Authority required (streamlined) Combination therapy with insulin Type 2 diabetes, in combination with insulin, in a patient whose HbA1c ^a is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment	Pioglitazone

Restriction	Drug
with insulin and oral anti-diabetic agents, or insulin alone where metformin is contraindicated.	
Authority required (streamlined) Triple oral combination therapy with metformin and a sulfonylurea Type 2 diabetes, in combination with metformin and a sulfonylurea, in a patient whose HbA1c ^a is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.	Pioglitazone Exenatide
Authority required (streamlined) 3543 Type 2 diabetes in a patient whose HbA1c ^a is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with metformin and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.	Metformin and sitagliptin FDC Metformin and vildagliptin FDC
Authority required (streamlined) 3149; 3686 Continuation of therapy in type 2 diabetes mellitus in a patient who has previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and sitagliptin / metformin and vildagliptin.	Metformin and sitagliptin FDC Metformin and vildagliptin FDC

^a The date and level of the qualifying HbA1c must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:

- (a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or
- (b) red cell transfusion within the previous 3 months

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per litre in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records

Changes to listing

Table 6: Date of PBS listing of drugs used to treat diabetes

Drug	Listing date	Summarised restriction
Glimepiride	Nov 2000	Unrestricted benefit
Rosiglitazone	Nov 2003	Dual oral – with either metformin or a sulfonylurea*
	Aug 2005	Combination therapy with insulin – PBS subsidisation ceased late 2008
	Aug 2006	Triple therapy with metformin and sulfonylurea– PBS subsidisation ceased Feb 2009
Rosiglitazone with metformin FDC	Dec 2006	Dual therapy when sulfonylurea is contraindicated or not tolerated
Pioglitazone	Nov 2003	Dual oral – with either metformin or a sulfonylurea*
	Nov 2003	Combination therapy with insulin
	Feb 2008	Triple therapy – with metformin and a sulfonylurea
Insulin detemir	Oct 2006	Restricted benefit – type one diabetes
Insulin glargine	Oct 2006	Unrestricted benefit
Insulin glulisine	Jul 2007	Unrestricted benefit
Sitagliptin	Aug 2008	Dual oral – with either metformin or a sulfonylurea*
Sitagliptin with metformin FDC	Aug 2009	Dual therapy when sulfonylurea is contraindicated or not tolerated
Exenatide	Aug 2010	Dual oral – with either metformin or a sulfonylurea*
	Aug 2010	Triple therapy – with metformin and a sulfonylurea
Vildagliptin	Aug 2010	Dual oral – with either metformin or a sulfonylurea*
Vildagliptin with metformin FDC	Apr 2011	Dual therapy when sulfonylurea is contraindicated or not tolerated
Saxagliptin	Jun 2011	Dual oral – with either metformin or a sulfonylurea*
Linagliptin	Mar 2012	Dual oral – with either metformin or a sulfonylurea*

* where one of metformin or a sulfonylurea is contraindicated or not tolerated

Metformin and insulin neutral were listed on the PBS in 1963. All other drugs covered by this analysis, except those in Table 6 above, were listed between 1992 and 2002.

Rosiglitazone was delisted for combination therapy with insulin in late 2008 and delisted for triple therapy with metformin and a sulfonylurea in February 2009.

In March 2010, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended that restrictions on all currently PBS subsidised gliptins and glitazones be modified to allow patients to switch between agents in these two classes without having to requalify with respect to glycosylated haemoglobin levels (HbA1c). Although the evidence to support switches from a gliptin to a glitazone and vice versa is limited, PBAC considered it

unreasonable to require a loss of diabetic control prior to switching. This same recommendation to allow switching was subsequently applied to exenatide.

Issues considered by the PBAC

The basis for listing (and relevant rejections of applications) of drugs covered by this analysis are presented in Tables 7 and 8.

Table 7: Basis for PBS listings of drugs in this analysis

Drug	PBAC meeting	Recommendation
Rosiglitazone	Mar 2001	Recommended for authority required listing for use in combination with metformin or sulfonylureas in patients whose blood glucose concentrations are inadequately controlled despite diet, exercise and maximal tolerated doses of metformin or sulfonylureas and in whom combination therapy with metformin plus a sulfonylurea is contraindicated or not tolerated) on a cost-minimisation basis with 8 mg rosiglitazone accepted as being similar in effectiveness and safety to 88 units insulin (including the non-drug cost offsets incurred with the use of insulin).
	Nov 2004	Recommended to extend the authority required listing to include triple therapy in combination with metformin and a sulfonylurea.
	Mar 2005	Recommended to extend the authority required listing to include dual therapy with insulin.
Rosiglitazone + metformin FDC	Jul 2006	Recommended for authority required listing for initiation of therapy in patients eligible for treatment with rosiglitazone and metformin on the grounds that the combination tablets are no worse than concomitant rosiglitazone and metformin. The combination tablet should be available to the same patient population as had access to individual components.
Pioglitazone	Sept 2001	Recommended for authority required listing for dual therapy* and in combination with insulin on a cost-minimisation basis compared with rosiglitazone.
	Nov 2007	Recommended to extend authority required listing to include triple therapy on a cost-minimisation basis compared with rosiglitazone.
Exenatide	Nov 2008	Recommended for authority required listing for dual* and triple therapy on a cost-minimisation basis compared with insulin glargine.
Sitagliptin	Mar 2008	Recommended for authority required listing for dual therapy* on a cost-minimisation basis compared with rosiglitazone.
Sitagliptin + metformin FDC	Mar 2009 (minor)	Recommended for authority required (streamlined) listing for dual therapy on a cost-minimisation basis compared with the individual components.
Saxagliptin	Mar 2010	Recommended for authority required (streamlined) listing for dual therapy* on a cost-minimisation basis compared with sitagliptin.
Vildagliptin	Mar 2010	Recommended for authority required (streamlined) listing for dual therapy* on a cost-minimisation basis compared with sitagliptin.

Drug	PBAC meeting	Recommendation
Vildagliptin + metformin FDC	Nov 2010 (minor)	Recommended for authority required (streamlined) listing for dual therapy on a cost-minimisation compared with the corresponding strengths of the constituent components given concomitantly, with a cost-offset to account for the cost of liver function testing.
Linagliptin	Jul 2011	PBAC was of a mind to recommend authority required (streamlined) listing for dual therapy* on a cost-minimisation basis compared with sitagliptin. However in the absence of a decision by the TGA Delegate on the registration of linagliptin, PBAC deferred a final recommendation.
Linagliptin	Nov 2011 (minor)	Recommended for authority required (streamlined) listing for dual therapy* on a cost-minimisation basis compared with sitagliptin.

* where one of metformin or a sulfonylurea is contraindicated or not tolerated

Table 8: Basis for rejections of applications for PBS listings of drugs in this review

Drug	PBAC meeting	Recommendation
Rosiglitazone	Nov 2007	Request for extension of current listing to include use as monotherapy and in combination with metformin rejected because of uncertain clinical benefit, concern about the safety of the drug and the resulting uncertain cost-effectiveness.
Exenatide	Jul 2007	Request for authority required listing for dual and triple therapy rejected on the grounds of high and uncertain cost-effectiveness against the comparators. The weight loss data is difficult to value and has not been shown to translate into morbidity or mortality benefits. PBAC also had some concerns regarding long term safety.
	Mar 2008	Request for authority required listing for dual and triple therapy rejected on the grounds of high and uncertain cost-effectiveness against the comparators. PBAC considered uncertainties around the clinical benefit result in uncertainty in the model outputs. Further, interpretation of model outputs were also marred by uncertainties in utility values and a lack of clarity in the model.
Sitagliptin	Mar 2008	Request to listing for use in combination with metformin in the absence of a sulfonylurea contraindication or intolerance rejected on the basis of highly uncertain cost-effectiveness.
Linagliptin	Jul 2012	Request to extend the current authority required (streamlined) listing to triple oral therapy rejected on the basis of uncertain comparative clinical effectiveness and considerable economic uncertainty.
Saxagliptin	Jul 2012	Request to extend the current authority required (streamlined) listing to include use in combination with insulin rejected on the basis of an inadequate comparison across appropriate comparators, uncertain comparative clinical effectiveness and uncertain cost-effectiveness.

Copies of the Public Summary Documents from all relevant meetings are available [by product](#) and by [meeting date](#).

Methods

Four aspects of utilisation were analysed:

- I: overall utilisation of PBS listed medicines for diabetes, including the number of prescriptions and expenditure
- II: patterns of use when patients start drug therapy for type 2 diabetes
- III: the extent to which the restricted benefit PBS medicines (gliptins, glitazones and exenatide) meet the restrictions for therapies that need to be tried prior to starting these medicines
- IV: the extent to which the restricted benefit PBS medicines meet the restrictions for co-administration with other medicines for type 2 diabetes.

I: Overall utilisation

The number of prescriptions and expenditure for all drugs used in the treatment of diabetes were extracted from the DUSC database for the period January 2002 to March 2012. The DUSC database combines data for PBS prescriptions submitted to the Department of Human Services (DHS) for payment of a PBS/RPBS subsidy by the Government, with an estimate of under-copayment and private prescriptions based on dispensing data from a sample of pharmacies. The prescription data presented in this analysis is based on the date of supply to the patient.¹

Government expenditure data are available for prescriptions where a PBS subsidy is paid. Government expenditure for subsidised PBS/RPBS prescriptions is based on the prices published in the PBS schedule minus patient copayment. Note that exenatide has a special pricing arrangement.

II: Patterns of use when patients start drug therapy for type 2 diabetes

This part of the analysis examined patterns of use when patients started drug therapy for type 2 diabetes.

De-identified pharmacy claim data for PBS-subsidised prescriptions for all diabetes medicines was extracted from the DHS (Medicare) database for the period July 2002 to December 2011. From this extract, four cohorts of concessional patients starting treatment for type 2 diabetes were defined to allow comparison of utilisation over time. The selected cohorts established for the years 2003/04, 2005/06, 2007/08 and 2009/10 were chosen to align with changes in availability of drugs on the PBS. Concession only cohorts were used because some medicines used to treat diabetes are priced below the general patient copayment, and the supply of under-copayment medicines is not captured for general patients in the dataset.

¹ PBS statistics available from the Department of Human Services (DHS) website are based on the date of prescription processing. There may be minor differences in prescription and expenditure data based on date of supply in this report, and publically available date of processing data from the DHS website.

A definition for a patient starting on treatment was no prescription supplied for any diabetes medicine in at least the previous 12 months.

Patients who started treatment with insulin alone and who were less than or equal to 20 years of age were excluded. These patients are assumed to have type 1 diabetes. It is acknowledged that an increasing proportion of people with type 1 diabetes are insulin resistant and may be co-prescribed oral drugs agents used in type 2 diabetes. These patients will be captured and included in this analysis, however, their numbers are likely to be small and unlikely to have significant impact on the results observed. Patients aged over 20 years at initiation who received insulin detemir and no other product over their prescription history, were excluded on the basis that these patients are also likely to have type 1 diabetes.

Treatment pathways post-initiation of treatment were assessed. For comparability across cohorts, it was necessary to specify a common follow-up period. A period of 3.5 years was defined for the 2003/04, 2005/06 and 2007/08 cohorts. For the 2009/10 cohort only a follow-up period of 18 to 30 months was possible from initiation to diabetes therapy. For the 2009/10 cohort, the distribution of initiating therapies was assessed, facilitating comparison with earlier cohorts. Treatment pathways were determined for individual de-identified patients from their prescription supply history. The analysis of prescription pathways included an assessment of whether new therapy was introduced as a replacement for an existing drug (switching) or as an additional form of therapy. All analyses were based on the date of supply of the medicines. (A more detailed description of the methods is provided in Appendix 3).

III: Therapies used before third line agents

This analysis examined patterns of use in an incident cohort of patients commencing therapy with a third line agent (gliptin, glitazone, exenatide), looking at prior prescription history.

De-identified PBS/RPBS pharmacy claim data for all anti-diabetic drugs supplied between July 2009 and July 2012 (inclusive) were extracted from the DHS (Medicare) database. From this extract, a cohort including all concession patients who received a first supply of a gliptin, glitazone or exenatide in the 6 months from July to December 2011 were extracted. A first supply was defined as no prescription dispensed for a gliptin, glitazone or exenatide in at least the previous 2 years. For this cohort, prescription histories were analysed to determine whether metformin and/or a sulfonylurea had been dispensed in the 2 years prior to initiation of the gliptin, glitazone or exenatide.

Following feedback from stakeholders, a subsequent analysis looked at whether metformin and/or a sulfonylurea had been dispensed in the 5 years prior to initiation of the gliptin, glitazone or exenatide.

The gliptins were considered as a group as they all have the same PBS restrictions. Rosiglitazone and pioglitazone were considered separately as pioglitazone currently has more subsidised indications than rosiglitazone and they have different safety profiles.

Patients who initiated a gliptin, glitazone or exenatide in the 6-month period July 2011 to December 2011 (inclusive) were classified into the following groups based on prescriptions supplied up to 24 months prior to the patient's initiation date:

1. metformin only
2. sulfonylurea only
3. neither metformin nor sulfonylurea
4. metformin and sulfonylurea supplied and deemed to be co-administered for more than 5 consecutive weeks.
5. metformin and sulfonylurea supplied and deemed to be co-administered from 1 to 5 consecutive weeks.
6. metformin and sulfonylurea supplied but not deemed to be co-administered at any time.

Group 5 above was included to distinguish patients who added metformin or sulfonylurea but did not persist with treatment. This group may represent patients who trialled, but were found to be intolerant to, one of the drugs in the combination.

To classify patients into the above groups, the analysis estimated drug treatment regimens from prescription supply data. Full details of the method for imputing treatment regimens from prescription supply data are provided in Appendix 4.

IV: Co-administration of medicines used to treat diabetes

This part of the analysis examined patterns of use of medicines used to treat diabetes in a prevalent (new and existing users) cohort of patients on a third line agent, to determine co-administered anti-diabetic drugs.

De-identified PBS/RPBS pharmacy claim data for all anti-diabetic drugs supplied between July 2010 and July 2012 (inclusive) were extracted from the DHS (Medicare) database. From these data, a cohort including all concession patients were extracted, and their medicine regimens were determined for the period February 2011 to May 2012. The data extract was longer than the analysis period, providing run in and over-run periods to establish the medication regimen correctly. Treatment regimens were determined for individual de-identified patients. The methods for determining episodes of duration for each prescription supplied are detailed in Appendix 4).

For regimens that included a gliptin, exenatide or a glitazone, the regimen was assessed for compliance with current PBS restrictions regarding co-administered medicines.

It was possible for regimens to be non-compliant with PBS restrictions in more than one way. For the purposes of this analysis, if a regimen did not comply with the PBS restriction, it was only counted once.

The regimens were classified into the following categories:

1. Regimen consistent with PBS restrictions
2. Use of a gliptin, rosiglitazone or exenatide without metformin or a sulfonylurea
3. Use of pioglitazone without metformin, a sulfonylurea or insulin

4. Use of insulin with a gliptin, exenatide or rosiglitazone
5. Use of two or more of gliptins, glitazones or exenatide agents together
6. Use of a gliptin or rosiglitazone with both metformin and a sulfonylurea.

Table 9: Drug regimens not meeting requirements for PBS subsidy

Drug or regimen	Use
Gliptin	<ul style="list-style-type: none"> ▪ as monotherapy ▪ with insulin ▪ with metformin and a sulfonylurea ▪ without either metformin or a sulfonylurea ▪ in combination with a glitazone, exenatide or another gliptin
Gliptin and metformin FDC	<ul style="list-style-type: none"> ▪ with insulin ▪ with a sulfonylurea ▪ in combination with a glitazone, exenatide or another gliptin
Exenatide	<ul style="list-style-type: none"> ▪ as monotherapy ▪ with insulin ▪ without metformin or a sulfonylurea ▪ in combination with a glitazone or a gliptin
Pioglitazone	<ul style="list-style-type: none"> ▪ as monotherapy ▪ with a gliptin or exenatide or rosiglitazone ▪ without metformin or a sulfonylurea (unless in combination with insulin)
Rosiglitazone	<ul style="list-style-type: none"> ▪ as monotherapy ▪ with insulin ▪ with metformin and a sulfonylurea ▪ without metformin or a sulfonylurea ▪ in combination with exenatide or a gliptin or pioglitazone
Rosiglitazone and metformin FDC	<ul style="list-style-type: none"> ▪ with insulin ▪ with a sulfonylurea ▪ in combination with exenatide or a gliptin or pioglitazone

Where therapies overlapped for 5 weeks or less, a switch was deemed to have occurred. Overlaps of greater than 5 weeks were considered co-administration of therapy. DUSC considered this overlap period to be appropriate, as the pack sizes for the third line agents provide approximately 1 month of therapy. The 5 week overlap window may misclassify some patients who co-administered therapy for less than one month as switching therapy, but was considered to represent a reasonable balance between sensitivity and specificity. Shorter overlap periods would potentially misclassify switching as co-administration.

Results

I: Overall utilisation

Metformin and sulfonylureas are the most commonly prescribed oral anti-diabetic drugs. The use of metformin has increased over time, while the use of sulfonylureas has stabilised (see Figure 2 below).

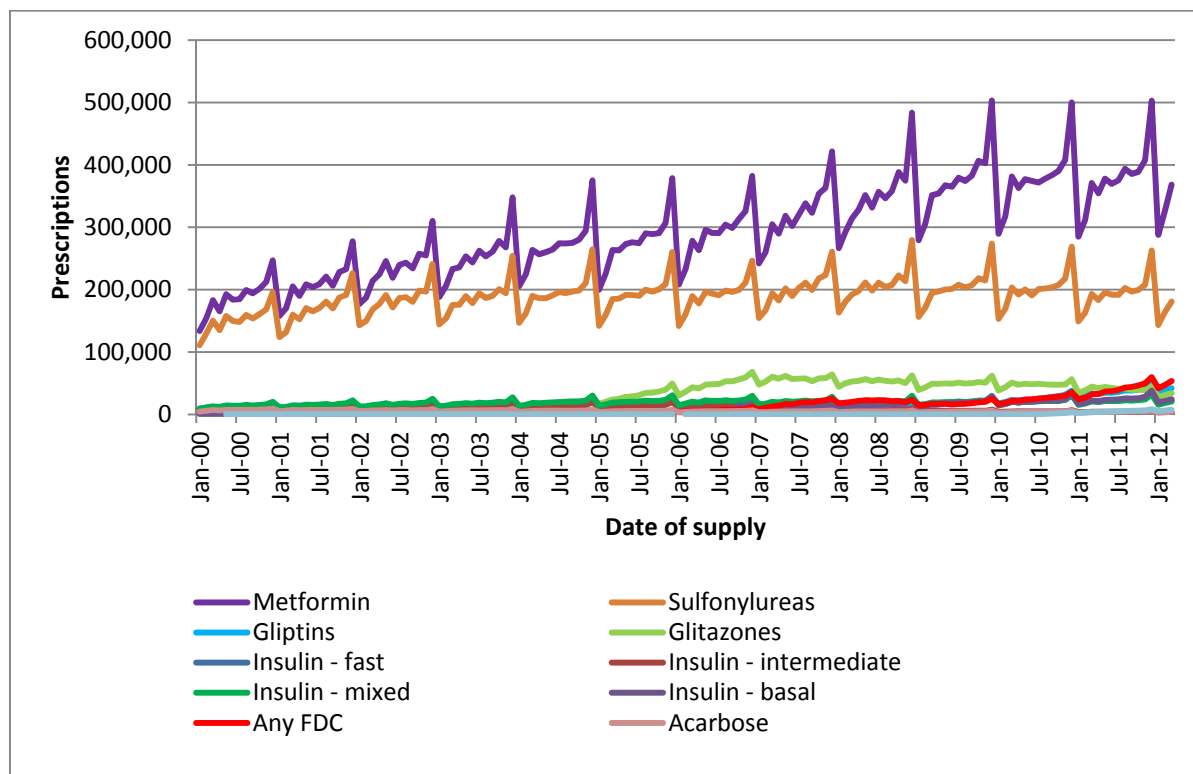


Figure 2: Prescriptions over time, all drugs

Source: DUSC database, accessed September 2012. Includes PBS/RPBS subsidised prescriptions, under-copayment and private prescriptions, FDC includes sitagliptin, vildagliptin or rosiglitazone with metformin, and metformin with glibenclamide

The increase in prescriptions in December and subsequent decline in January each year, is due to seasonal fluctuations associated with the safety net.

Figures 3 and 4 show the number of prescriptions dispensed for the anti-diabetic agents, excluding metformin and sulfonylureas.

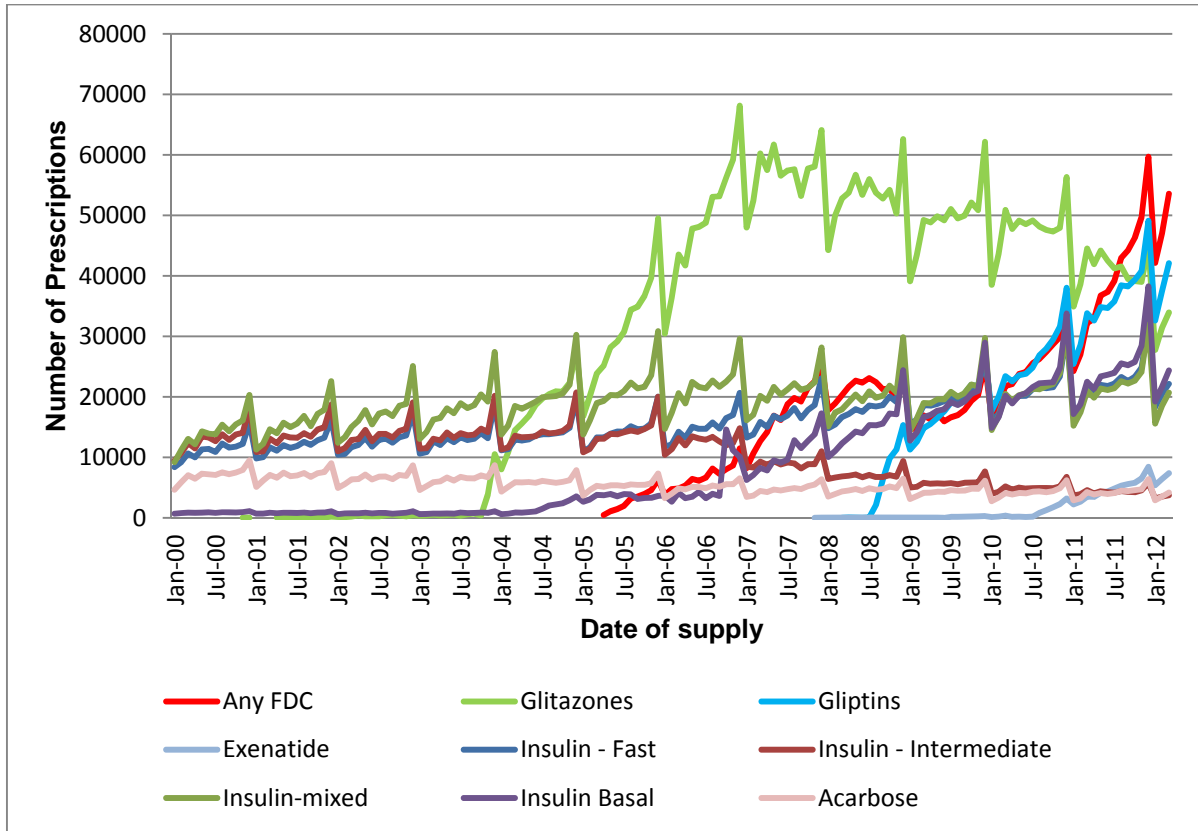


Figure 3: Prescriptions over time, excluding metformin and sulfonylureas

Source: DUSC database, accessed September 2012. Includes PBS/RPBS subsidised prescriptions, under-copayment and private prescriptions, FDC includes sitagliptin, vildagliptin or rosiglitazone with metformin, and metformin with glibenclamide

There has been rapid uptake of the FDC products (Figure 3) and gliptins (Figure 4). The utilisation of glitazones rose quickly to 2007, and has since declined (Figures 3 and 4). The utilisation of acarbose was reasonably stable, with a slight decline (Figure 3). The utilisation of basal insulin increased over time; other insulins were relatively stable (Figure 3).

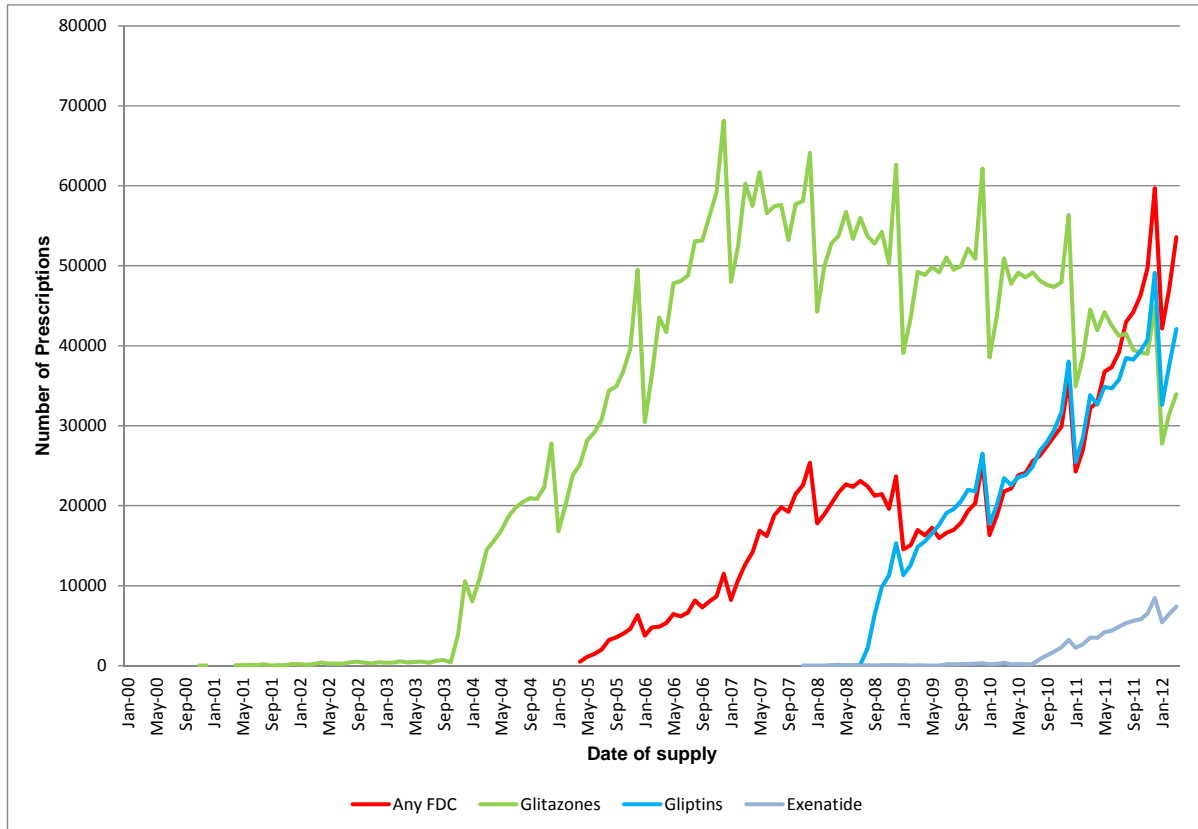


Figure 4: Prescriptions over time for therapies listed after 2002, excluding insulin and acarbose

Source: DUSC database, accessed September 2012

Government expenditure

Government expenditure on drugs used to treat diabetes was about \$428 million in last 12 months of the study period (April 2011 to March 2012 inclusive), based on the published price of these medicines.

Table 10: Overall annual cost to Government, by year

Year	Government expenditure	Annual growth (%)
2000	\$128,676,827	n.a.
2001	\$143,638,991	12%
2002	\$157,041,319	9%
2003	\$166,354,479	6%
2004	\$194,807,528	17%
2005	\$210,414,933	8%
2006	\$233,840,721	11%
2007	\$280,856,067	20%
2008	\$309,689,641	10%
2009	\$339,186,445	10%
2010	\$379,502,345	12%
2011	\$419,125,598	10%

Source: DUSC database, accessed September 2012, includes PBS and RPBS prescriptions where there is a subsidy paid by government. Under-copayment and private prescriptions are not included. Prices based on published price

The higher rates of growth in 2004 and 2007 coincide with the first 12 months after listing of the glitazones and insulin glargine, respectively.

Monthly expenditure trends are presented in Figure 5.

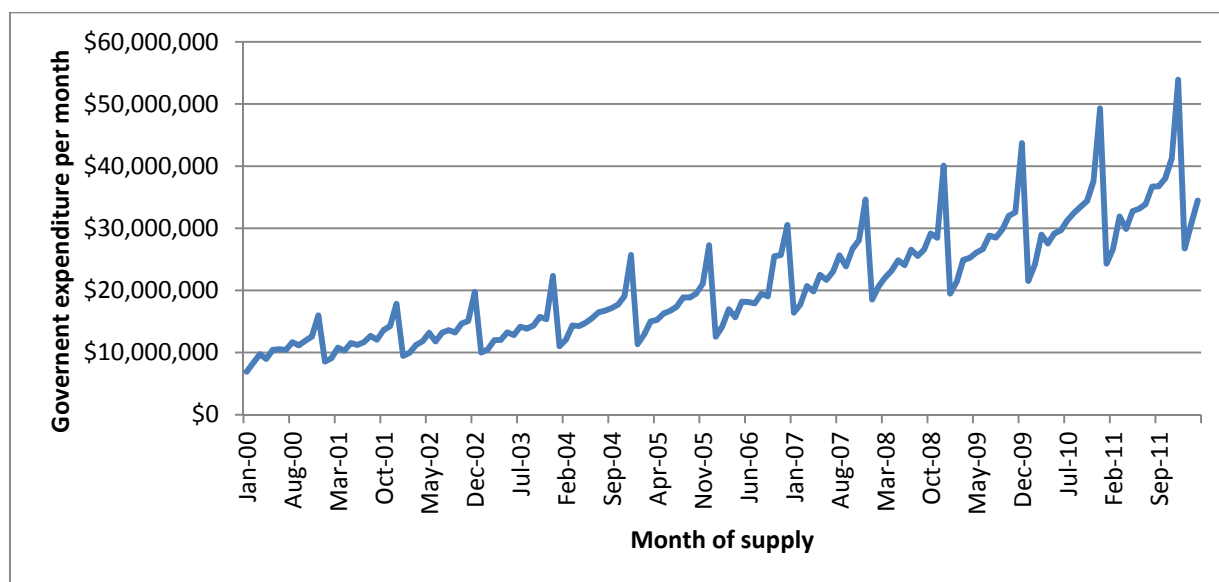


Figure 5: Overall Government expenditure, by month

Source: DUSC database, accessed September 2012, includes PBS and RPBS prescriptions where there is a subsidy paid by government. Under-copayment and private prescriptions are not included. Prices based on published price

The increasing expenditure can be viewed by drug. The highest expenditure is on insulins (see Figure 6). Note that special pricing arrangements apply for basal insulins.

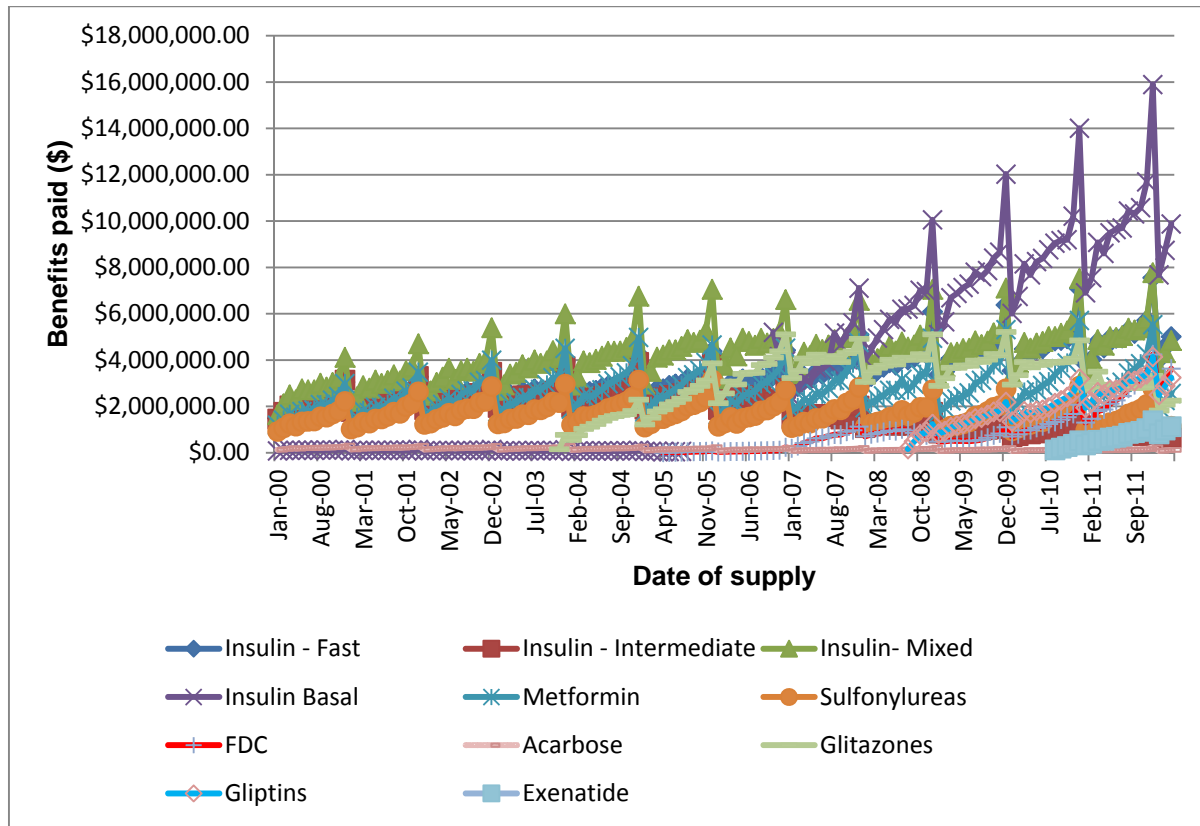


Figure 6: PBS/RPBS expenditure per month by drug

Source: DUSC database, accessed September 2012, includes PBS and RPBS prescriptions where there is a subsidy paid by government. Under-copayment and private prescriptions are not included. Based on published price

II: Patterns of use when patients start drug therapy for type 2 diabetes

The analysis of initiating therapies shows a marked increase over time in the proportion of people initiating metformin as their first anti-diabetic therapy, with a corresponding decrease in patients initiating a sulfonylurea. There appears to be a small trend away from insulin as initial therapy.

Table 11 summarises initiating therapy for each of the four cohorts.

Table 11: Initiating therapy by cohort

Initiating therapy	Cohort 1 2003/04	Cohort 2 2005/06	Cohort 3 2007/08	Cohort 4 2009/10
Metformin	61.8%	69.1%	75.4%	79.4%
Sulfonylurea	27.6%	19.8%	13.1%	9.7%
Metformin + sulfonylurea	4.3%	3.5%	3.4%	3.4%
Glitazones	0.2%	7%	9%	7%
Acarbose	0.1%	0.4%	0.5%	0.4%
Mixed insulin	2.4%	0.1%	0.2%	0.1%
Short acting insulin	1.5%	2.1%	1.6%	1.1%
Basal + short acting insulin	0.6%	0.5%	1.9%	1.4%
Basal insulin	1%	1%	0.8%	0.7%

Source: A review of treatment patterns and utilisation of anti-diabetic medications in treatment-naïve Type 2 diabetics in Australia, Adelaide Health Technology Assessment for the October 2012 DUSC meeting, Executive Summary, page v

The predominance of metformin as initiation therapy has increased over time.

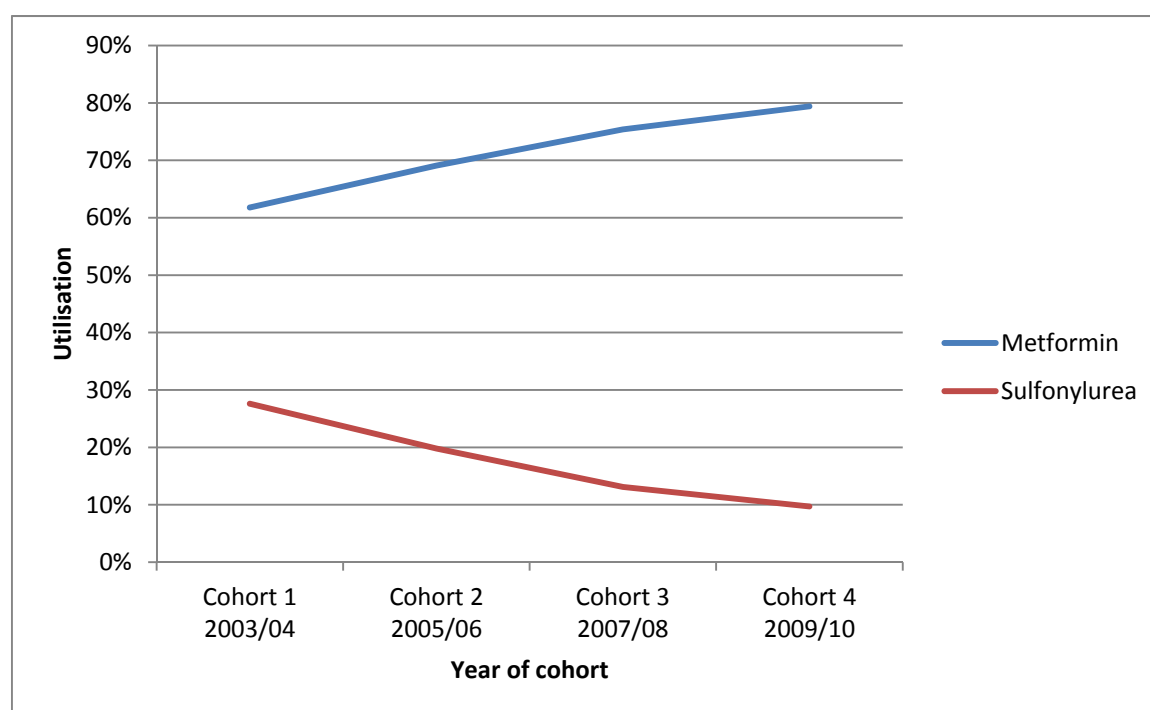


Figure 7: Initiation therapy

Table 12 shows the proportion of people who had additional therapy or switched therapy within 3.5 years of initiation for the first three cohorts. Most patients do not progress to a second or third line agent within 3.5 years.

There is a small amount of use beyond the PBS restrictions, generally involving the addition of a second line agent without trialing both metformin and a sulfonylurea first (see Table 12).

Table 12: Addition and switching during first 3.5 years of therapy

	Cohort 1 2003/04	Cohort 2 2005/06	Cohort 3 2007/08	Cohort 4 2009/10
No addition or switch	62.9%	65.4%	62.8%	Insufficient follow-up time
Add within PBS restrictions	27.0%	23.6%	21.0%	
Add beyond PBS restrictions	0.8%	1.7%	3.0%	
Switch within PBS restrictions	3.8%	4.3%	4.2%	
Switch beyond PBS restrictions	0.0%	0.0%	0.5%	

Source: A review of treatment patterns and utilisation of anti-diabetic medications in treatment-naïve Type 2 diabetics in Australia, by Adelaide Health Technology Assessment for the October 2012 DUSC meeting, Executive Summary, page v

III: Therapies used before third line agents

An analysis that examined the previous treatment regimens of patients starting a third line therapy shows that almost half were not on both metformin and a sulfonylurea in the 2 years.

The results of this analysis are summarised in Table 13 below. Overall, 47.7% of patients initiating on a gliptin, glitazone or exenatide had not received a supply of both metformin and a sulfonylurea in the previous 2 years. Breaking that down further:

- 36.1% of patients had metformin supplied, but not a sulfonylurea
- 6.7% of patients had a sulfonylurea supplied, but no metformin
- 4.9% of patients had no evidence of a supply of metformin or sulfonylurea in the previous 2 years.

Table 13: Regimen histories before initiation on a third line agent for concession patients

Pre-initiation treatment regimen summary	Patients (no.)	Patients (%)
Regimen histories not containing both metformin and a sulfonylurea	8,233	47.7%
1. metformin only supplied	6,230	36.1%
2. sulfonylurea only supplied	1,158	6.7%
3. neither metformin nor sulfonylurea supplied	845	4.9%
Regimen histories containing both metformin and a sulfonylurea	9,014	52.3%
4. metformin and sulfonylurea deemed to be co-administered for more than 5 consecutive weeks	7,515	43.6%
5. metformin and sulfonylurea deemed to be co-administered from 1–5 consecutive weeks	352	2.0%
6. metformin and sulfonylurea supplied but not deemed to be co-administered at any time	1,147	6.7%
Total	17,247	100.0%

Note: Analysis is based on drugs supplied in the 24 months prior to initiation of a third line agent. Analysis includes metformin as a single agent and metformin with a sulfonylurea in a fixed dose combination in the data for metformin prior to initiation

Further analysis suggests that the degree of compliance with restrictions on use of therapies before initiation on third line agents varies according to the third line agents in use (see Tables 14 and 15). Table 14 shows that of all initiations to third line agents between July 2011 and December 2011, 85% were for gliptins. Less than 1% of initiations on third line agents were for rosiglitazone.

Table 14: Number of concession patients (%) starting on each third line therapy between July and December 2011

Patients	Number of patients (%) with drug regimen containing					
	Glip	Glip + met FDC	Pio	Exen	Rosi + met FDC	Rosi
Total (% of patient drug regimens)	7,686 (45%)	6,940 (40%)	1,481 (9%)	1,015 (6%)	66 (<1%)	59 (<1%)

Table 15 shows the percentage of patients who started on a third line therapy with previous use of metformin and/or a sulfonylurea.

Table 15: Regimen histories before initiation on each third line agent for concession patients as percentage of patients initiating the therapy

Patients	Drug regimen contains					
	Glip	Glip + met FDC	Pio	Exen	Rosi + met FDC	Rosi
Total histories not containing both metformin and a sulfonylurea	49%	55%	27%	20%	46%	39%
metformin only supplied	34%	47%	11%	17%	33%	22%
sulfonylurea only supplied	11%	3%	7%	2%	2%	12%
neither metformin nor sulfonylurea supplied	4%	6%	9%	1%	11%	5%
Total histories containing both metformin and a sulfonylurea	51%	45%	73%	80%	54%	61%
metformin and sulfonylurea co-administered for > 5 consecutive weeks	42%	38%	64%	62%	50%	46%
metformin and sulfonylurea co-administered from 1 to 5 consecutive weeks	2%	2%	2%	3%	0%	5%
metformin and sulfonylurea supplied but not co-administered at any time	7%	5%	7%	15%	4%	10%

The results summarised in Table 15 show that about half the patients who started on a third line regimen containing a gliptin, or a FDC containing metformin and a gliptin or rosiglitazone, do so *without* being supplied both metformin and a sulfonylurea in the previous 2 years.

For other third line regimens, fewer patients proceed to that regimen without taking both metformin and a sulfonylurea in the previous 2 years.

IV: Co-administration of medicines used to treat diabetes

The gliptins, glitazones and exenatide are restricted PBS benefits and can only be prescribed with certain combinations of medicines to qualify for PBS subsidy (see Table 9). Medication regimens were estimated for all concessional patients on any diabetes medicines, and the regimens containing a gliptin, glitazone or exenatide were assessed further to determine compliance with PBS restrictions.

Figure 8 shows there is increasing use of regimens containing the gliptins. There is decreasing utilisation of pioglitazone and very low utilisation of rosiglitazone (see Figure 8).

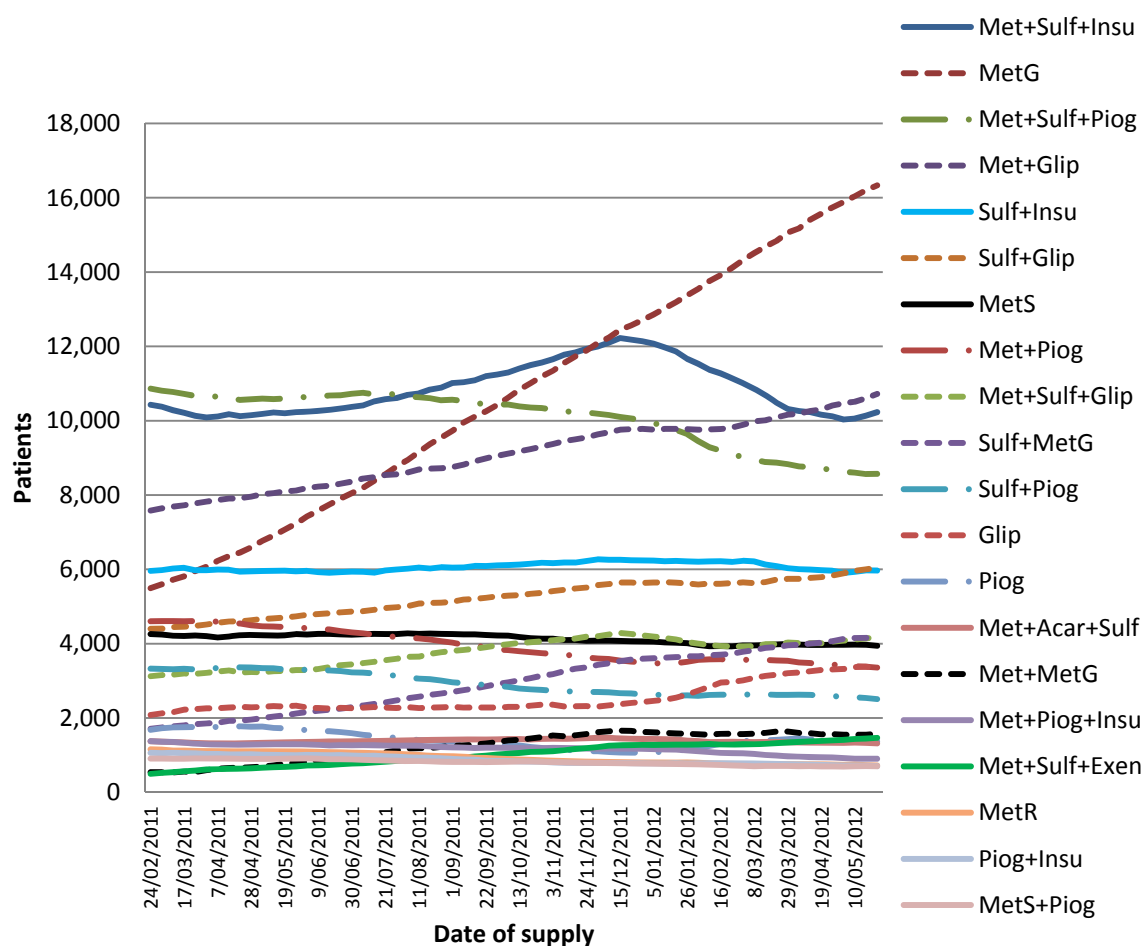


Figure 8: Most common drug regimens that include a third line therapy

Notes: Data for period February 2011 to May 2012, concessional patients only. Dashed plots contain a gliptin and long dash-dot plots contain pioglitazone

The rate of compliance with PBS restrictions for medicine regimens that contain a gliptin, glitazone or exenatide is presented in Table 16 below.

Table 16: Proportion of patients taking regimens containing a gliptin, a glitazone or exenatide that comply with PBS restrictions for co-administered therapy criteria

Regimen status	Sub-total	Total
Regimen complies with PBS restrictions		72.1%
Regimen does not comply with PBS restrictions		27.9%
Use of a gliptin or rosiglitazone with both metformin and a sulfonylurea	13.7%	
Use of insulin with a gliptin, rosiglitazone or exenatide	5.8%	
Use of a gliptin, rosiglitazone or exenatide without metformin or a sulfonylurea	4.8%	
Use of pioglitazone without metformin, a sulfonylurea or insulin	1.7%	
Use of two or more of gliptins, glitazones and/or exenatide together	2.0%	
TOTAL		100%

Source: Analysis of PBS/RPBS pharmacy claim data (see Methods)

Note: Data from week beginning 24 May 2012. (Most recent week of data from Figure 8)

Table 17 shows that the non-compliance rate is highest for regimens containing rosiglitazone (at 48.4% of rosiglitazone users) and lowest for regimens containing pioglitazone (at 12.9% of pioglitazone users).

Table 17: Regimens complying with PBS criteria by drug/drug group

Compliance status +/- reason	Regimen containing			
	a gliptin	pioglitazone	rosiglitazone	exenatide
Compliant	65.4%	87.0%	51.7%	70.4%
Non-compliant	34.6%	13.0%	48.3%	29.6%
Use of a gliptin or rosiglitazone with both metformin and a sulfonylurea	18.5%	n.a.	33.3%	n.a.
Use of insulin with a 3rd line agent (except pioglitazone)	7.1%	n.a.	4.9%	16.1%
Use of a gliptin, rosiglitazone or exenatide without metformin or a sulfonylurea	6.3%	n.a.	5.6%	5.9%
Use of two or more 3rd line agents	2.7%	6.2%	4.6%	7.7%
Use of pioglitazone without metformin, a sulfonylurea or insulin	n.a.	6.7%	n.a.	n.a.

Source: Analysis of PBS/RPBS pharmacy claim data (see Methods)

Notes: n.a. = not applicable

Data for the week beginning 17 May 2012

Gliptins and rosiglitazone includes the single component products and the FDCs

Assessment of compliance with PBS restrictions in part IV of the analysis only considers agents co-administered in the current regimen. The analysis is unable to simultaneously assess whether the pathway to treatment with the third line agent complied with PBS

restrictions. Some regimens classified as compliant with PBS restrictions in part IV, would not have complied with requirements to try metformin and a sulfonylurea unless contraindicated before the third line agent. This was assessed separately in part III.

Discussion

I: Overall utilisation

The prevalence of diabetes is increasing,² and accordingly, the utilisation of medicines to manage diabetes is also increasing. The most frequently prescribed drug is metformin, and utilisation of metformin is increasing over time (Figure 2). In 2009/10, 80% of patients who commenced drug therapy for diabetes were prescribed metformin monotherapy (Table 10). This is consistent with clinical guidelines, which recommend metformin as first line therapy, and metformin has an unrestricted PBS listing.

The next most commonly prescribed drugs are the sulfonylureas. Most often sulfonylureas are prescribed in a dual therapy regimen with metformin (Figure 8). Despite the increasing prevalence of diabetes, the number of prescriptions of sulfonylureas has stabilised over the past few years and may be in decline (Figure 2).

There is rapid growth in utilisation of gliptins, particularly gliptins in FDC formulations with metformin (Figures 4 and 8). The most common regimens are gliptin with metformin FDC, followed by gliptin with metformin as the component products (Figure 8). Gliptins are listed on the PBS only for use in combination with either metformin or a sulfonylurea, in patients whose HbA1c is greater than 7% prior to initiation of a gliptin, a glitazone or a glucagon-like peptide-1 analogue despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

Utilisation of pioglitazone has been declining steadily since 2007 (Figure 4). At the most recent time point in this report (May 2012), the most common pioglitazone containing regimens were triple therapy with metformin and a sulfonylurea, followed by dual therapy with metformin (Figure 8). A much higher number of patients are on a regimen containing a gliptin rather than pioglitazone, despite pioglitazone currently having additional listings and potentially a much larger eligible patient population. Safety concerns may be contributing to declining use of glitazones. Exenatide has a broader PBS restriction than gliptins, but has relatively lower utilisation. Exenatide was first listed on the PBS in August 2010 and may not yet have an established market. There may also be patient reluctance to the use of injections.

The overall government expenditure on PBS subsidised diabetes medicines is increasing at an average rate of about 10% per year. The highest expenditure is on insulins. Note that special pricing arrangements apply for basal insulins.

II: Patterns of use when patients start drug therapy for type 2 diabetes

In the first 3.5 years of pharmacological treatment for diabetes, the vast majority of patients are treated in accordance with the PBS restrictions and clinical guidelines; within

this time period few patients add to or switch their therapy (Table 11). DUSC was concerned that the proportion of use outside of the restriction is growing over time, appears to occur more frequently with gliptins and FDCs, and is likely to be more extensive in patients who have been treated for diabetes for longer than 3.5 years. Although use outside of the restriction may seem relatively small, due to the sheer size of the population with type 2 diabetes, the total cost of use outside of PBS criteria could be high.

The part III and part IV analyses were undertaken to assess the proportion of use of third line agents that is in accordance with PBS restrictions.

III: Therapies used before third line agents

Overall 47.7% of patients initiating on a third line agent had not received a supply of both metformin and a sulfonylurea in the preceding 2 years. When the prior history period is extended to 5 years, 44.6% of patients had not received metformin and a sulfonylurea (data not shown).

The proportion of people not taking metformin prior to the commencement of a third line agent (6.7%) appears reasonable based on reported rates of metformin contraindication in patients with type 2 diabetes.³

The high percentage of patients (41%) who started third line agents without a trial of a sulfonylurea (i.e. those who had received metformin only or neither metformin or a sulfonylurea) appears to represent substantial use outside of the anticipated listing. This pattern of prescribing is most extensive with gliptin + metformin FDCs (52.4%), rosiglitazone + metformin FDC (43.9%), and gliptin single agents (37.9%).

Although no precise estimates are available, the prevalence of true contraindication to a sulfonylurea (primarily severe hepatic dysfunction and severe renal impairment according to the Product Information) is low. To establish intolerance to a sulfonylurea, a trial of the medicine is required. However, the utilisation analysis showed that the proportion of patients co-administered metformin with a sulfonylurea for a short period of time, which would be consistent with a trial of treatment, was very low at 2%.

A number of Sponsors commented that use of sample packs of sulfonylureas was not taken into consideration and so the rate of outside restriction use was overestimated. While sample packs could be used, this would not greatly affect the conclusions regarding the extent of usage beyond the PBS restriction. Anecdotally, there were few sample packs of sulfonylureas being provided.

Of most concern was the apparent high use of gliptin with metformin in lieu of sulfonylurea with metformin. Gliptins are much more costly than sulfonylureas and are not PBS listed as an alternative to those drugs, unless there is a contraindication or intolerance. The cost-effectiveness of this treatment regimen has not been established.

In addition, a proportion of patients classified as meeting the PBS restriction for a gliptin due to previous history of co-administered metformin and a sulfonylurea for more than 5 weeks, may have switched to a gliptin for reasons other than genuine intolerance. The

extent of this use beyond PBS criteria is unable to be captured with prescription data. The rate of prescribing not complying with PBS subsidy criteria from the results of part III is likely to be a conservative estimate.

IV: Co-administration of medicines used to treat diabetes

Overall, 27.9% of patients are prescribed a gliptin, a glitazone or exenatide in a regimen of co-prescribed therapies that does not comply with PBS subsidy criteria (Table 16). This figure of 27.9% is the lower estimate of use outside of PBS restrictions, as the pathway to the third line therapy has not been simultaneously assessed in this analysis. A proportion of regimens containing a third line agent, that have been categorised as complying with restrictions in other analyses, would be reached via a pathway inconsistent with PBS criteria. This was assessed in part III.

Pioglitazone has the least use beyond the PBS restriction of the third line therapies, and the greatest alignment between PBS restrictions and clinical guidelines. This probably reflects that there are more combinations of therapy covered by the additional PBS restrictions for pioglitazone compared to rosiglitazone, gliptins or exenatide.

The use of a gliptin with both metformin and a sulfonylurea ('triple oral therapy') contributes most to use outside restriction. Use of gliptin monotherapy is also evident (see Table 16 and Figure 8). Gliptins are being used in a number of ways that either have not been considered, or have not been accepted, to be cost-effective by PBAC. The long-term safety of this relatively new class of agents has not been established. Gliptins are of high cost compared to some of the therapies they are substituting in practice (such as sulfonylureas and pioglitazone).

The highest rate of use outside of the restriction by drug is with rosiglitazone (48.4%), however total utilisation of rosiglitazone is very low and continues to decline. Use outside of the restriction may reflect patients who remain on a regimen that no longer meets the current PBS restriction, refractory patients or prescriber confusion due to multiple changes to the restrictions for rosiglitazone.

For exenatide, some use beyond PBS restrictions is apparent, most of which is combination use with insulin (Table 16). This indication has not been assessed as cost-effective by the PBAC.

There is concern that use outside of the restriction may occur more frequently with FDC products. This pattern is evident in part III (see Tables 14 and 15). However, use beyond the restriction is associated not just with FDC but with individual agents.

Although the methodology of analysis is complex, it is sound and therefore a good representation of the actual utilisation in practice. For the analyses described in parts II-IV, patterns of use in general and concessional patients are likely to be sufficiently similar to allow extrapolation of the concessional cohort findings to the total population with diabetes. It is also worth noting that the majority of patients with diabetes are concessional patients.

Actions

The DUSC:

- Referred the utilisation analyses to the PBAC; and
- Provided a copy of the report to the National Prescribing Service MedicineWise.

Context for review

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.

Sponsor's comments

Alphapharm Pty Limited: The sponsor has no comment.

Apotex Pty Ltd: The sponsor has no comment.

Aspen Pharma Pty Ltd: The sponsor has no comment.

Aurobindo Pharma (Australia) Pty Ltd: The sponsor has no comment.

Bayer Australia Ltd: The sponsor has no comment.

Boehringer Ingelheim Pty Limited: The sponsor has no comment.

Eli Lilly Australia Pty Limited: Lilly notes the vast majority of prescribing for T2DM, even outside PBS restrictions, reflects evidence-based clinical practice consistent with international guidelines. Lilly remains concerned that some methodological limitations have not been adequately considered.

Generic Health Pty Ltd: The sponsor has no comment.

GlaxoSmithKline Australia Pty Ltd: The sponsor has no comment.

Merck Sharp & Dohme (Australia) Pty Ltd: MSD understands the important role of utilisation analyses in the management of the PBS. And although useful at the time the report was written, MSD notes that the DUSC analyses of diabetes medications were conducted prior to changes to the restrictions of DPP-4-inhibitors that took effect on 1 April 2014 and the listing of SGLT-2 inhibitors* which affect the relevance of the report's conclusions in the current environment.

*The sodium glucose co-transporter 2 (SGLT 2) inhibitors canagliflozin and dapagliflozin were listed on the PBS on 1 December 2013.

Novartis Pharmaceuticals Australia Pty Ltd: The sponsor has no comment.

Novo Nordisk Pharmaceuticals Pty Ltd: The sponsor has no comment.

Pharmacor Limited: The sponsor has no comment.

Ranbaxy Australia Pty Limited: The sponsor has no comment.

Sandoz Pty Ltd: The sponsor has no comment.

Sanofi-Aventis Australia Pty Ltd: The sponsor has no comment.

Servier Laboratories (Aust.) Pty Ltd: The sponsor has no comment.

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3. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD; DARTS/MEMO Collaboration. Contraindications to metformin therapy in patients with Type 2 diabetes--a population-based study of adherence to prescribing guidelines. *Diabetic Medicine* 2001 Jun; 18(6):483-8).

Appendix 1: Dosage and administration

Table A1: Dosage and administration of drugs used in the treatment of type 2 diabetes

Product	Patient age (or combination)	Dose and frequency of administration
Metformin	Adult	<i>Conventional tablet</i> : initially 500mg 1–3 times daily; may be increased up to 850mg 2 or 3 times daily. Maximum daily dose 3g <i>Controlled release tablet</i> : initially 500mg once daily with the evening meal; may be increased up to 2g once daily
	Child	<i>Conventional tablet</i> : initially 500–850mg once daily; maximum daily dose 2g in 2 or 3 doses
Metformin + glibenclamide FDC	Adult	Initially 1 tablet of 500mg metformin with 2.5mg glibenclamide daily with breakfast. Increase by 1 tablet (of this strength) every 2 weeks or longer as required Maximum dose 1 tablet of 500mg metformin with 5mg glibenclamide 3 times a day
Glibenclamide	Adult, child >12	2.5–20mg daily in 1 or 2 doses (up to 10 mg as single dose). Maximum daily dose 15mg if 12–18 years
Gliclazide	Adult, child >12	40–320mg daily in 1 or 2 doses (up to 160 mg as single dose). Start with 20 mg once daily if 12–18 years <i>Controlled release product</i> : initially 30mg once daily; increase dose as required by 30mg once daily at not less than 2 week intervals; maximum daily dose 120mg
Glimepiride	Adult	Initially 1mg once daily, increase as required in 1mg steps at 1–2 week intervals to a maximum of 4mg once daily
Glipizide	Adult	2.5–40mg daily in 1 or 2 doses; doses >15 mg daily should be divided. If CrCl <50 mL/minute, then 50mg once daily
Vildagliptin	(with metformin)	1 tablet (of any strength) twice daily Patients stabilised on each drug separately, start with the current daily doses of vildagliptin and metformin. To add vildagliptin, start with the tablet corresponding to the current metformin dose
	(with a sulfonylurea)	50mg once daily
	(with pioglitazone)	50mg once or twice daily
Exenatide	Adult	SC initially 5mcg twice daily, within 60 minutes before morning and evening meals (or before 2 main meals at least 6 hours apart). If initial dose is tolerated, after 1 month increase to 10mcg twice daily
Rosiglitazone	Adult	Initially 4mg once daily; may be increased to 8mg daily in 1 or 2 doses after 6–8 weeks

Product	Patient age (or combination)	Dose and frequency of administration
	(with metformin)	Give as 2 divided doses, with or after food Adjust dose according to response. Wait 1–2 weeks after changing metformin dose and 6–8 weeks after changing rosiglitazone dose before further increasing dose Maximum daily dose, rosiglitazone 8mg with metformin 2000mg
Sitagliptin	Adult	100mg once daily. Reduce dose in renal impairment. If CrCl 30–50 mL/minute, 50mg once daily. If CrCl <30 mL/minute, 25mg once daily
	(with metformin)	1 tablet (of any strength) twice daily. Usual initial dose is sitagliptin 100mg daily with current daily metformin dose
Pioglitazone	Adult men	15–30mg once daily; may be increased to a maximum dose of 45mg once daily after 6–8 weeks
	Adult women	Start with 15mg once daily
	Adult with heart failure NYHA class I	Start with 15mg once daily; wait several months before increasing dose
	(with insulin)	Start with 15mg once daily and monitor carefully
Saxagliptin	Adults	5mg once daily. 2.5mg once daily if creatinine clearance <50 mL/minute
Linagliptin	Adult	5mg once daily
Acarbose	Adult	Initially 50mg once daily, gradually increased to 50mg 3 times daily. May be increased after 6–8 weeks to 100mg 3 times daily as required. Maximum daily dose 600mg
Insulins	(with oral diabetes drugs)	Long-acting insulin is usually given once daily in the morning or evening. Start with low dose (e.g. 10 units SC before evening meal); increase dose in 2–4 unit increments at intervals of 2–4 days
	(without oral diabetes drugs)	Regimens combining short-acting with long-acting insulins are commonly used; they are given SC in a single daily dose or 2 divided doses before the morning and evening meals

Source: Australian Medicines Handbook Online

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA website PI and CMI page](#).

Appendix 2: PBS listing details (as at February 2013)

Table A2: PBS listing of drugs used in the treatment of type 2 diabetes

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ
1801T	METFORMIN metformin hydrochloride 850mg tablet, 60	1	5	\$11.76
2430X	METFORMIN metformin hydrochloride 500mg tablet, 100	1	5	\$11.76
3439B	METFORMIN metformin hydrochloride 1g tablet: modified release, 60 tablets	1	5	\$14.92
8607B	METFORMIN metformin hydrochloride 1g tablet, 90	1	5	\$15.67
9435N	METFORMIN metformin hydrochloride 500mg tablet: modified release, 120 tablets	1	5	\$14.92
8810Q	METFORMIN + GLIBENCLAMIDE metformin hydrochloride 500mg + glibenclamide 2.5mg tablet, 90	1	5	\$15.58
8811R	METFORMIN + GLIBENCLAMIDE metformin hydrochloride 500mg + glibenclamide 5mg tablet, 90	1	5	\$16.70
8838E	METFORMIN + GLIBENCLAMIDE metformin hydrochloride 250mg + glibenclamide 1.25mg tablet, 90	1	5	\$14.57
2939Q	GLIBENCLAMIDE glibenclamide 5mg tablet, 100	1	5	\$11.49
2449X	GLICLAZIDE gliclazide 80mg tablet, 100	1	5	\$13.26
8535F	GLICLAZIDE gliclazide 30mg tablet: modified release, 100 tablets	1	5	\$13.45
9302N	GLICLAZIDE gliclazide 60mg tablet: modified release, 60 tablets	1	5	\$14.85
8450R	GLIMEPIRIDE glimepiride 1mg tablet, 30	1	5	\$8.15
8451T	GLIMEPIRIDE glimepiride 2mg tablet, 30	1	5	\$9.65
8452W	GLIMEPIRIDE glimepiride 4mg tablet, 30	1	5	\$11.42

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ
8533D	GLIMEPIRIDE glimepiride 3mg tablet, 30	1	5	\$10.51
2440K	GLIPIZIDE glipizide 5mg tablet, 100	1	5	\$12.37
3415R	VILDAGLIPTIN vildagliptin 50mg tablet, 60	1	5	\$96.71
5474D	VILDAGLIPTIN + METFORMIN vildagliptin 50mg + metformin hydrochloride 500mg tablet, 60	1	5	\$96.65
5475E	VILDAGLIPTIN + METFORMIN vildagliptin 50mg + metformin hydrochloride 850mg tablet, 60	1	5	\$98.66
5476F	VILDAGLIPTIN + METFORMIN vildagliptin 50mg + metformin hydrochloride 1g tablet, 60	1	5	\$99.48
3423E	EXENATIDE exenatide 5mcg/20mL injection, 60 unit doses	1 pack	5	\$176.49*
3424F	EXENATIDE exenatide 10mcg/40mL injection, 60 unit doses	1 pack	5	\$176.49*
8689H	ROSIGLITAZONE rosiglitazone 4mg tablet, 28	1	5	\$61.25
8690J	ROSIGLITAZONE rosiglitazone 8mg tablet, 28	1	5	\$90.70
9059T	ROSIGLITAZONE + METFORMIN rosiglitazone 2mg + metformin hydrochloride 500mg tablet, 56	1	5	\$64.05
9060W	ROSIGLITAZONE + METFORMIN rosiglitazone 2mg + metformin hydrochloride 1g tablet, 56	1	5	\$66.69
9061X	ROSIGLITAZONE + METFORMIN rosiglitazone 4mg + metformin hydrochloride 500mg tablet, 56	1	5	\$93.51
9062Y	ROSIGLITAZONE + METFORMIN rosiglitazone 4mg + metformin hydrochloride 1g tablet, 56	1	5	\$96.15
9180E	SITAGLIPTIN sitagliptin 25mg tablet, 28	1	5	\$90.70
9181F	SITAGLIPTIN sitagliptin 50mg tablet, 28	1	5	\$90.70

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ
9182G	SITAGLIPTIN sitagliptin 100mg tablet, 28	1	5	\$90.70
9449H	SITAGLIPTIN + METFORMIN Sitagliptin 50mg + metformin hydrochloride 500mg tablet, 56	1	5	\$93.20
9450J	SITAGLIPTIN + METFORMIN Sitagliptin 50mg + metformin hydrochloride 850mg tablet, 56	1	5	\$94.80
9451K	SITAGLIPTIN + METFORMIN Sitagliptin 50mg + metformin hydrochloride 1g tablet, 56	1	5	\$95.44
8694N	PIOGLITAZONE pioglitazone 15mg tablet, 28	1	5	\$40.82
8695P	PIOGLITAZONE pioglitazone 30mg tablet, 28	1	5	\$56.99
8696Q	PIOGLITAZONE pioglitazone 45mg tablet, 28	1	5	\$72.14
8983T	SAXAGLIPTIN saxagliptin 5mg tablet, 28	1	5	\$90.70
3387G	LINAGLIPTIN linagliptin 5mg tablet, 30	1	5	\$96.71
8188Y	ACARBOSE acarbose 50mg tablet, 90 (PI, CMI)	1	5	\$34.63
8189B	ACARBOSE acarbose 100mg tablet, 90 (PI, CMI)	1	5	\$45.63
8435Y	INSULIN ASPART insulin aspart 100IU/mL injection, 5 x 3mL cartridges	5	1	\$264.32
8571D	INSULIN ASPART insulin aspart 100IU/mL injection, 1 x 10mL vial	5	2	\$159.37
8609D	INSULIN ASPART + INSULIN ASPART PROTAMINE insulin aspart 30IU/mL + insulin aspart protamine 70IU/mL injection, 5 x 3mL syringes	5	1	\$264.32
9040T	INSULIN DETEMIR insulin detemir 100IU/mL injection, 5 x 3mL cartridges	5	1	\$432.82*
9039R	INSULIN GLARGINE insulin glargine 100IU/mL injection, 5 x 3mL cartridges	5	1	\$432.82*
1921D	INSULIN GLULISINE insulin glulisine 100IU/mL injection, 5 x 3mL cartridges	5	1	\$264.32
9224L	INSULIN GLULISINE insulin glulisine 100IU/mL injection, 1 x 10mL vial	5	2	\$159.37

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ
1711C	INSULIN ISOPHANE BOVINE insulin isophane bovine 100IU/mL injection, 1 x 10mL vial	5	2	\$172.12
1533Q	INSULIN ISOPHANE HUMAN insulin isophane human 100IU/mL injection, 1 x 10mL vial	5	2	\$133.92
1761Q	INSULIN ISOPHANE HUMAN insulin isophane human 100IU/mL injection, 5 x 3mL cartridges	5	1	\$224.42
1426C	INSULIN ISOPHANE HUMAN + INSULIN NEUTRAL HUMAN insulin neutral human 30IU/mL + insulin isophane human 70IU/mL injection, 1 x 10mL vial	5	2	\$133.92
1763T	INSULIN ISOPHANE HUMAN + INSULIN NEUTRAL HUMAN insulin isophane human 70IU/mL + insulin neutral human 30IU/mL injection, 5 x 3mL cartridges	5	1	\$224.42
2062M	INSULIN ISOPHANE HUMAN + INSULIN NEUTRAL HUMAN insulin neutral human 50IU/mL + insulin isophane human 50IU/mL injection, 5 x 3mL cartridges	5	1	\$224.42
8084L	INSULIN LISPRO insulin lispro 100IU/mL injection, 1 x 10mL vial	5	2	\$159.37
8212F	INSULIN LISPRO insulin lispro 100IU/mL injection, 5 x 3mL cartridges	5	1	\$264.32
8390N	INSULIN LISPRO + INSULIN LISPRO PROTAMINE insulin lispro 25IU/mL + insulin lispro protamine 75IU/mL injection, 5 x 3mL cartridges	5	1	\$264.32
8874C	INSULIN LISPRO + INSULIN LISPRO PROTAMINE insulin lispro 50IU/mL + insulin lispro protamine 50IU/mL injection, 5 x 3mL cartridges	5	1	\$264.32
1713E	INSULIN NEUTRAL BOVINE insulin neutral bovine 100IU/mL injection, 1 x 10mL vial	5	2	\$172.12
1531N	INSULIN NEUTRAL HUMAN insulin neutral human 100IU/mL injection, 1 x 10mL vial	5	2	\$133.92
1762R	INSULIN NEUTRAL HUMAN insulin neutral human 100IU/mL injection, 5 x 3mL cartridges	5	1	\$224.42

Source: pbs.gov.au

*Special Pricing Arrangements apply

Appendix 3: Study design for part II of the analysis

Analyses were based on individual medications within a class or groups, as follows.

Grouped drugs:

- insulin - basal
- insulin - intermediate or insulin -mixed
- insulin fast
- sulfonylureas
- metformin.

Non-grouped (at the drug level):

- glitazones (pioglitazone, rosiglitazone)
- exenatide
- acarbose
- oral agents in a fixed dose combination (metformin with sulfonylureas, rosiglitazone with metformin, metformin with sitagliptin, metformin with vildagliptin)
- gliptins (saxagliptin, sitagliptin, vildagliptin, linagliptin).

Identifying patterns of utilisation and treatment

The following process was used to generate prescription pathways that informed the assessment of patterns of anti-diabetic medicine treatment and utilisation.

Estimation of the actual time to refill between prescriptions

The time between prescriptions of anti-diabetic medicines was estimated for each drug or drug group for each individual. These estimates were defined by generating prescription sequences ordered by date of supply for each patient, and calculating the number of days between prescriptions.

Estimation of the predicted time to refill between prescriptions

The predicted refill date for each first prescription within each of the 16 drug groups was assumed to be the supply date plus the standard number of days of supply for that drug group. Multiple prescriptions on the same day was calculated from counting the number of prescriptions of all forms and strength of drugs within a drug group that were dispensed on the same day. This count excludes the extra scripts associated with Regulation 24 supply (i.e. supply of all repeats with the original). The predicted refill date for each subsequent prescription was estimated to be the greater of:

- the predicted refill date of the previous prescription plus the standard supply days; and

- the actual refill date of the previous prescription plus the standard supply days.²

This way of calculating the expected length of medication possession takes into account medication stockpiling (i.e. early supply).

In the main analysis, the standard number of days of supply for each drug was based on estimates provided by the DUSC Secretariat.

The standard number of days' supply was specified as:

- 28 days for saxagliptin, sitagliptin, pioglitazone, rosiglitazone and FDCs
- 30 days for exenatide and acarbose
- 50 days for metformin and sulfonylureas
- 70 days for vildagliptin
- 125 days for insulins.

The standard number of days' supply was determined based on pack size for products that have a standard daily dosage or based on clinical advice for agents such as metformin that have variable daily doses. Vildagliptin has two different dosing regimens, either twice daily in combination with metformin or once daily if in combination with a sulfonylurea. For this reason it was assumed that a standard pack could last up to 60 days for patients taking it in combination with a sulfonylurea, and this conservative approach was taken.

In a sensitivity analysis (data not shown), the standard number of days of supply for each drug was based on the empirically observed median time to refill for each drug.

Identification of the status of each supply date observation and creating prescription events

Along the drug pathway for each patient, the process of identifying the switching or addition of new drug groups to existing therapies used a method where the predicted time to refill for each individual for each drug group was tracked over prescriptions.

A patient was assumed to have switched from drug group A to drug group B if group A was not prescribed again after the first prescription of drug group B, or if drug group B was prescribed and there was a break in supply between the immediately prior prescription of drug group A and the next prescription of drug group A that was greater than the predicted date of refill plus two times the standard supply days for drug group A.

In all other cases, drug group B was assumed to have been prescribed in addition to drug group A.

Multiple initiations of the same drug were relatively infrequent. Such cases occurred, for example, where a patient initiated drug group A, switched to drug group B, then switched back to drug group A, etc., and where the latter switch occurred outside of the threshold period (the predicted date of refill plus two times the standard supply days). Such cases,

² The exception is if multiple prescriptions are supplied on the same day, in which case the standard supply days are multiplied by the number of prescriptions.

while infrequent, add significant complexity to the analysis and reported pathways. We focused on the first use of each drug group in representing the drug pathways. The assessments of duration of use and dose consider all prescriptions of a drug.

The cessation of all treatment was identified from the final prescription of any anti-diabetic medicine. However, patients with a prescription towards the end of the observational period may have stopped treatment or may have been continuing treatment beyond the observation period. In such cases, patients were assumed to have ceased all treatment if the predicted date of refill (as described above) plus two times the standard supply days was earlier than the end of the observational period (31 December 2011). Where this was not the case, it was assumed that the patient remained on treatment at the end of the observational period.

Appendix 4: Method for imputing treatment regimens from prescription supply data for parts III and IV

The prescription data contains the date of supply of each prescription, but no information on whether or not medicines should be or were co-administered. Thus this information was imputed from the data in the following way:

- Step 1: Determine the imputed medicine coverage days for each drug or drug group. This involved detecting breaks in treatment – the outcome was the start and imputed end date for each episode for each drug or drug group.
- Step 2: Determine the imputed medicine coverage days across all drug and drug group episodes defined in Step 1. The outcome was an imputed treatment regimen for each patient for every day in the data period.

Similar methods have been used for assessing medicine use in Australian populations.^{3,4} Hallas⁵ describes the method and provides references to early variants.

Figure A4.1 illustrates the method specified above. 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 resulted in the production of the episodes (pink bars) and the Step 2 process resulted in the production of the treatment regimen (blue bar). The days in this illustration are days from initiation (which is applicable to part III) but they could also be calendar days (which is applicable to part IV).

In this illustration, a break in treatment was defined as a coverage gap of two or more SCDs (i.e. the patient had not received re-supply at two consecutive expected refill dates. The first gap in drug A coverage (from days -39 to -35) was not deemed to be a break in the drug A Episode 1 as the imputed gap in coverage was only 1 x SCD. The second gap in drug A coverage from days -29 to -20 was deemed to be a break in treatment and the imputed end of Episode 1 because the gap in imputed coverage was 2 x SCD.

The two prescriptions for drug B supplied on day -9 were interpreted as dose escalation of drug B, if each prescription was for a different strength. The two prescriptions were deemed to be necessary to supply one SCD period and were not used to extend the drug coverage period.

³ 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.

⁴ Vitry, AJ, 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

⁵ Hallas J. 2005 "Drug utilization statistics for individual-level pharmacy dispensing data" *Pharmacoepidemiol Drug Saf.* 14:455–463. doi: 10.1002/pds.1063

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

The final method for imputing the drug treatment regimen included several refinements. Briefly they are:

- calculation of the treatment regimen on a weekly rather than daily basis
- adjustment to allow for switching when the prior medication was not fully used
- adjustment to allow for stockpiling of medication
- adjustment to allow for multiple prescriptions supplied on the same day
- adjustment to allow for Regulation 24 prescriptions
- sensitivity analyses relating to the definition of a break in treatment
- sensitivity analyses relating to imputing if treatment is on-going at the end of the data period.

The drug/drug groups used in the analysis are defined below. The standard coverage days used in analysis results are shown in brackets.

1. insulin (88 days)
2. metformin (35 days)
3. sulfonylureas (32 days)
4. metformin + sulfonylurea combination product (29 days)
5. gliptins (30 days)
6. metformin + gliptin combination product (29 days)
7. rosiglitazone (28 days)
8. metformin + rosiglitazone combination product (, 29 days,)
9. pioglitazone (28 days)
10. exenatide (31 days)
11. acarbose (31 days)

The SCD values in the above lists are median times to re-supply for all diabetes prescriptions supplied in the period July 2010 to July 2011 (allowing resupply data up to July 2012) for the 'concessional only' cohort.

Acknowledgements

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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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