

Exenatide for type 2 diabetes: analysis of predicted versus actual utilisation

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To assess the predicted versus actual use of exenatide for the treatment of type 2 diabetes mellitus.

Background

At the time of the 12 month predicted versus actual analysis of exenatide the DUSC considered that utilisation would increase. There was higher than expected use of the 5 microgram strength. The DUSC recalled that 16 % of exenatide use appeared to be co-administered with insulin, for which exenatide was not subsidised for.

Date of listing on PBS

Exenatide was listed on 1 August 2010 for the treatment of diabetes mellitus type 2:

- as dual therapy with metformin or a sulfonylurea in patients contraindicated or intolerant to a combination of a sulfonylurea and metformin; and
- as triple therapy with metformin and a sulfonylurea.

Data Source / methodology

The pharmacy claims data from the DUSC database and the Department of Human Services (DHS) prescription database was used for the analyses.

Key Findings

- An estimated 31 % of exenatide use is outside the PBS criteria, of which about half is in combination with insulin;
- There continues to be much higher than expected use of the 5 microgram strength;

- Exenatide is most often used in triple therapy regimens (50.4 %) and dual therapy regimens (34.1 %). It is also prescribed as monotherapy (5.6 %) and as quadruple therapy (9.9 %).
- The treatment pathways prior to exenatide are diverse.

Purpose of analysis

To assess the predicted versus actual use of exenatide for the treatment of type 2 diabetes mellitus.

Background

Pharmacology

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist. The ATC code is A10BX04.¹

Therapeutic Goods Administration (TGA) approved indications

Exenatide is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, or a combination of metformin and a basal insulin, but are not achieving adequate glycaemic control.¹

Dosage and administration

Exenatide should be initiated at 5 micrograms administered twice daily subcutaneously for at least one month in order to improve tolerability. The dose can then be increased to 10 microgram twice daily to further improve glycaemic control. Doses higher than 10 microgram twice daily are not recommended.¹

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

PBS listing details (as at 1 July 2014)

Table 1 shows the PBS listing details for exenatide.

Table 1: PBS listing for exenatide

Item	Form and Strength	Max. Qty. (packs)	Max. Repeats.	DPMQ*	Brand Name
3423E	5 microgram/0.02 mL injection, 60 unit doses	1	5	\$ 122.79	Byetta® 5 microgram
3424F	10 microgram/0.04 mL injection, 60 unit doses	1	5	\$ 131.65	Byetta® 10 microgram

Source: PBS Schedule 1/7/2014

¹ Byetta (exenatide). Approved Product Information. Sydney: AstraZeneca. Approved 13 June 2007. Updated 19 May 2014. Available from <www.ebs.tga.gov.au>. Accessed 2 July 2014.

*Note: Special Pricing Arrangements apply. The published price decreased on 1/12/2013.

Restriction

Exenatide is listed as an Authority Required (streamlined) benefit for the treatment of diabetes mellitus type 2:

- as dual therapy with metformin or a sulfonylurea in patients contraindicated or intolerant to a combination of a sulfonylurea and metformin; and
- as triple therapy with metformin and a sulfonylurea.

The full restriction wording is available from the [PBS website](#).

Date of listing on PBS

Exenatide was listed on the PBS on 1 August 2010.

Changes to listing

Exenatide was initially listed as an Authority Required benefit. It was changed to an Authority Required (streamlined) benefit on 1 March 2012.

Sponsor details

These products were sponsored by Eli Lilly when they were listed on the PBS. The sponsor changed to Bristol-Myers Squibb on 1 May 2013 and then to Astra Zeneca on 1 May 2014.

Relevant aspects of the PBAC consideration

Exenatide was considered by the PBAC on three occasions. On the first and second occasions in July 2007 and March 2008, the PBAC rejected the submission on the grounds of high and uncertain cost-effectiveness against the comparators (rosiglitazone and insulin glargine) in the absence of any evidence of clinical benefit other than the observational finding of weight loss which had not been shown to be durable or to translate into morbidity or mortality benefits, and because of unresolved safety concerns. For further details refer to the Public Summary Documents from the [July 2007](#) and [March 2008](#) PBAC meetings.

The PBAC recommended the listing of exenatide on the Pharmaceutical Benefits Scheme on a cost-minimisation basis with insulin glargine taking into account the higher costs associated with the initiation and titration of the dose of insulin glargine at its November 2008 meeting.

The equi-effective doses were exenatide 9.07 micrograms twice daily and insulin glargine 24.93 international units (IU) per day when these agents were in used in triple combination therapy with metformin and a sulfonylurea; and exenatide 9.35 micrograms twice daily and insulin glargine 27.30 IU per day when these agents were used as part of dual combination

therapy with either metformin or a sulfonylurea. The submission's choice of insulin glargine dose of 75 IU per day to establish equi-effective doses was in contrast not derived from clinical trials and was much higher than the mean final glargine dose (less than 30 IU per day) in the direct randomised trials. For further details refer to the [Public Summary Document](#) from the November 2008 PBAC meeting.

A fourth submission was considered by the PBAC in November 2009 requesting a change in comparator and price parity with the highest strengths of pioglitazone and rosiglitazone. The PBAC advised the Minister and the Pharmaceutical Benefits Pricing Authority that the price of exenatide should be based on a rate of a 50:50 substitution for rosiglitazone and insulin glargine. The equi-effective doses are exenatide 10 micrograms twice daily is equivalent to rosiglitazone 8 mg daily and exenatide 9.07 micrograms twice daily and insulin glargine 24.93 IU per day for triple therapy and exenatide 9.35 micrograms twice daily and 27.30 IU per day for dual therapy. This pricing recommendation was reiterated at the PBAC's March 2010 meeting where the sponsor requested the PBAC reconsider the pricing recommendation made at the November 2009 meeting. Public Summary Documents are not available for these considerations.

Two other GLP-1 receptor agonists, liraglutide and lixisenatide, have also been considered by the PBAC for listing on the PBS.

Liraglutide was recommended at the March 2013 PBAC meeting for the same restrictions as exenatide (i.e. dual therapy with metformin or a sulfonylurea, or triple therapy with metformin and a sulfonylurea). It was recommended on a cost minimisation basis with exenatide. As at 1 August 2014 liraglutide was yet to be listed on the PBS. For further details refer to the [Public Summary Document](#) from the March 2013 PBAC meeting.

Lixisenatide was considered at the July 2014 PBAC meeting for the same restrictions as exenatide. In addition there was a separate submission for listing lixisenatide for treatment in combination with insulin. Both submissions were rejected. The submission for dual and triple therapies was rejected on the basis that non-inferiority to exenatide (twice daily) had not been adequately established. The submission for use in combination with insulin was rejected on the basis that the clinical place of glucagon-like peptide-1 drugs in type 2 diabetic patients requiring insulin therapy is yet to be established and therefore the appropriate comparator is not only up titrated insulin. The basis for the cost minimisation analysis of lixisenatide compared to up titrated insulin was therefore not accepted. For further details refer to the [Public Summary Documents \(dual and triple therapies\)](#) and [\(in combination with insulin\)](#) from the July 2014 PBAC meeting.

Exenatide once weekly formulation was recommended by PBAC at its November 2013 meeting. For further details refer to the [Public Summary Document](#) from the November 2013 PBAC meeting. As at 1 August 2014 this formulation was yet to be listed on the PBS.

Approach taken to estimate utilisation

The estimated population eligible for exenatide was based on an epidemiological approach. The prevalence of diabetes was based on AusDiab data^{2,3} that estimated prevalence to be 7.5 % in 2000 and then assumed an increase in prevalence of 0.16 % per year⁴. This gave an estimated prevalence of 8.94 % in the first year after listing, increasing to 9.58 % in the fifth year after listing.

The estimates were based on the following key parameters outlined in Table 2:

² Dunstan D, Zimmet P, Welborn T, Cameron A, Shaw J, de Courten M, Jolley D, McCarty D, on behalf of the AusDiab Steering Committee: The Australian Diabetes, Obesity and Lifestyle Study (AusDiab): methods and response rates. *Diabetes Res Clin Pract* 2002; 57(2): 119-29.

³ Dunstan, P.Z. Zimmet, T.A. Welborn, J. Shaw, M. de Courten, A. Cameron, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian diabetes obesity and lifestyle study. *Diabetes Care* 2002; 25(5): 829-34.

⁴ Davis WA, M. Knudman, D. V. Hendrie, Davis TM. The Obesity driven rising costs of Type 2 diabetes in Australia: projections from the Fremantle Diabetes Study. *Internal Medicine Journal* 2006; 36: 155-61.

Table 2: Parameters used to calculate utilisation in the sponsors estimates

Parameter	Source	Parameter Estimate
Diagnosed with Type 2 diabetes	Simmons et al 2005 ⁵	74%
% patients treated with oral hypoglycaemic agents	Stancombe research	70%
% Treated on oral monotherapy	Stancombe research	31%
Proportion treated with metformin monotherapy	Stancombe research	74%
unable to use metformin in combination with SU	Stancombe research	15%
Proportion treated with a sulfonylurea monotherapy	Stancombe research	21%
unable to use metformin in combination with SU	Stancombe research	16%
Proportion treated with dual oral combination	Stancombe research	31%
Proportion treated with met + SU	Stancombe research	72%
Proportion treated with MET + TZD	Stancombe research	19%
Proportion treated with SU + TZD	Stancombe research	9%
Treated with triple therapy oral combination	Stancombe research	8%
% TZD + MET + SU	Stancombe research	97%
Not achieving adequate glycaemic control	AUSDIAB suggests 49.5%	49.5%
Assumptions affecting financial impact		
Prescriber behaviour		
GP behaviour	Stancombe research	
Will prescribe exenatide instead of TZD	Stancombe research	20%
Will prescribe exenatide after TZD	Stancombe research	37%
Will refer to specialist	Stancombe research	40%
Will prescribe exenatide instead of TZD	Pretium research	25%
Will prescribe exenatide after TZD	Pretium research	25%
Will prescribe insulin	Pretium research	50%
Disposition - drop-out after titration	Not specified	20%
Drug consumed within 30 days	Shelf life for pen in use is 30 days	100%
Exenatide 5 microgram	Maximum 4 weeks (1 pen per initiation)	
Exenatide 10 microgram (second script onwards)	Based on equal monthly initiations	
Assumed uptake rate	Year 0 (private market before listing)	2.0%
	Year 1	10.0%
	Year 2	18.0%
	Year 3	23.0%
	Year 4	25.5%
	Year 5	28.0%

Source: Submission section E spreadsheet "BYETTA_SECTION E_ JULY 2008.xls"

DUSC Advice

The DUSC reviewed the major submissions to the PBAC for exenatide in July 2007 and November 2008. The DUSC considered the estimates presented in the submission to be highly uncertain. The main areas of uncertainty were suggested to be:

⁵ Simmons et al Prevalence of Diabetes in Rural Victoria, Diabetes Research and Clinical Practice 70 (2005) 287–290

- Uncertainty in assumptions supporting the numbers of eligible patients, particularly in the number of patients who have poor glycaemic control, resulting in a likely over-estimation of patient numbers.
- The use of a GP survey of 150 practitioners to inform parts of the utilisation estimates.
- The prevalence of diabetes is based on AusDiab data which was very old. The DUSC noted that there was no more reliable data available.
- External factors that will have an impact on prescribing diabetic therapies, both oral and injectable are difficult to quantify and will have a variable impact on the estimates. The sponsor would not have known some of these when preparing the submission. These include:
 - Availability of PBS subsidised sitagliptin which will have an unknown impact on prescriber choices;
 - Removal of TGA registration for two indications for rosiglitazone, and the preferred substituted therapy is not clear in Australia;
 - Continuing ADE reports for exenatide, particularly the development of antibodies;
 - The perception of the clinical benefits of an alternate injectable diabetic medication; and
 - Promotion of insulin therapy earlier in treatment, as an alternative to some oral therapy rather than as a 'last resort' therapy.

Previous reviews by the DUSC

The utilisation of exenatide has been assessed previously by the DUSC in a;

- 12 month predicted vs actual analysis considered at the October 2012 meeting; and as part of;
- Type 2 diabetes medicines analyses presented to the October 2012 and February 2013 DUSC meetings.

Key finding of the 12 month predicted versus actual review include;

The uptake associated with exenatide was approximately 50 % of that expected; however the utilisation of the 5 microgram strength was greater than expected.

In the submission the Sponsor suggested patients would use the 5 microgram strength to initiate therapy, and then increase to the 10 microgram strength for maintenance therapy. The DUSC suggested that one reason for the lower use of the 10 microgram strength may be due to the time previously required to seek authorisation (when exenatide had an Authority Required listing). The DUSC considered that prescribers may be leaving patients on the initial 5 microgram strength until they require a new authority prescription. The DUSC considered that the change of exenatide's listing to an Authority Required (streamlined) benefit could change this utilisation pattern. The DUSC also suggested that the adverse effect profile, particularly nausea, or attainment of sufficient glycaemic control may also be contributing to the higher than expected use of the 5 microgram strength.

Key findings of the type 2 diabetes analysis regarding exenatide include:

- the majority of patients on exenatide (80.3 %) had a history of receiving both metformin and a sulfonylurea in the previous 2 years; and
- some use of exenatide beyond PBS restrictions was apparent, most of which is in combination use with insulin. The DUSC noted that this indication has not been assessed as cost-effective by the PBAC.

Methods

PBS/RPBS prescriptions and benefits paid for exenatide were extracted from the Department of Human Services (DHS) PBS prescription database for the period August 2010 to March 2014 inclusive, based on the date that the prescription was supplied to the patient. Private prescription data were extracted from the DUSC database for the period January 2009 to August 2012.

The number of patients treated was determined by counting the number of individual de-identified personal identification numbers in the R/PBS data for the specified time period. New (initiating) patients were defined as those with no prior PBS or RPBS prescription of the drug or drug group of interest.

Most patients on treatment with exenatide would be expected to receive a supply each month because each pack provides 60 doses, standard dosing is twice daily, and the shelf life for a pen in use is 30 days. However determining point prevalence for exenatide supplied in a calendar month will slightly underestimate prevalence as some patients may have more than 30 days between supplies. For example, a patient may get their next prescription dispensed just before they run out of their previous supply and then may wait until they have completely finished the drug before obtaining the subsequent prescription. Also prevalent patients for exenatide may not receive a supply every month if some doses are missed (i.e. they are not fully adherent). Therefore, prevalent patient numbers were counted quarterly as most patients on treatment would receive a supply at least once each quarter. The quarterly prevalent patient numbers cannot be added to give annual or six-monthly numbers as this would result in some double-counting.

Individual, de-identified patient prescription data were used to examine diabetes medicines supplied prior to initiation of exenatide, and co-administered with exenatide. Utilisation was then compared with the PBS restrictions. To enable drug regimen estimation from the date of PBS listing of exenatide (1 August 2010), prescription data back to July 2009 were used. The methodology is fully described in Appendix A.

Exenatide use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhoea. Therefore a supplementary analysis, using the method described in Appendix A, was undertaken to assess co-administration of exenatide and anti-emetics.

Data manipulation was undertaken using SAS.

Results

Analysis of drug utilisation

Patients

The number of patients initiating and prevalent to treatment with exenatide is shown in Figure 1.

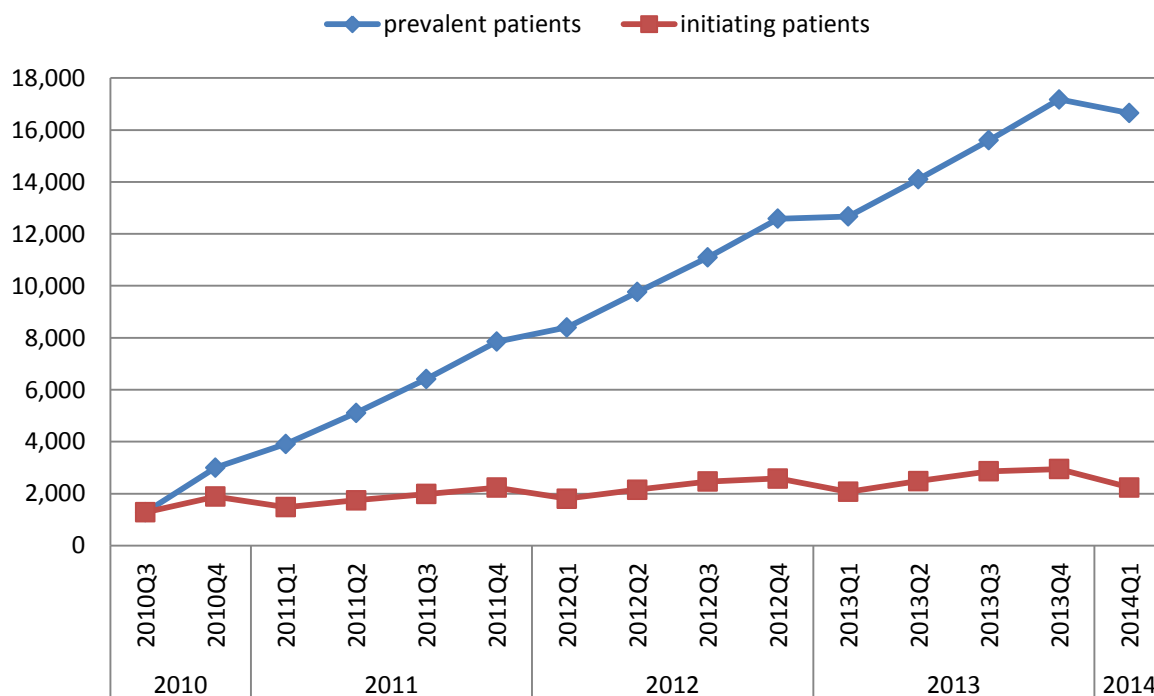


Figure 1: Patients - initiating and prevalent to treatment with exenatide

Note: 2010Q3 only contains 2 months of data as listing occurred 1 August 2010.

Figure 1 illustrates that the number of patients starting exenatide has increased steadily since listing. In the first, second and third years of listing, 6,978, 8,364 and 9,735 patients received their first PBS prescription for exenatide, respectively. As many patients who start on treatment continue into the following years, the number of prevalent patients has increased accordingly. Approximately 17,000 patients were on treatment with exenatide at the end of 2013.

Patient age and gender at initiation to exenatide

Patient age and gender at initiation to exenatide is shown in Figure 2.

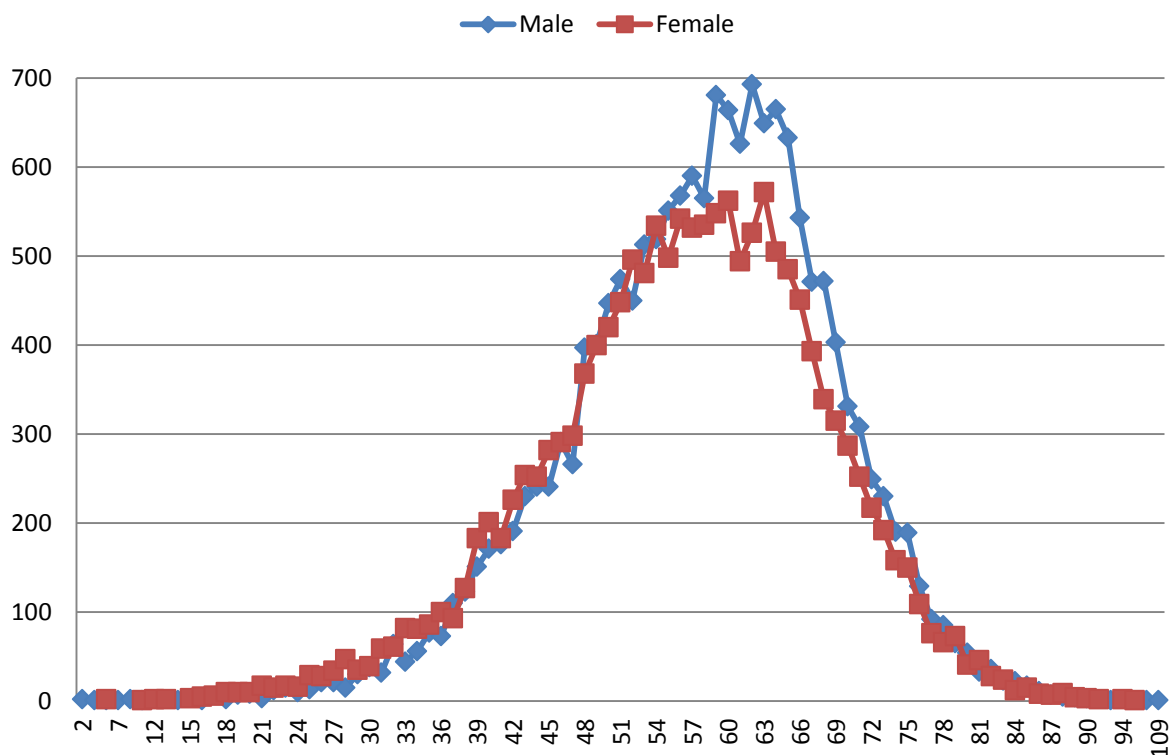


Figure 2: Patient age and gender distribution at initiation to exenatide

Note: Initiations from PBS listing (1 August 2010) to March 2014.

The mean age of patients starting treatment with exenatide is 57.1 years. This is similar to the mean age of patients in the exenatide arms of the three pivotal trials that formed the basis of the PBAC submission of 59.8, 59 and 54.31 years, though noting that two of the trials had an age inclusion criterion of between 30 and 75 years and the third had a criterion of at least 30 years of age.

At the time this analysis was undertaken, the most recent Australian Institute of Health and Welfare estimate of Australians ever diagnosed with type 2 diabetes, by age, was for the period 2007-08 and was reported in 5 year age groups. The median age for these patients falls in the 60-64 years age group (derived from Table A8⁶ on p19 of the report). The median age of patients in initiating PBS subsidised exenatide (Figure 2) is 58 years.

The very small number of patients (n=31) with an age less than 18 years is probably due to administrative misclassification. Information about the patient (such as age and gender) is derived from Medicare enrolment files based on data entered at the time of dispensing. There are some errors in the data owing to incorrect recording of Medicare number and/or errors in the Medicare enrolment file. Overall these errors are small and have minimal impact on the analysis.

⁶ AIHW 2011. Diabetes prevalence in Australia: detailed estimates for 2007-08. Diabetes series no. 17. Cat. no. CVD 56. Canberra: AIHW. Viewed 8 January 2015 <<http://www.aihw.gov.au/publication-detail/?id=10737419311>>.

Prescriptions

The number of PBS, RPBS and private prescriptions supplied for either strength of exenatide is shown in Figure 3.

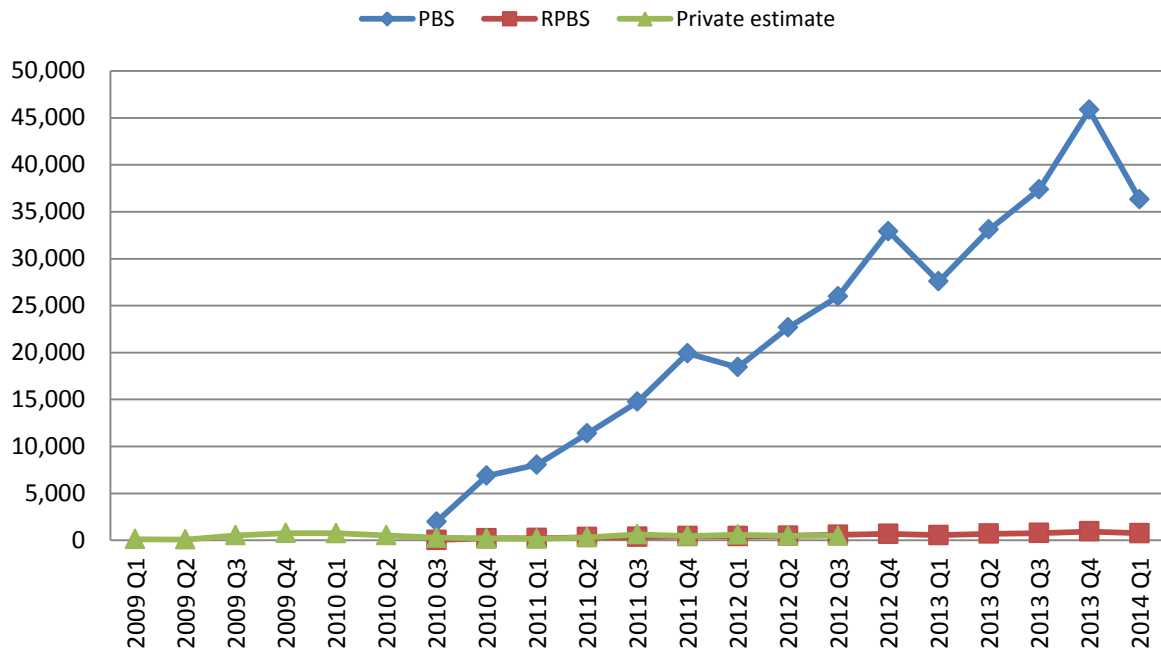


Figure 3: Prescriptions supplied for exenatide by prescription type

Note: The Private Estimate in the DUSC database ceased after August 2012.

Consistent with the increasing number of patients treated with exenatide (see Figure 1), the number of R/PBS prescriptions for exenatide is also increasing. The increase in prescriptions in December and subsequent decline in January each year is due to fluctuations associated with the PBS Safety Net.

The pharmacy survey data available until August 2012 shows some exenatide was being prescribed on private prescription. The DUSC had previously considered that private prescriptions could be for patients on insulin who do not qualify for PBS subsidised exenatide.

The number of prescriptions, classified by their item code (5 microgram or 10 microgram exenatide) is shown in Figure 4.

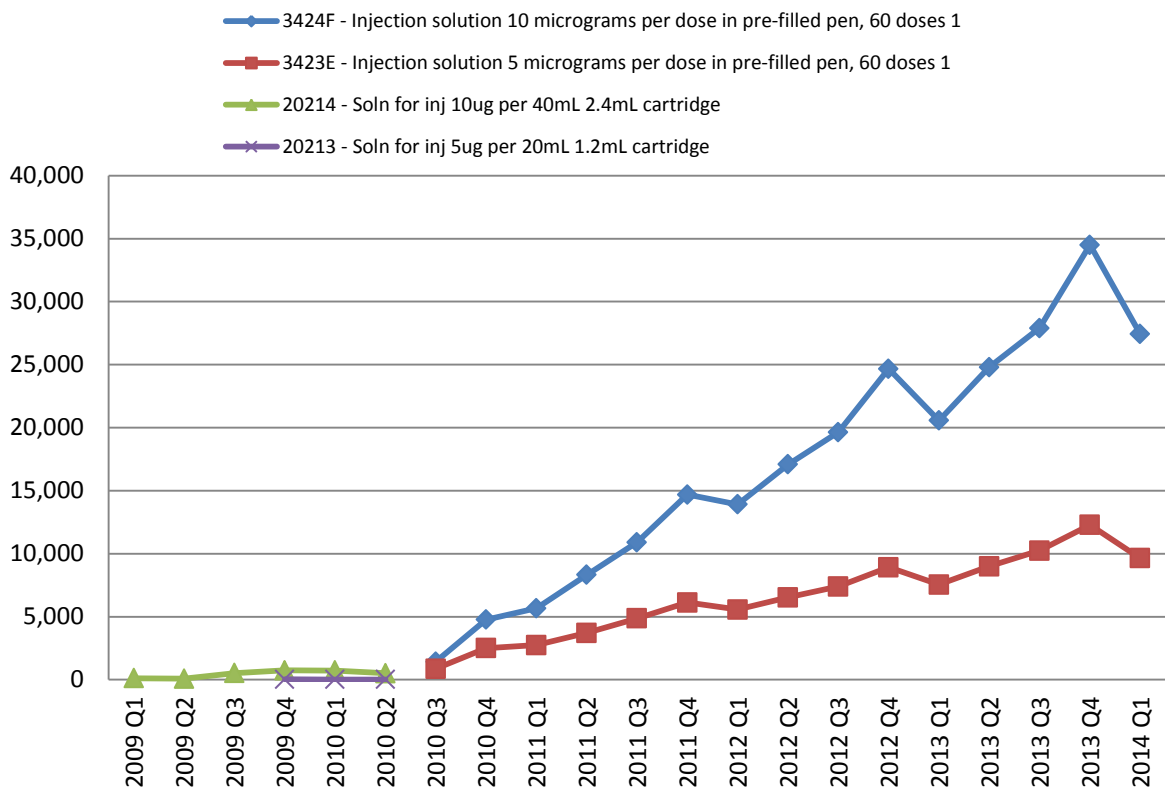


Figure 4: Prescriptions supplied for exenatide by item code

Note: The Private Estimate ceased after August 2012. The items coded 20214 and 20213 are the private item codes used prior to PBS listing of the products. Private use continued post listing (see Figure 3) but was recorded under the PBS item codes.

Patients starting on exenatide are usually prescribed the 5 microgram dose and then may progress to the 10 microgram dose.

Analysis of expenditure

The PBS and RPBS expenditure in the first three years of listing is shown in Table 3. The figures shown are based on the published price for exenatide and hence are indicative only. A special pricing arrangement applies to exenatide. There was a reduction in the published price on 1 December 2013; however the effective price remained unchanged.

Table 3: PBS & RPBS (R/PBS) expenditure (published price, date of supply)

Year 1	Year 2	Year 3
Aug10 to Jul11	Aug11 to Jul12	Aug12 to Jul13
\$5,367,202	\$13,059,861	\$20,255,282

Note: Special pricing arrangements apply to exenatide and there was a reduction in the published price for both items on 1 December 2013 however the effective price remained unchanged.

Analysis of actual versus predicted utilisation

The predicted and actual numbers of patients initiating treatment with exenatide in the first three years of PBS listing is shown in Table 4.

Table 4: Predicted versus actual initiating PBS patients

	Year 1	Year 2	Year 3
	Aug10 to Jul11	Aug11 to Jul12	Aug12 to Jul13
Predicted (P)	8,088	8,538	7,749
Actual (A)	6,978	8,364	9,735
Difference (A-P)	-1,110	-174	1,986
% Difference (A-P)/P	-14%	-2%	+26%

The predicted and actual numbers of prevalent patients treated with exenatide in the first three years of PBS listing is shown in Table 5.

Table 5: Predicted versus actual prevalent PBS patients

	Year 1	Year 2	Year 3
	Aug10 to Jul11	Aug11 to Jul12	Aug12 to Jul13
Predicted (P)	8,088	15,009	19,757
Actual (A)	6,978	13,436	19,485
Difference (A-P)	-1,110	-1,573	-272
% Difference (A-P)/P	-14%	-10%	-1%

In the predicted versus actual analysis the number of initiating patients is determined by counting the number of individuals receiving their first R/PBS prescription for exenatide. The number of prevalent patients is a count of patients who received at least one exenatide prescription in the year.

In the third year of listing 26 % more patients initiated exenatide than predicted, whilst the number of prevalent patients was approximately as predicted (i.e. -1 %). The difference in the ratio of initiating to prevalent treated patients is probably because the market for exenatide has not yet stabilised. The submission determined the eligible prevalent pool for exenatide (see Table 2), and assumed an increasing uptake within this pool (10 % in Y1 to 23 % in Y3). New patients were calculated from the predicted percentage uptake in the prevalent pool minus patients remaining on treatment from the previous year. Twenty percent of new patients were assumed to cease treatment after one prescription. The submission did not otherwise account for patients ceasing treatment for example due to patients no longer achieving adequate glycaemic control with exenatide.

The predicted versus actual numbers of prescriptions supplied in the first three years of listing are shown in Table 6.

Table 6: Predicted vs Actual prescriptions

	Year 1	Year 2	Year 3
	Aug10 to Jul11	Aug11 to Jul12	Aug12 to Jul13
Predicted (P)	65,071	116,604	149,998
Actual (A)	33,601	81,386	126,004
Difference (A-P)	-31,470	-35,218	-23,994
% Difference (A-P)/P	-48%	-30%	-16%

In Year 1 the lower than expected number of prescriptions is partly due to the submission not applying a “half cycle” correction (i.e. not allowing for patient initiations being spread throughout the year). Application of a “half-cycle” correction to all patients would not have been appropriate in this case as there was an assumed non-PBS prevalent pool of patients using private prescriptions prior to listing.

By Year 3, the number of prevalent patients treated with exenatide was approximately as expected, although the number of prescriptions was 16 % lower than expected.

The predicted versus actual prescriptions for exenatide in the first three years of listing by strength are shown in Table 7.

Table 7: Predicted vs Actual prescriptions by PBS item

	Year 1	Year 2	Year 3
	Aug10 to Jul11	Aug11 to Jul12	Aug12 to Jul13
PBS item:	3423E - 5 microgram	3423E - 5 microgram	3423E - 5 microgram
Predicted (P)	6,834	8,538	7,749
Actual (A)	11,121	23,070	33,651
Difference (A-P)	4,287	14,532	25,902
% Difference (A-P)/P	63%	170%	334%
PBS item:	3424F - 10 microgram	3424F - 10 microgram	3424F - 10 microgram
Predicted (P)	58,237	108,066	142,249
Actual (A)	22,480	58,316	92,353
Difference (A-P)	-35,757	-49,750	-49,896
% Difference (A-P)/P	-61%	-46%	-35%

The submission assumed that:

- *‘Each patient will be dispensed only one 5 microgram pen at the initiation of therapy, thereafter all patients will advance to 10 microgram pens. The Australian approved PI recommends that the 5 microgram pen is used for the first month of therapy to reduce gastrointestinal side effects. Some patients may need to use the 5 microgram pen beyond the first month of treatment but this extended usage is anticipated to be low. As the 5 microgram pen and 10 microgram pen are priced equivalently there is no financial benefit to the patient to continue on the lower dose.*
- *For simplicity, we have assumed all patients will be prescribed a maximum of 1x5 microgram pen, followed by 9x10 microgram pens per annum’*

In Advice to the PBAC for the November 2008 PBAC submission, the DUSC had considered that some variation in practice (from the assumption that patients will increase to the 10 microgram dose after the first month) would be expected, particularly if some of the side effects of treatment, such as nausea, are dose dependent.

Table 7 shows that the 5 microgram item was used much more than predicted, especially in Year 3, whilst the 10 microgram item was used less than expected. The most likely explanation is that a proportion of patients remain on 5 microgram exenatide twice daily beyond the one month initiation period. In one of the clinical trials presented in the submission, 18.6 % of patients at the completion of the study were on 5 microgram exenatide.⁷ An observational study of 452 type 2 diabetes patients in the United States reported that 28 % of patients continue to use 5 microgram exenatide twice daily six months after initiation.⁸

To help elucidate the reasons for the greater than predicted utilisation of 5 microgram exenatide, a prescription sequence analysis was performed at the PBS item level. For each patient, the strength of each exenatide prescription and the exenatide prescription immediately before it was determined for all prescriptions in the period from August 2010 to March 2014, inclusive. The results of this analysis are shown in Table 8.

Table 8: Exenatide prescription by strength and strength of prior prescription

Prior prescription strength	Prescription strength	Prescriptions	% Prescriptions
None	5 microgram	22,742	6.6 %
5 microgram	5 microgram	66,927	19.3 %
5 microgram	10 microgram	19,264	5.6 %
None	10 microgram	9,513	2.7 %
10 microgram	10 microgram	222,273	64.1 %
10 microgram	5 microgram	6,157	1.8 %

As can be seen in Table 8, most prescriptions (64.1 %) are for continuing treatment on 10 microgram. However there are some sequences not accounted for in the submission that would have contributed to the greater than expected utilisation of the 5 microgram strength. These are;

- 5 microgram → 5 microgram (19.3 %), continuation on 5 microgram; and
- 10 microgram → 5 microgram (1.8 %), down titrating from 10 microgram to 5 microgram.

Some patients (2.7 %) also received the 10 microgram strength as their first PBS prescription. These patients may have been on private prescription of exenatide prior to listing or have initiated in hospital and therefore titration not captured in the PBS data.

Overall, approximately one quarter of the 5 microgram prescriptions were for initiation and titration and the remaining three quarters for ongoing therapy explaining the difference in predicted versus actual estimates by strength. The DUSC suggested that the higher than

⁷ Heine RJ1, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; 143(8):559-69.

⁸ Bergenstal RM1, Garrison LP Jr, Miller LA, Hou L, Blickensderfer A, Zagar A, et al. Exenatide BID Observational Study (ExOS): results for primary and secondary endpoints of a prospective research study to evaluate the clinical effectiveness of exenatide BID use in patients with type 2 diabetes in a real-world setting. *Curr Med Res Opin* 2011; 27(12):2335-42. doi: 10.1185/03007995.2011.628305.

expected use of the 5 microgram strength may also be because of some combination use as an insulin sparing agent. The extent of this could not be assessed because whilst the analysis reported the extent of co-administration of exenatide with insulin (see Figure 5 and Table 10), this analysis was not performed for the separate strengths of exenatide.

The DUSC had previously suggested (October 2012) that a possible reason for the higher than expected use of the 5 microgram strength could be the adverse event profile, particularly nausea. The DUSC noted that the current analysis did not suggest a significant amount of co-administration of exenatide and antiemetics (see Table 12 and Figure 7), and that if nausea was experienced while on exenatide therapy that it was not being treated with PBS subsidised pharmacotherapy.

The predicted versus actual R/PBS expenditure for exenatide in the first three years of listing is shown in Table 9. The figures are based on the published price and the date of supply.

Table 9: Predicted vs Actual R/PBS expenditure (published, date of supply)

	Year 1	Year 2	Year 3
	Aug10 to Jul11	Aug11 to Jul12	Aug12 to Jul13
Predicted (P)	\$9,745,956	\$17,464,375	\$22,465,934
Actual (A)	\$5,367,202	\$13,059,861	\$20,255,282
Difference (A-P)	-\$4,378,754	-\$4,404,514	-\$2,210,652
% Difference (A-P)/P	-45 %	-25 %	-10 %

The submission predictions of expenditure were based on the published price of exenatide. The percentage differences between predicted and actual expenditure are similar to differences for overall prescription utilisation (see Table 5).

The effective expenditure was not predicted in the submission.

Exenatide Treatment Patterns

Co-administration analysis

The PBS restrictions for exenatide are as dual therapy with either metformin or a sulfonylurea, or as triple therapy with both metformin and a sulfonylurea. The restriction note specifies that exenatide is not PBS-subsidised for use as monotherapy or in combination with a gliptin, a glitazone, insulin or a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Figure 5 shows the ten most common exenatide containing regimens. The data is shown from August 2012 as regimens for all patients (general, concessional and safety net) can be estimated including medicines priced below the general patient co-payment. Collection of under co-payment prescriptions by the Department of Human Services commenced in April 2012. Detailed methodology on the estimation of drug regimens is provided in Appendix A.

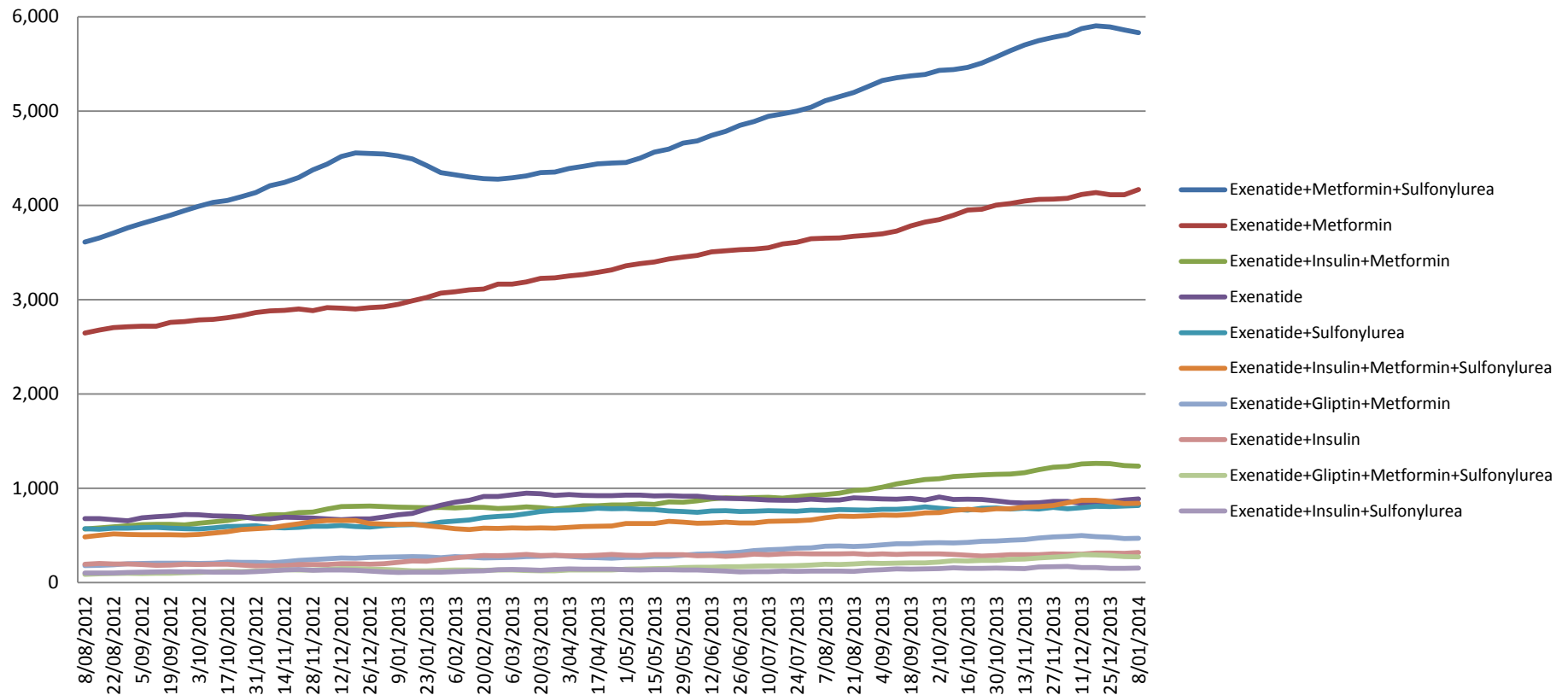


Figure 5: Top 10 exenatide containing regimens

The most common regimens are exenatide as triple therapy with metformin and a sulfonylurea and exenatide as dual therapy with metformin. The use of exenatide with metformin and insulin is increasing and has become the third most common regimen since August 2013. This regimen is not consistent with the PBS restriction. Figure 5 also shows that 7 of the top 10 regimens, representing 27.9 % of the top ten exenatide regimens at the most recent time point, do not align with the PBS restrictions. Table 10 provides more details.

Table 10: Exenatide containing regimens (as at 8 January 2014) by therapy type and compliance with PBS restrictions

Compliance with PBS restriction	Therapy Type	Drug regimen ²	Patients	% Patients
Within PBS restriction	Dual	Exenatide+Metformin	4,169	26.5 %
		Exenatide+Sulfonylurea	818	5.2 %
	Dual Total		4,987	31.7 %
	Triple	Exenatide+Metformin+Sulfonylurea	5,832	37.1 %
Within PBS restriction Total			10,819	68.9 %
Outside PBS restriction	Mono	Exenatide	886	5.6 %
	Dual	Exenatide+Insulin	320	2.0 %
		Exenatide+Gliptin	42	0.3 %
		Other regimens with < 20 patients each	14	0.1 %
		Dual Total	376	2.4 %
	Triple	Exenatide+Insulin+Metformin	1,235	7.9 %
		Exenatide+Gliptin+Metformin	471	3.0 %
		Exenatide+Insulin+Sulfonylurea	153	1.0 %
		Exenatide+Gliptin+Sulfonylurea	86	0.5 %
		Exenatide+Metformin+Pioglitazone	47	0.3 %
		Acarbose+Exenatide+Metformin	31	0.2 %
		Acarbose+Exenatide+Sulfonylurea	10	0.1 %
		Other regimens with < 20 patients each	40	0.3 %
	Triple Total	2,073	13.3 %	
	Quad or more	Exenatide+Insulin+Metformin+Sulfonylurea	840	5.3 %
Exenatide+Gliptin+Metformin+Sulfonylurea		272	1.7 %	
Other regimens with < 20 patients each		203	1.3 %	
Exenatide+Metformin+Pioglitazone+Sulfonylurea		106	0.7 %	
Acarbose+Exenatide+Metformin+Sulfonylurea		95	0.6 %	
Exenatide+Gliptin+Insulin+Metformin		38	0.2 %	
Quad or more Total	1,554	9.9 %		
Outside PBS restriction Total			4,889	31.1 %
Total			15,708	100.0 %

Note: Combination products are represented as their components in the above regimens.

Exenatide is most commonly prescribed as a component of triple therapy, representing 50.4 % of regimens. For regimens that meet the PBS restrictions, triple therapy regimens are slightly more common than dual therapy regimens.

Use of exenatide outside the PBS criteria is occurring in approximately 31 % of cases, with 17.4 % of all patients on exenatide in January 2014 using exenatide in combination with insulin. The February 2013 DUSC analysis found that 16 % of exenatide was co-administered with insulin (in a prevalent snapshot of concessional patient regimens in May 2012).

The remaining regimens that are outside of the PBS criteria involve monotherapy or co-administration with a gliptin, a glitazone or a SGLT2 inhibitor. Exenatide was prescribed as monotherapy in 5.6 % of patients and as quadruple therapy in 9.9 % of patients. In the pre-Subcommittee response the sponsor of exenatide stated that all apparent monotherapy use may not be single agent use since patients could also be receiving other therapies as private prescriptions. The DUSC agreed that this is possible and if it is occurring would be more apparent in the General patients than concessional patients. The proportion of "concession only" patients using exenatide monotherapy of 5.2 % (361 of 6,931 patients) is similar to that in the total population of 5.6 % (886 of 15,708). By inference, the extent of monotherapy in the concessional only and general population is similar.

A concern raised by stakeholders with the February 2013 DUSC analysis of diabetes medicines, was the representativeness of the concession only population. A concession-only cohort was required at this time because some diabetes medicines are priced below the general PBS co-payment and for general beneficiary patients supply was not captured in the dataset. The DUSC considered that 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, and also noted that the majority of patients with diabetes are concession patients. The current analysis, with results shown in Figure 5 and Table 10, includes all patients (concessional and general). For comparison the same analysis undertaken in the concession only population is provided in Appendix B. Compared with 17.4 % of all patient regimens being in combination with insulin, the concession only cohort result is 19.3 % confirming that there is not a large difference in the regimen distribution between the concessional only cohort and all patients on exenatide. Comparing the distribution of the top 10 exenatide containing regimens for all patients in Figure 6 with the concession only cohort in Appendix B, shows that the drug regimens are similar for the two cohorts.

Place of exenatide in therapy

To improve our understanding of the place of exenatide in therapy, the current analysis examines regimens used immediately prior to initiation of exenatide. This analysis was undertaken in a cohort of patients (n=2,072) who received their first PBS prescription for exenatide between January 2013 and March 2013, inclusive. This time period represents a reasonable balance between recent clinical practice and having sufficient period of time prior to initiation (6 months of under co-payment data) and after initiation (12 months follow-up) to distinguish switching and co-administration of medicines. Full details of the methodology are provided in Appendix A. The results of the analysis are presented in Table 11 and Figure 6.

Table 11: Top 25 drug regimen transitions at initiation

Rank	Pre-initiation regimen (week=-1)	Post-initiation regimen (week=0)	Patients	% Patients
1	Metformin+Sulfonylurea	Exenatide+Metformin+Sulfonylurea	356	17.2 %
2	Metformin	Exenatide+Metformin	154	7.4 %
3	Insulin+Metformin	Exenatide+Insulin+Metformin	129	6.2 %
4	None	Exenatide	116	5.6 %
5	Gliptin+Metformin	Exenatide+Metformin	113	5.5 %
6	Gliptin+Metformin	Exenatide+Gliptin+Metformin	75	3.6 %
7	Insulin+Metformin+Sulfonylurea	Exenatide+Metformin+Sulfonylurea	61	2.9 %
8	Gliptin+Metformin+Sulfonylurea	Exenatide+Metformin+Sulfonylurea	53	2.6 %
9	Insulin+Metformin	Exenatide+Metformin	52	2.5 %
10	Metformin+Sulfonylurea	Exenatide+Metformin	52	2.5 %
11	Insulin	Exenatide+Insulin	52	2.5 %
12	Insulin+Metformin+Sulfonylurea	Exenatide+Insulin+Metformin+Sulfonylurea	44	2.1 %
13	Sulfonylurea	Exenatide+Sulfonylurea	42	2.0 %
14	Metformin	Exenatide	37	1.8 %
15	Gliptin+Metformin+Sulfonylurea	Exenatide+Gliptin+Metformin+Sulfonylurea	35	1.7 %
16	Metformin+Pioglitazone+Sulfonylurea	Exenatide+Metformin+Sulfonylurea	31	1.5 %
17	Gliptin+Metformin+Metformin	Exenatide+Metformin	30	1.4 %
18	None	Exenatide+Metformin	26	1.3 %
19	Gliptin+Sulfonylurea	Exenatide+Sulfonylurea	25	1.2 %
20	Gliptin+Metformin	Exenatide+Metformin+Sulfonylurea	23	1.1 %
21	Metformin+Sulfonylurea	Exenatide+Sulfonylurea	20	1.0 %
22	Gliptin+Metformin+Metformin+Sulfonylurea	Exenatide+Metformin+Sulfonylurea	20	1.0 %
23	Insulin+Metformin	Exenatide+Insulin	20	1.0 %
24	Insulin+Metformin	Exenatide+Metformin+Sulfonylurea	18	0.9 %
25	Insulin	Exenatide	16	0.8 %
		Other transitions	472	22.8 %
		Grand Total	2,072	100.0 %

Note: Combination products are represented as their components in the above regimens

The regimens used immediately prior to exenatide are diverse. Most frequently exenatide was initiated as add on therapy to metformin and a sulfonylurea (17.2 %). Exenatide added to metformin was the next most common regimen (7.4 %). The third most common was use of exenatide as add on to metformin and insulin (6.2 %). This may represent use as an insulin sparing regimen but is not a regimen that meets subsidy criteria. The fourth most common regimen transition was from no therapy to monotherapy exenatide (5.6 %).

Of the top 25 drug regimen transitions at initiation to exenatide, 64 % are exenatide added on to the prior regimen and 36 % are exenatide substituting at least one drug in the prior regimen. Of the add-on transitions, 22 % are add-ons to a regimen containing insulin. Of the substituting transitions, 26 % are substituting insulin.

When considering prevalent patients treated with exenatide (Figure 5) approximately 17.4 % were on a regimen containing insulin. In the cohort of patients initiating exenatide

between January and March 2013, 572 (28 %) were on an insulin containing regimen just prior to initiation to exenatide (i.e. week = -1). Of these, 387 patients (68 %) were on an insulin containing regimen at initiation (i.e. week 0) (i.e. exenatide was added to insulin) and 185 patients (32 %) were on an insulin free regimen (i.e. exenatide substituted insulin).

Figure 6 illustrates changes in regimens in the first 11 months after initiation to exenatide.

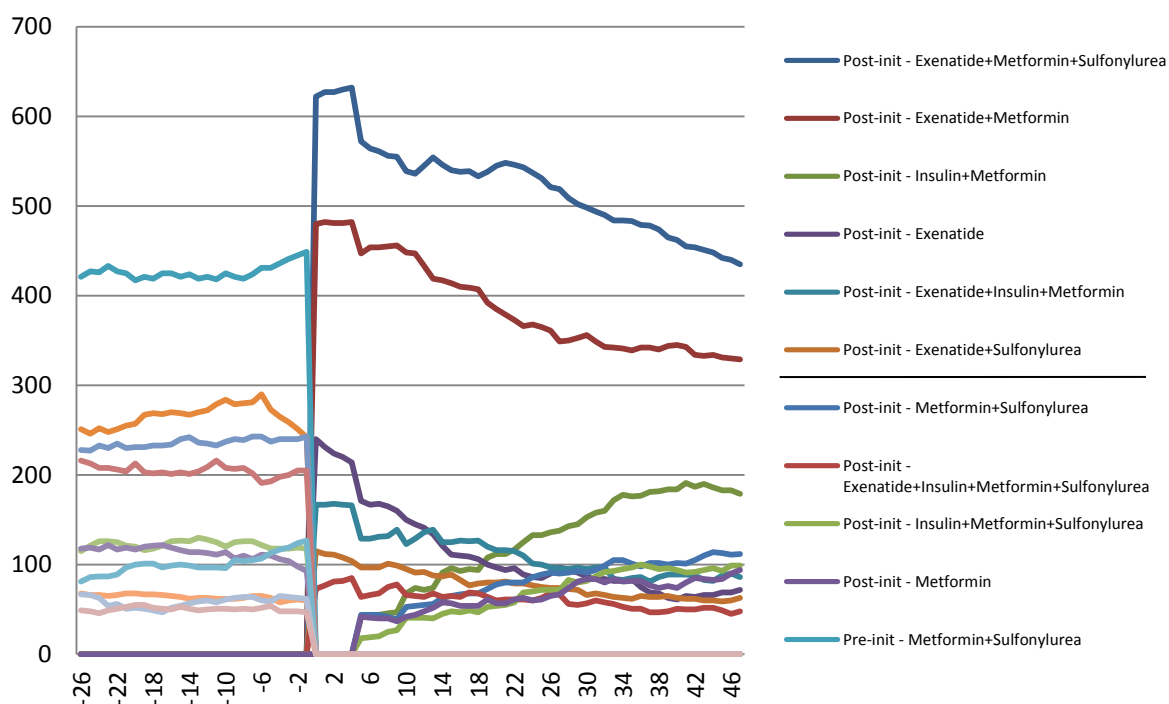


Figure 6: Treatment regimens pre & post initiation to exenatide

There is significant shift away from exenatide containing regimens in the 12 months post-initiation. Of the 2,072 patients who initiated in this period 1,396 (67 %) and 1,171 (57 %) were still on an exenatide containing regimen after 6 and 11 months (i.e. 48 weeks), respectively. An observational study conducted by Bergenstal et al.⁸ reported that after 6 and 12 months, 66.6 % and 54.0 % respectively of the original 452 patients were still on exenatide treatment. This is very similar to the continuation rates in this analysis.

The submission Section E assumed that 20 % of patients would stop treatment after one pen (i.e. one prescription). Although not explicit in the submission, this was presumably based on completion rates of 80.6 % and 78 % or discontinuation rates of 8-9 % reported for the two key trials presented in the submission. The current analysis shows that there were 1,760 patients (85 %) remaining on an exenatide regimen at week 5. Thus the discontinuation rate after one script was 15 % which is reasonably close to the assumption in the submission.

Use of exenatide with anti-emetics

Drugs for nausea and vomiting treatment were added to the co-administration analysis. The drugs included are presented in Table 12.

Table 12: Anti-emetics used in co-administration analysis

PBS ATC code	Drug Name
A03FA01	Metoclopramide
A03FA03	Domperidone
A04AA01	Ondansetron
A04AA02	Granisetron
A04AA03	Tropisetron
A04AA04	Dolasetron
A04AA05	Palonosetron
A04AD12	Aprepitant
A04AD	Prochlorperazine
A04AD	Promethazine

Drug regimens containing an anti-emetic for patients initiating exenatide for the period January to March 2013 are shown in Figure 7.

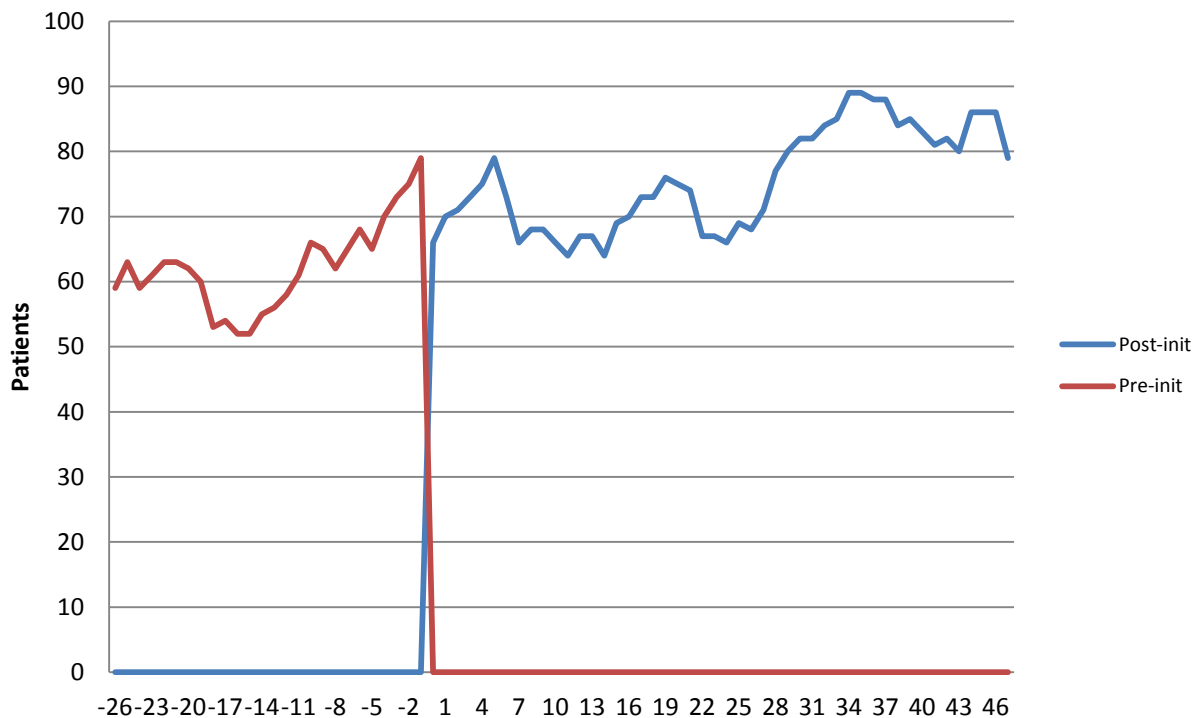


Figure 7: Drug regimens containing an anti-emetic for patients initiating exenatide from January to March 2013 inclusive.

Figure 7 shows that anti-emetic drugs were used relatively infrequently. The rate of anti-emetic drug use does not appear to be much higher following initiation of exenatide. At week 5 after initiation only 79 patients (3.8 %) of the 2072 patients initiating to exenatide had a regimen containing an anti-emetic.

DUSC actions

- The DUSC requested that the report be provided to the PBAC, noting that while the extent of utilisation has been similar to predicted at the time of listing, patterns of exenatide use are diverse and not all use is consistent with the PBS restrictions.
- The DUSC considered that education may be required on the PBS prescribing criteria for exenatide.

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.

Sponsor's comments

AstraZeneca Pty Ltd: The sponsor has no comment.

Appendices

Appendix A:

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 A1 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 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 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 2nd 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.

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.

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 3rd 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 stockpiling rule
5. Estimating if a patient is continuing or stopping 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 None \rightarrow A (starting therapy).

The transitions can be;

- A. previous drug regimen \rightarrow drug regimen at week x, or
- B. drug regimen at week -1 \rightarrow drug regimen at week x

Option A has the advantage that it can be calculated at any week, whereas Option B can only be calculated after initiation (i.e. from week 0). The main advantages of Option B are that it can easily be used to adjust the drug regimen in the first few weeks after initiation to allow for switching when the prior medication is not fully used. That is, if a patient switches from A to B, in the first few weeks after initiation to drug B the drug regimen may be incorrectly estimated to be A+B if the patient still has drug A "on hand" (i.e. some is unused) when drug B is initiated.

The regimen transitions are adjusted so that if a regimen transition corresponding to a switch (e.g. $A \rightarrow B$) is detected within the first X weeks after initiation (e.g. at week Y), then all weeks between the initiation (i.e. week 0) and week Y are modified to the switch transition (i.e. $A \rightarrow B$). This means some instances of " $A \rightarrow A+B$ " (apparent co-administration after a switch) are modified to " $A \rightarrow B$ " from week 0 to week Y (where $Y \leq X$). The value of X is the 1 week + SCD (expressed in weeks) for the drug or drug group that is being substituted.

This means that if a drug A was supplied 1 day before an initiation to drug B and then there were no further supplies of drug A, then there would be apparent co-administration of A and B from week 0 to week X-1 and in week X the drug regimen would be drug B only and considered a switch. Thus the regimens from weeks 0 to X-1 would be modified to be drug B only. If a switch is first detected in week X+1 then the A script would have been supplied in week 0 (i.e. at or after initiation to drug B) and this would mean that the transition was not a switch, but an add. Thus the logic is only applied to weeks 0 to X.

A transition is considered a switch if a drug in the regimen prior to initiation (the week=-1 regimen) is not in the regimen post initiation (i.e. the week=0 regimen).

After this transition adjustment, the drug regimens can also be adjusted by using the regimen after the arrow in the adjusted regimen transition. That is, if a transition gets adjusted from $A \rightarrow A+B$ to $A \rightarrow B$ in week Y then the adjusted drug regimen for week Y changes from $A+B$ to B. Thus even though the drug regimen is calculated first, its adjustment is dependent on both the regimen transition and adjusted regimen transition. Thus the sequence of calculations is;

1. drug regimens
2. drug regimen transitions around initiation
3. adjusted drug regimen transitions
4. adjusted drug regimens

The above adjustment process is reliant on having regard to drug initiations. If the analysis is for prevalent drug regimens only (i.e. regimens by calendar week and not relative to an initiation date) then the above adjustment is not possible. This is not a major problem as the overestimation of co-administration (e.g. $A \rightarrow A+B$ instead of $A \rightarrow B$) is greatest in the month after initiation. In a prevalent patient analysis, patient initiations (to any and all drugs) are spread out in time (i.e. all patients do not generally initiate in the same week), and so the overestimation is also spread out over time and so minimised. In an initiating patient analysis, all over-estimations occur at the same time (as time is relative to the initiation week) and so the overestimation is significant and so needs to be adjusted for. In theory in a prevalent patient analysis, it is possible to do an initiation analysis for every drug and so find adjusted drug regimens that can then be re-expressed in calendar weeks. In practice this is too resource intensive and is unlikely to be make a significant difference to the prevalent patient drug regimens.

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 refill date of the previous 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 $n \times \text{SCD}$; and,
- the actual refill date of the previous 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).

4. Change in the rules for prescriptions whose coverage spans the initiation data; - 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 x 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 x SCD.

Table A1: Standard Coverage Days used in this analysis

Drug or Drug Group	Standard Coverage Days (i.e. Median time to re-supply by any item of the same drug or drug group)
Acarbose	31
Antiemetic	35
Dapagliflozin	28*
Exenatide	32
Gliptin	29
Insulin	80
MetGlipCombo	29
MetRosiCombo	30
MetSulfCombo	27
Metformin	32
Pioglitazone	29
Rosiglitazone	28
Sulfonylurea	31

* The number of dapagliflozin prescriptions included in the analysis is small and so the estimate is uncertain.

**Appendix B:
Estimated drug regimens for “Concession Only” patients**

The “Concession Only” cohort is defined as those patients who initiated exenatide in the period August 2010 to March 2014 inclusive and who did not have a General Patient script in the period July 2009 to March 2014.

It is possible to show a longer time series of drug regimens for “Concession Only” patients as patient level under-co-payment prescriptions were not required to estimate drug regimens.

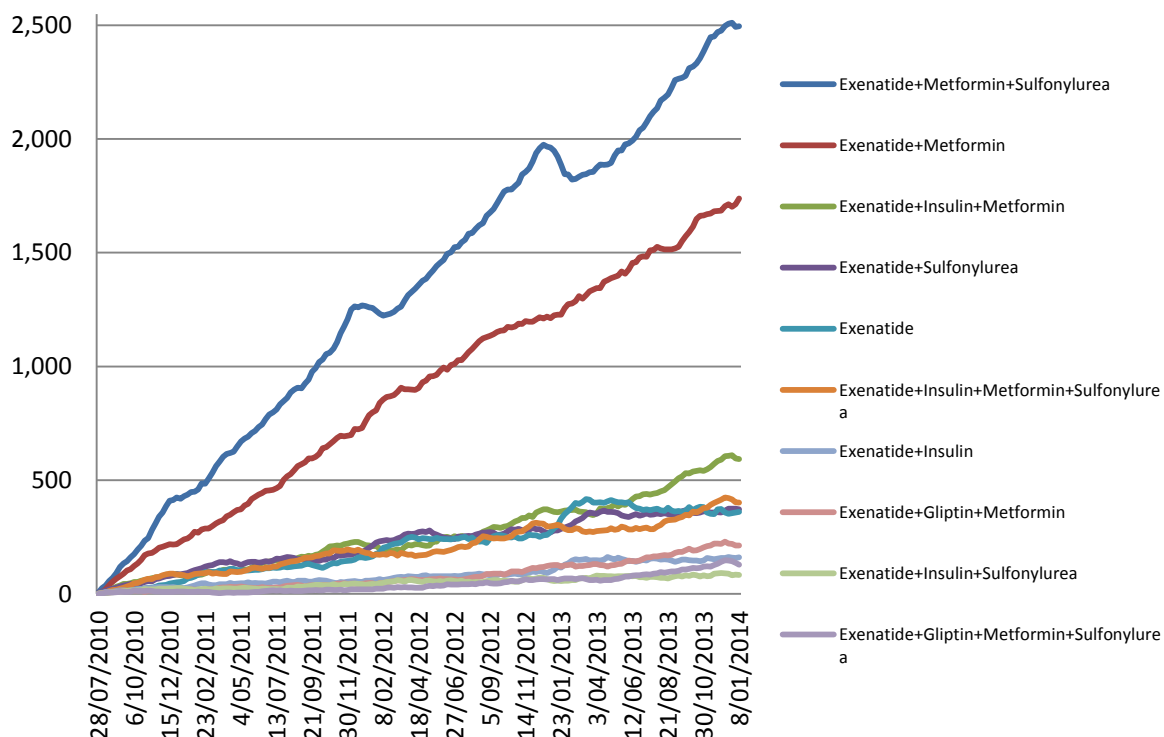


Figure C.1: Top 10 exenatide containing regimens for Concession Only patients

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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