

7.03 EXENATIDE
2 mg, powder for injection, vial
Bydureon®
AstraZeneca Pty Ltd

1 Purpose of Application

1.1 Authority required (STREAMLINED) listing for exenatide 2 mg once weekly for the treatment of type 2 diabetes mellitus (T2DM) as dual or triple therapy in combination with metformin and/or a sulfonylurea at a higher price than that previously requested.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
EXENATIDE Powder for injection 2 mg	4	5	\$ [REDACTED]	Bydureon® AZ

Abbreviated version (refer to Section 8 for complete details of the recommended restriction)

Dual combination therapy with metformin or a sulfonylurea	
Indication	Type 2 diabetes mellitus
Restriction	Authority Required (streamlined)
Clinical criteria	The treatment must be in combination with metformin OR The treatment must be in combination with a sulfonylurea AND patient must have a contraindication to a combination of metformin and a sulfonylurea OR patients must not have tolerated a combination of metformin and a sulfonylurea AND patient must have, or have had, a HbA1c measurement greater than 7%
Triple combination therapy with metformin and a sulfonylurea	
Clinical criteria	The treatment must be in combination with metformin AND the treatment must be in combination with a sulfonylurea AND patient must have, or have had, a HbA1c measurement greater than 7%

- 2.1 The re-submission did not dispute the clinical claim accepted by the PBAC at the November 2013 meeting that exenatide once weekly has at least non-inferior efficacy and non-inferior safety compared to exenatide 10 mcg twice daily.
- 2.2 Compared to the November 2013 re-submission that requested a DPMQ of \$ [REDACTED], this re-submission requested a higher price of \$ [REDACTED] for a 28-day supply. The price advantage is based on a cost-analysis, including analysis of the treatment of patients with a high clinical need, and a local willingness to pay (WTP) study. The reference to the special pricing arrangement was also removed since the special pricing arrangement for exenatide twice daily expired in April 2015.
- 2.3 The re-submission indicated that a new dual chamber pen (containing a vial of powder, a prefilled syringe of diluent, a vial connector and two needles), rather than the single dose tray that currently has TGA approval, has been submitted to the TGA for regulatory approval. The re-submission stated that, due to legislative instrument 99ACB, the sponsor is only intending to launch one presentation of exenatide

weekly. The Secretariat noted that if the PBAC recommends exenatide weekly for listing at the proposed price, a minor submission to the PBAC would be required to request a change to the recommended listing to the dual chamber pen presentation. The Pre-Sub Committee Response (PSCR) stated that the current submission is for both the single dose tray and the dual chamber pen presentations of exenatide. The Secretariat confirmed that a secretariat listing submission will be required to request listing of the dual chamber pen presentation following TGA registration.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Exenatide 2 mg powder for injection once weekly was TGA registered on 20 December 2012 for the treatment of T2DM in combination with metformin, sulfonylureas or metformin and a sulfonylurea, in patients who have not achieved adequate glycaemic control.
- 3.2 This was the fourth submission to the PBAC for exenatide 2 mg once weekly. Previous submissions were considered in July 2011 and November 2013 with a minor submission in July 2013.
- 3.3 At its July 2011 meeting, the PBAC rejected the submission for exenatide once weekly on the basis of uncertain cost-effectiveness, with particular concern over the model assumptions regarding duration of treatment benefit, timing of the switch to insulin, disutilities associated with gastrointestinal events and injections, and overestimation of cardiovascular benefits. The claim of non-inferior safety to the twice daily injection was also considered uncertain, as the long-term safety of exenatide once weekly was unknown.
- 3.4 At its July 2013 meeting, the PBAC rejected the minor submission for exenatide 2 mg once weekly on the basis that no new data was presented to support the claims of comparative effectiveness and safety and unclear cost-offsets.
- 3.5 At its November 2013 meeting, the PBAC approved the requested listing for exenatide 2 mg once weekly as an Authority Required (Streamlined) benefit for dual combination therapy with metformin or a sulfonylurea and triple combination therapy with metformin and a sulfonylurea in patients with type 2 diabetes, on a cost-minimisation basis with exenatide 10 mcg twice daily. The PBAC considered that the data presented supported exenatide once weekly being at least non-inferior to exenatide twice daily in terms of efficacy and non-inferior in terms of safety. The Committee agreed that while some cost offsets for reduced needle use would be appropriate, the assumption in the submission of 100% compliance with twice daily exenatide dosing and use of a new needle for each dose was not substantiated by any data. The PBAC considered that approximately 50% of that use would be a reasonable basis for a claimed offset and that this be used in pricing negotiations.

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

4 Clinical place for the proposed therapy

- 4.1 The re-submission assumed that exenatide weekly would mainly substitute for exenatide twice daily and that additional use would occur in patients of high clinical need (said to be the Indigenous, aged and mental health population). The ESC considered this was reasonable.
- 4.2 The re-submission suggested that fewer patients would be eligible for exenatide because the sodium-glucose co-transporters (SGLT2s) are now PBS listed and are aligned with the dipeptidyl peptidase-4 inhibitors (DPP-4s, also known as gliptins). The ESC considered this was reasonable.

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

5 Comparator

- 5.1 As accepted by the PBAC for the November 2013 re-submission, the current re-submission nominated exenatide 10 mcg twice daily as the main comparator. The ESC considered this remained the appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an individual (1) and a health care professional (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with exenatide once weekly including the acceptability to patients who are eager to avoid injectables, better compliance and fewer side effects. The comments also claimed that exenatide once weekly has clearly superior efficacy and tolerability to exenatide twice daily. The PBAC noted that superior efficacy was not reflective of the submission's claim. The current submission accepted the PBAC's November 2013 consideration that there were issues about the appropriateness of pooling of the trial data used to support the superiority claim and that the data presented supported exenatide once weekly being at least non-inferior to exenatide twice daily.

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

Clinical trials

- 6.3 No new clinical trial data were provided in the re-submission.

Comparative effectiveness

- 6.4 At its November 2013 meeting, the PBAC accepted that exenatide 2 mg once weekly has non-inferior efficacy to exenatide 10 mcg twice daily. This was not disputed in the re-submission. A summary of the results that this recommendation was based on is provided in Table 1.

Table 1: Mean change in HbA1c from baseline to endpoint for Studies 105 and 108

	Study 105 (30 weeks)		Study 108 (24 weeks)	
	Exenatide once weekly N = 148	Exenatide twice daily N=147	Exenatide once weekly N=129	Exenatide twice daily N=123
Baseline mean HbA1c (SE)	8.3 (0.08)	8.3 (0.08)	8.5 (0.10)	8.4 (0.10)
LS mean change in HbA1c (SE)	-1.9 (0.08)	-1.5 (0.08)	-1.6 (0.10)	-0.9 (0.10)
LS mean difference (95% CI)	-0.33 (-0.54, -0.12)		-0.7 (-0.90, -0.40)	
Pooled difference (95% CI)	-0.53 (-0.70, -0.36)			

Abbreviations: CI = confidence interval; LS = least squares; SE = standard error

Note: Treatment group difference (exenatide weekly minus comparator).

Source: Table B.6.1, p35 and Table B.6.10, p48 of the November 2013 re-submission

Comparative harms

- 6.5 At its November 2013 meeting, the PBAC accepted that exenatide 2 mg once weekly has non-inferior safety to exenatide 10 mcg twice daily. This was not disputed in the re-submission, although the re-submission applied impacts of safety claims in its economic analysis that were not supported by clinical evidence. In one of the cost analyses presented, the re-submission linked the occurrence of less nausea with exenatide once weekly to fewer treatment discontinuations, although there was no statistical support for the link between nausea and discontinuation. Consequently, the claims underlying the economic analysis were not supported by clinical data (see the Economic analysis section below).
- 6.6 The PBAC noted, however, that in July 2011, it had recognised there were statistically significantly more exenatide twice daily patients reporting nausea and vomiting than exenatide once weekly patients. The PBAC also noted in July 2011 that injection site reactions are more common with exenatide once weekly.

Clinical claim

- 6.7 The re-submission did not make a new clinical claim. The claim accepted by the PBAC at the November 2013 meeting of at least non-inferior efficacy compared to exenatide 10 mcg twice daily and non-inferior safety was not disputed in the re-submission.
- 6.8 The PBAC confirmed its November 2013 consideration of the clinical claim.

Economic analysis

- 6.9 The re-submission presented both a series of cost analyses and the results of a WTP study to justify the requested price advantage, for convenience of use. The re-submission provided supportive argument in claiming greater acceptability and adherence would be realised in difficult to treat patients with high clinical need (stated

in the re-submission to be the Indigenous, aged and mental health populations). The ESC considered the submission did not provide any specific evidence that once weekly dosing will result in better health outcomes for Indigenous Australians with T2DM. While there may be a case that once weekly dosing would improve adherence over twice daily dosing, the ESC did not consider this was adequately established by the submission.

- 6.10 The PBAC considered that the simplified treatment regimen of reducing dosing frequency by 13 injections per week may translate into fulfilling an unmet need for high clinical need populations; specifically Indigenous, aged and mental health populations.
- 6.11 In addition, the PBAC noted there may be benefits of once weekly dosing in mental health patients who have less access to medical care and may be less compliant with their regimens.

WTP study

- 6.12 The following table provides a summary of the WTP study.

Table 2: Summary of WTP

Component	Summary
Design	<ul style="list-style-type: none"> • Commissioned Australian discrete choice experiment (DCE) to derive a consumer surplus for a once weekly injectable compared to a twice daily injectable preparation for T2DM. • Participants were asked to choose between a series of three comparisons at a time for either: their current therapy and two injectable preparations and an oral preparation (for participants currently using an injectable preparation); two oral and one injectable preparation (for participants currently using an oral preparation). • Each comparison contained different values for the key attributes of interest: frequency of dosing, weight change, needle used to inject, storage, nausea, mode of administration, injection site reactions, hypoglycaemic events per month, cost per script and instructions with eating.
Population	<ul style="list-style-type: none"> • The DCE was conducted in two populations: <ol style="list-style-type: none"> 1) A current patient with T2DM switching from a twice daily to a once weekly injection (N=58); and 2) A patient with T2DM using oral medications only who is choosing between a twice daily and a once weekly injection (N=113). • The study aimed to recruit 100 patients in each population.
Analysis methods	<ul style="list-style-type: none"> • Multinomial logit model (MLM) with error components (EC) model.
Determination of consumer surplus	<ul style="list-style-type: none"> • A weighted consumer surplus for each population was calculated based on split of concessional and general patients (results for population 1 \$██████; population 2 \$██████). • These two consumer surplus values were then weighted based on the re-submission's financial estimates, assuming 58% are exenatide twice daily users and 42% are oral medication users, to arrive at a final weighted consumer surplus of \$██████. This was converted to a daily value (\$██████) and a 28-day value (\$██████).

Abbreviations: DCE = discrete choice experiment; NDSS = National Diabetes Services Scheme; T2DM = type 2 diabetes mellitus. Source: compiled during the evaluation

- 6.13 The consumer surplus derived from the DCE formed the major component of the price advantage sought in the re-submission (see Table 5).
- 6.14 The DCE aimed to recruit 100 patients in each of the two PBS sub-populations likely to be prescribed exenatide 2 mg once weekly injections, i.e. patients switching from a

twice daily to a once weekly injection (N=58), and patients using oral medications only who are choosing between a twice daily and a once weekly injection (N=113). The more limited sample size for the exenatide twice daily population may be of concern because it is not clear how this affected the number of respondents assigned to each block in the DCE design for the smaller than expected sample. The ESC expressed concern about the small number of respondents for each version of the DCE, and considered this contributed to high uncertainty with respect to the WTP estimates. A number of coefficients were noted to be non-significant. Thus, to the extent that blocking was used, the possibility exists that the results were in fact underpowered.

- 6.15 To determine willingness to pay, participants were asked to choose between a series of three comparisons at a time, for either:
- their current therapy and two injectable preparations and an oral preparation (for participants currently using an injectable preparation); or
 - two oral and one injectable preparation (for participants currently using an oral preparation).

For example, Figure 1 presents the choice scenario for patients currently on exenatide 10 mcg twice daily. Each comparison contained different values for the key attributes of interest: frequency of dosing, weight change, needle used to inject, storage, nausea, mode of administration, injection site reactions, hypoglycaemic events per month, cost per script and instructions with eating. The attributes of weight change and hypoglycaemic events per month were not based on advantages claimed in the previous submissions, nor accepted by the PBAC, for exenatide 2 mg once weekly (July 2011 and November 2013 exenatide public summary documents (PSDs)). However, the ESC considered that it was not unreasonable for these attributes to be included in the DCE in order to capture what the consumer might value and be willing to trade and noted that by setting these attributes to zero for both medications, the WTP price advantage was appropriately calculated solely on the basis of reduced injection frequency.

Figure 1: Example Stated Choice scenario for exenatide twice daily patients

Set 1 of 8

Please take a moment to review the new type 2 diabetes medicines shown below. Assuming that these treatments work just as well in controlling your blood glucose as your current treatment and your doctor has recommended these treatments, which medicine would you prefer? You may choose to stay on your existing injectable medication Byetta (exenatide) or choose one of the new medications presented.

Please note, some fields have been left blank for Byetta (exenatide) as this is dependent on your personal experience.

	Current Treatment	Injectable Treatment A	Injectable Treatment B	Oral Treatment A
Frequency	Twice a day 	Twice a day 	Once a month 	Once a day
Weight change (% body weight)		No change	Gain 5%	No change
Nausea		Moderate	Moderate	None
Hypoglycaemic events per month		>2	1	1
Instructions with eating	Taken / Used within a certain time of eating	Taken / Used anytime (unrestricted)	Taken / Used anytime (unrestricted)	Taken / Used anytime (unrestricted)
Cost per script	\$36.90	\$53.50	\$48.00	\$55.40
Storage	Keep in the fridge until first use	No refrigeration required	Keep in the fridge until first use	N/A
Mode of administration (device)	Multi use pen	Multi use pen (no mixing required)	Single use pen (some mixing required)	N/A
Needle you use to inject		Longer / thicker (A very weak pain sensation)	Longer / thicker (A very weak pain sensation)	N/A
Injection site reaction / Nodules		Yes	Yes	N/A
Which medicine would you MOST prefer?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Which medicine would you LEAST prefer?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Would you ever consider using this medicine (even if you did not choose it)?		<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No

6.16 Limited information regarding the design of the DCE, including the experimental design, was provided in the submission. Additional information was provided in the PSCR.

- Attributes and ranges were chosen in consultation with the sponsor. The PSCR stated that these were based on clinical trial results and tested in a pilot study.
- The experimental design was generated in NGene using a D-efficient design. This approach was reasonable. The overall design comprised 72 scenarios, blocked into 9 blocks with 8 scenarios each (thus each respondent saw 8 scenarios). However, the ESC noted that this translated to a relatively small sample of individuals in the sub-sample of respondents switching from twice daily to once weekly injections (the more relevant sub-sample). A sample of 58 suggests around 7 respondents per block, and it is not clear that there was balance in the blocks.
- Attributes were dummy coded. This approach was reasonable.

6.17 The following points were unstated in the submission (additional information was provided in the PSCR:

- Whether background information was given to those surveyed and whether instructions provided were appropriate and clear. The PSCR provided additional details, however the additional detail did not make clear that respondents would necessarily understand the cost to be an ongoing monthly cost.
- Whether any conflict of interest declaration was required by participants and whether this might have caused them to be excluded. The PSCR stated that this was not required. The respondents were largely from an on-line panel, supplemented by respondents recruited through advertising.

- Confidence intervals for results. Without confidence intervals, the accuracy of the estimates is unknown. It is not clear whether the estimates of WTP are statistically significantly different from zero. The PSCR stated that calculation of confidence intervals is a very difficult process and requires model simulation. Given that a number of the co-efficients in the estimated model were not-significant, the ESC considered that this remained a concern that contributed to uncertainty regarding the results of the WTP study. The ESC did not consider it was appropriate to expect the PBAC to make decisions without some information about the bounds of the WTP estimates. The Pre-PBAC response presented 95% confidence intervals around the estimates of consumer surplus based on the reduced injection frequency for those patients currently treated with exenatide twice-daily. The monthly consumer surplus was calculated at \$ [REDACTED] (95% CI: \$ [REDACTED], \$ [REDACTED]) for concessional patients and \$ [REDACTED] (95% CI: \$ [REDACTED], \$ [REDACTED]) for general patients, resulting in a weighted point estimate of \$ [REDACTED] based on 63.7% concessional patients. These results were not independently confirmed.
- 6.18 The additional information regarding the DCE provided in the PSCR indicated that the study was subject to significant bias. In particular, the PSCR stated that respondents with a conflict of interest could have participated and the attributes selected were chosen in consultation with the sponsor.
- 6.19 The re-submission used a multinomial logit model (MLM) with error components (EC) model to analyse the DCE data. In general the EC method is a standard and well-accepted approach, but it would have been useful for the re-submission to have considered other models. There are different extensions to MLMs which haven't been investigated, such as the mixed logit model. Although the re-submission stated the "model fit results illustrate that the model provides a superior fit to a constant only model", the model fit in comparison with other types of MLM models was not presented. This would be necessary to determine whether the consumer surplus remains positive and of similar value.
- 6.20 The most important attribute in the DCE was reported to be weight change, followed by frequency of treatment (either oral or injectable) and nausea. The re-submission did not claim any benefit related to weight. The original submission in July 2011 for exenatide once weekly reported that there was no statistically significant difference in change in body weight between exenatide once weekly and twice daily in the two pivotal trials. Clinical benefit was based on change in HbA1c in both the July 2011 submission and the November 2013 re-submission, which was accepted by the PBAC (p9, July 2011 exenatide PSD; p5 November 2013 exenatide PSD). During evaluation it was considered the results of the DCE were therefore inconsistent with the identified benefit of once weekly exenatide treatment. The PSCR argued that the WTP price advantage was calculated solely on the basis of reduced injection frequency and that it did not include weight change or changes to HbA1c. The ESC noted that the calculation of consumer surplus in the submission appropriately excluded any benefit relating to weight and therefore only reflected the gain in consumer surplus arising from the change in injection frequency.
- 6.21 Table 3 provides a summary of the overall consumer surplus. Across the two populations, those on exenatide twice daily and those on oral medication, the re-submission used weightings from the first year of its financial estimates to determine a weighted consumer surplus per month. The re-submission assumed 58% are

existing exenatide twice daily users and 42% are oral medication users. This resulted in a weighted consumer surplus of \$[REDACTED]. The re-submission converted this to a daily value (\$[REDACTED] = \$[REDACTED]/30) and then a 28-day value (\$[REDACTED] × 28 = \$[REDACTED]) to arrive at a price advantage per 28 days (the pack duration of exenatide weekly).

Table 3: Estimated consumer surplus

	Consumer surplus
Population 1: A current patient switching from a twice daily to a once weekly injection	\$[REDACTED]
Population 2: A patient using oral medications only who is choosing between a twice daily and a once weekly injection	\$[REDACTED]
Weighted consumer surplus/month	\$[REDACTED]
Price advantage per day (\$33.52/30)	\$[REDACTED]
Price advantage/28 days	\$[REDACTED]

Source: compiled during the evaluation

- 6.22 The results of the DCE were highly dependent upon the proportion of patients switching from a twice daily injectable preparation compared to those switching from oral medications. The re-submission’s argument that estimating the value of a consumer’s preference for once weekly injections should be based on both patients currently treated with exenatide twice daily and oral patients was not considered reasonable by the evaluation. While the re-submission acknowledged that the higher consumer surplus for oral patients could be driven by fear of the unknown, any such fear may reasonably be expected to apply for only an initial period, after which the dissipation effect will be observable. Thus, the long-term consumer surplus, even for oral patients, is likely to be no greater than the results reported for patients switching from twice daily injections to weekly. Consequently, the consumer surplus of \$[REDACTED] (see Table 3 above) was considered more likely to apply to the entire PBS population treated with exenatide weekly injections (rather than the re-submission’s weighted estimate of \$[REDACTED]). This would reduce the price advantage per quantity of 28 to \$[REDACTED] (re-submission is requesting \$[REDACTED]).
- 6.23 The PSCR argued that the WTP for oral patients switching to exenatide will not dissipate and therefore that the WTP for these patients should not be excluded. Furthermore, the PSCR argued that even if some of the value related to a transient preference it should be incorporated. The ESC considered that the long-term consumer surplus is likely to be overstated and partly reflects an overall distaste for injectables. This distaste would further overstate the relative benefits of exenatide once weekly to exenatide twice daily, as the fear of injections could only be avoided completely by remaining on oral medication. The Pre-PBAC response argued that \$[REDACTED] is the minimum WTP estimate per month and that the true value is above this estimate.
- 6.24 Notably, the financial estimates did not assume any switching from oral to once weekly exenatide.
- 6.25 The PBAC considered that the WTP study at best provided evidence that there would be a perceived benefit to patients from listing the simplified once weekly regimen. However, the PBAC considered that this did not provide a sufficient basis for quantifying the price advantage that should be paid for this benefit for the following reasons:

- The PBAC agreed with the ESC that there were a number of flaws in the methodology for estimating the consumer surplus in the WTP study, as outlined above. In particular, the PBAC noted the fact that several key parameters were not significant, but were included in the model used to estimate the consumer surplus.
- The PBAC considered the measured perceived benefit for the population shifting from exenatide twice daily to once weekly (as opposed to from oral to injectable) was of relevance, but noted the small sample size for this population, which provided a very uncertain basis for estimating population benefit. At the lower 95% CI of the estimates of consumer surplus based on the reduced injection frequency for those patients currently treated with exenatide twice-daily of \$ [REDACTED] for concessional patients and \$ [REDACTED] for general patients, the weighted point estimate would be \$ [REDACTED], rather than the \$ [REDACTED] claimed by the submission.
- The PBAC agreed with the ESC that the WTP estimate for patients switching from oral therapies would be driven by distaste for injections, which is likely to be transient.
- The PBAC noted that if the requested restriction for exenatide once weekly resulted in leakage into dual therapy with insulin, recommended for PBS listing in March 2015, the perceived benefit of fewer injections would no longer hold.

Cost analyses

- 6.26 The following table provides a summary of the cost analyses presented in the re-submission. With the exception of a partial cost offset for reduced needle use (approximately 50% of that requested, or one needle per day, as previously recommended by the PBAC in November 2013), the cost offsets proposed in the cost analyses were considered by the evaluation to be unsubstantiated and unlikely to be realised.
- 6.27 The PSCR stated that the requested cost offsets have been reduced from \$ [REDACTED] per pack to \$ [REDACTED], bringing the requested price advantage down from \$ [REDACTED] to \$ [REDACTED] per 28-day pack. The price advantage requested is reduced as the sponsor agreed to a reduced cost offset per pack for: needle and other consumable use from \$ [REDACTED] to \$ [REDACTED]; reduced discontinuations due to nausea and vomiting from \$ [REDACTED] to \$ [REDACTED]; and the requested advantage per pack for Indigenous patients of \$ [REDACTED] was removed. The calculations presented are numerically correct. The revised cost offsets presented in the PSCR (which were unchanged in the pre-PBAC response) are included in the following table.

Table 4: Summary of cost analyses

Cost offset and claim		Submission		PSCR	
		Per day	Per 28-day pack*	Per day	Per 28-day pack*
Price advantage based on Closing the Gap	<p><u>Evaluation:</u> Assumption that there will be improvement in adherence to T2DM treatment regimens and subsequent improvement in Indigenous health outcomes, with a price advantage based on the current average co-payment already funded by the Government under the Closing the Gap program. No data was provided to show adherence and/or health outcomes improvement. Justification for the extent of the price advantage was not supported and since Closing the Gap is already an expenditure of the Government, to assume the Government will contribute an additional amount to the sponsor is not appropriate.</p> <p><u>PSCR:</u> Offset removed.</p> <p><u>ESC:</u> The ESC noted that the PSCR appropriately removed this offset.</p>	\$█	\$█	\$0.00	\$0.00
Reduced care costs for aged care	<p><u>Evaluation:</u> Claimed that due to the reduced frequency of administration required for exenatide once weekly compared to exenatide twice daily there would be lower costs for patients in residential aged care. Likely to be an overestimate given assumptions made regarding patients with co-morbidities.</p> <p><u>PSCR:</u> Unchanged, defer to ESC.</p> <p><u>ESC:</u> The approach in the submission was likely to overestimate the impact of weekly vs twice daily injections as patients requiring exenatide are likely to have other high care needs and this has not been accounted for. As this cost offset was not sufficiently justified, it should be removed.</p>	\$█	\$█	\$█	\$█

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Cost offset and claim		Submission		PSCR	
		Per day	Per 28-day pack*	Per day	Per 28-day pack*
Reduced care costs for home nursing visits	<p><u>Evaluation:</u> Claimed that since exenatide once weekly needs to be dosed less frequently than exenatide twice daily this will reduce the frequency of home nursing visits for patients in the community with T2DM. Home nursing visits for non-insulin users were not considered a reasonable proxy for exenatide once weekly. Consequently there was no basis for assuming that home visits will differ between the patients using twice daily versus once weekly exenatide.</p> <p><u>PSCR:</u> The basis of the claim was that exenatide twice daily users would have more visits. The offset was \$█ per year (less than one visit) which was entirely reasonable given there are 678 fewer injections per year with once weekly exenatide. Request unchanged.</p> <p><u>ESC:</u> This was an assumption and not substantiated however it may be reasonable to assume some reduction in home nursing visits (but not necessarily for the whole population).</p>	\$█	\$█	\$█	\$█
Avoidance of the need to up-titrate	<p><u>Evaluation:</u> Patients using exenatide twice daily require up-titration; re-submission assumed this would not occur with exenatide once weekly. It was not clear that an additional GP consultation would be required for up-titration.</p> <p><u>PSCR:</u> Unchanged, defer to ESC.</p> <p><u>ESC:</u> As this cost offset was not sufficiently justified, it should be removed.</p>	\$█	\$█	\$█	\$█
Reduced discontinuations due to nausea and vomiting	<p><u>Evaluation:</u> Claim there will be fewer discontinuations due to a reduced rate of nausea and vomiting for patients treated with exenatide once weekly compared to exenatide twice daily. There was no trial-based data directly linking nausea and vomiting with discontinuation; and there was no data to support the extent and nature of the proposed additional resource use.</p> <p><u>PSCR:</u> Removed care plan component. Offset calculated on a pro-rata basis over 3 years.</p> <p><u>ESC:</u> As this cost offset was not sufficiently justified, it should be removed.</p>	\$█	\$█	\$█	\$█

Cost offset and claim		Submission		PSCR	
		Per day	Per 28-day pack*	Per day	Per 28-day pack*
Reduced use of NDSS needles and other consumables	<u>E</u> valuation: Claim of a 100% cost offset for use of 2 needles per day, plus costs for other consumables including alcohol swabs and sharps disposal units. The PBAC previously recommended needle cost offsets at 50% of the requested level, i.e. one per day and other consumables were not included (p8, November 2013 PSD).	\$█	\$█	\$█	\$█
	<u>P</u> SCR: Needle offset reduced to previously recommended 1 per day consistent with previous negotiations				
	<u>E</u> SC: Agree with the evaluation; no evidence for reduced swabs cost, or for the additional cost-offsets above \$█ per day already agreed.				
Total cost analysis			\$█		\$█

Abbreviations: NDSS = National Diabetes Services Scheme; T2DM = type 2 diabetes mellitus; EQW = Exenatide 2 mg once weekly

Source: compiled during the evaluation

* Differences in costs calculated based on per day cost multiplied by 28 days are due to rounding

- 6.28 The PBAC agreed with the ESC that, with the exception of a partial cost offset for reduced needle use, the cost offsets proposed in the costs analyses were unsubstantiated. However, the PBAC also agreed with the ESC that it may be reasonable to assume some reduction in home nursing visits and treatment benefits for older patients (which was one of the high clinical need populations identified by the submission), but not to the extent proposed by the submission.
- 6.29 The PBAC recalled that, in November 2013, the assumptions in the submission of 100% compliance with twice daily exenatide dosing and use of a new needle for each dose were not substantiated by any data. The PBAC considered that approximately 50% of that use would be a reasonable basis for a claimed offset and that this be used in pricing negotiations.

Summary of the requested price advantage

- 6.30 Table 5 provides a summary of the components of the requested price for exenatide once weekly. An alternate cost for exenatide once weekly is also provided in the table, based on the cost offset for needles only at the 50% level accepted by PBAC in November 2013, with the proposed consumer surplus for WTP and all other cost offsets from the re-submission’s cost analyses excluded.

Table 5: Summary of the requested price advantage and price proposed in the re-submission

	Requested cost per 28-day pack	Alternate cost per 28 day pack ^A	
		92.7% adherence	100% adherence
Equi-effective dosing	\$91.54	\$91.54	\$91.54
Cost analyses	\$ [REDACTED] ^B	\$ [REDACTED]	\$ [REDACTED]
Willingness to pay	\$ [REDACTED]	\$0	\$0
Total DPMQ	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Ex-manufacturer price	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: compiled during the evaluation

Abbreviations: DPMQ = dispensed price for maximum quantity

^A Alternate cost assumed cost offset for needles only at 50% level accepted by PBAC in November 2013; all other cost offsets from the re-submission's cost analyses were excluded as was the proposed consumer surplus for WTP. Values for 100% adherence are provided as they concur with the adherence level assumed in the November 2013 re-submission.

^B The cost analyses figure was updated based on the changes in the PSCR (see Table 4).

- 6.31 Given that the estimated consumer surplus based on the DCE was considered to be overstated and highly uncertain, and with the exception of a partial cost offset for needle costs, the requested cost offsets are not likely to be realised, the evaluation and the ESC did not consider the price advantage requested by the re-submission to be reasonable.
- 6.32 The evaluation and the ESC questioned whether a consumer surplus should be funded for the convenience of administration. If an advantage is to be funded, consideration should be given to how much should be funded from the health budget given that the consumer surplus appeared to have been derived entirely based on patient convenience associated with reduced injection frequency. Without corresponding clinical evidence to show that reduced injection frequency leads to improved adherence and improved health outcomes, funding a price advantage for patient convenience will lead to an opportunity cost of foregone health benefits that could otherwise accrue from funds invested elsewhere in the health system.
- 6.33 In addition, in the case of tobramycin (p7, November 2013 PSD) the PBAC disagreed that the Government should pay the calculated consumer surplus in its entirety to the sponsor. Instead, any consumer surplus should be shared between the sponsor, the consumer and the Government.
- 6.34 The ESC considered that, to the extent that there was a gain in consumer surplus associated with reduced frequency of injections, this should not all be reflected in the price to the sponsor, as this would effectively transfer all this consumer surplus to the sponsor. The ESC considered the PBAC's previous position regarding sharing of any consumer surplus between the sponsor, the consumer and the Government should also apply in this case.
- 6.35 The PSCR argued that because weight loss, HbA1c control and improved nausea were not included in the requested WTP estimate, the consumer surplus is already being shared to some extent. The ESC considered this was not appropriate as the clinical trial did not demonstrate a statistically significant benefit in weight change. Furthermore, the re-submission did not claim any benefits relating to weight loss and improved nausea for exenatide 2 mg once weekly compared with 10 mcg twice daily. The re-submission did not dispute the claim accepted by the PBAC of at least non-inferior efficacy compared with exenatide twice daily, in terms of mean change in HbA1c. The ESC agreed that it was appropriate that the submission did not quantify

any consumer surplus related to weight loss, HbA1c control and improved nausea. Accordingly, the ESC considered it would be inappropriate to consider the consumer surplus that may be associated with these potential (but unsubstantiated) benefits of exenatide 2 mg once weekly in determining the relativities for sharing the consumer surplus associated with reduced frequency of injections.

- 6.36 While the PBAC did not accept the results of the WTP study (see paragraph 6.25), it considered that the consumer surplus estimate for patients switching from twice daily to once weekly exenatide would be more relevant than the requested WTP price advantage, which included a weighting for patients switching from oral therapies. However the PBAC noted that the consumer surplus estimate of \$ [REDACTED] was itself highly uncertain (see paragraph 6.25) and could be as low as \$ [REDACTED], if the model was accepted. The PBAC also noted that a number of parameters in the model used to derive the consumer surplus were not statistically significant.
- 6.37 The PBAC also recalled that, in its November 2013 recommendation of tobramycin, it considered that it would be inappropriate for the estimated consumer surplus to be translated into a price advantage, as this, in effect, would transfer the entire surplus to the sponsor. The PBAC noted that in a usual welfare economics framework, the surplus from a subsidy (or from an additional benefit of a product) is shared between consumers and producers, whereas the requested price advantage suggests that the entire welfare gain from the new product would accrue to the sponsor and be borne by the government. The PBAC considered a more reasonable approach would be for the welfare gain to be equally shared by consumers, the sponsor and government.
- 6.38 The pre-PBAC response indicated the sponsor was comfortable with the principle of sharing and the precedent set within the tobramycin consideration.
- 6.39 Although the PBAC did not accept the extent of the price advantage based on the WTP results for patients switching from twice daily to once weekly exenatide, it considered that a small incremental price advantage could be acceptable to account for the potential health benefits in high clinical need populations who may have better adherence with exenatide once weekly than with twice daily.
- 6.40 The PBAC recalled that it was more persuaded that the new formulation of tobramycin provided significant impacts on quality of life for patients that were likely to lead to health benefits.
- 6.41 Accordingly, the PBAC considered that the price advantage should be substantially less in absolute and relative terms than the estimated WTP advantage for patients swapping from exenatide twice daily to once weekly of \$ [REDACTED].

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

Drug cost/patient/year: \$ [REDACTED].

- 6.42 The estimated cost per patient per year was \$ [REDACTED] (based on the DPMQ requested in the submission of \$ [REDACTED]) compared with \$1,295.18 for exenatide 10 mcg twice daily (based on a DPMQ of \$99.36) assuming 13.04 prescriptions per year.

Estimated PBS usage & financial implications

- 6.43 This re-submission was not considered by DUSC.
- 6.44 The estimated extent of use and financial implications presented in the submission are summarised in Table 6.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Market share	%	%	%	%	%
Scripts ^a					
Scripts ^a - Nov 2013					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS	\$	\$	\$	\$	\$
Net cost to PBS Nov 2013	\$	\$	\$	\$	\$
Cost reduction due to NDSS and MBS savings	-\$	-\$	-\$	-\$	-\$
Estimated total net cost to Government					
November 2013	\$	\$	\$	\$	\$

^a Assuming 13.04 scripts per year as estimated by the November 2013 re-submission and the current re-submission.
 Source: Table E-7, p108; Tables E-16 to E-17, p113; Table E-21, p116; Table E-23, p118; Table E-24, p 118 of the re-submission; Tables E.2.1 to E.2.3, p168 and Table E.5.3, p174 of the November 2013 re-submission
 Abbreviations: NDSS = National Diabetes Services Scheme

- 6.45 The expected financial cost to the Government with the full cost offsets proposed in the submission would be less than \$10 million in year 1, increasing to \$10-\$20 million in year 5. This significant increase over that expected in the November 2013 re-submission (estimated to be cost-neutral) was due to the higher price requested and the treatment of less than 10,000 additional patients per year with unmet clinical needs from the Indigenous population to 10,000-50,000 additional patients in year 5.
- 6.46 The ESC noted the high opportunity cost of listing exenatide once weekly with the requested price advantage. Specifically, the lost opportunity for the Government to pay for actual health gains as opposed to paying for convenience of use. However, the PBAC considered that there could be potential health benefits of listing exenatide 2 mg once weekly in patients who may have better adherence compared with the twice daily exenatide treatment regimen.
- 6.47 Sensitivity analyses of the financial estimates were not provided by the re-submission. An analysis assuming a price advantage based solely on the 50% level of needle cost offsets recommended by the PBAC in November 2013 (DPMQ of \$ [redacted] instead of the requested \$ [redacted]), resulted in net costs to the Government of less than \$10 million in Year 1 increasing to less than \$10 million in Year 5, a decrease of approximately 70% from costs estimated by the re-submission.
- 6.48 The financial estimates did not consider that exenatide once weekly may substitute for exenatide 5 mcg twice daily when the latter is used outside of titration purposes; or that additional use may also occur in non-Indigenous patients taking oral

anti-diabetic agents. Consequently the estimated net cost was considered underestimated. This underestimation was considered still likely even with removal of the requested consumer surplus for WTP and a significant reduction in the requested cost offsets. The PSCR argued that use is unlikely to occur in non-Indigenous patients switching from oral therapies and that patient numbers were therefore not underestimated.

- 6.49 The PBAC noted that the financial impact of the listing recommended by the PBAC would be less than was estimated in the submission given the substantially lower price advantage recommended by the PBAC.

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

Quality Use of Medicines

- 6.50 The re-submission indicated that exenatide once weekly will improve quality use of medicines by reducing the likelihood of needle reuse. Given that needles can be accessed at no cost to the patients through the NDSS, it is unlikely that needle reuse is a large problem in Australia. The pre-PBAC response argues that this point contradicts the PBAC recommendation in November 2013 to halve the requested needle cost offset because it was assumed that needle reuse occurred such that, on average, each needle is used for two injections. The PBAC noted that it considered that 50% of the estimated needle use would be appropriate for the purpose of pricing negotiations in the absence of any data proving 100% compliance with twice daily exenatide dosing and use of a new needle for each dose. However, the PBAC conceded that there may be some small improvement in quality use of medicines by reducing the likelihood of needle reuse.
- 6.51 The re-submission provided a brief description of a sponsored study that is scheduled to begin in mid-2015. The aim of the study is to investigate the acceptability, feasibility and efficacy of a model of care based on exenatide once weekly and associated weekly clinician contact for an Indigenous population. Given that the sponsor is commissioning a study to assess the acceptability of exenatide once weekly in Indigenous patients, and whether there will be an impact on HbA1c, the assumed increased use of exenatide once weekly by this population, along with improved health outcomes assumed in the re-submission cannot be substantiated.

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

7 PBAC Outcome

- 7.1 The PBAC recalled that, in November 2013, it had recommended exenatide 2 mg once weekly as an Authority Required (Streamlined) benefit for dual combination therapy with metformin or a sulfonylurea and triple combination therapy with metformin and a sulfonylurea in patients with T2DM, on a cost-minimisation basis with exenatide 10 mcg twice daily (with a cost offset for reduced needle use). The PBAC re-endorsed its November 2013 recommendation (of cost-minimisation with a partial cost offset for reduced needle use) and recommended a further small price advantage for exenatide 2 mg once weekly on the basis of potential health benefits from likely improved adherence by a small number of high clinical need populations.

- 7.2 The PBAC considered that the data presented in the November 2013 submission supported exenatide 2 mg once weekly being at least non-inferior to exenatide 10 mcg twice daily in terms of efficacy (based on mean change in HbA1c from baseline) and non-inferior in terms of safety. The PBAC noted that the re-submission did not present any new clinical data or make a new clinical claim.
- 7.3 The PBAC noted that the requested restriction was in line with that recommended in November 2013 and it had previously accepted that exenatide 10 mcg twice daily was the appropriate comparator.
- 7.4 The PBAC noted that exenatide 2 mg once weekly would mainly substitute for exenatide 10 mcg twice daily. The PBAC considered that the simplified treatment regimen of reducing dosing frequency by 13 injections per week may translate into fulfilling an unmet need for high clinical need populations; specifically Indigenous, aged and mental health patients (see paragraphs 6.9-6.11 and 6.28). In this regard, the PBAC noted the consumer comments described the benefits of once weekly administration compared with twice daily, including the potential compliance benefit. The PBAC considered that the sponsor-funded study in Indigenous Australians (see paragraph 6.51) may provide confirmation of an unmet need for a simplified treatment regimen for that population.
- 7.5 The PBAC noted that the re-submission requested a price advantage on the basis of patient preferences as measured by consumer surplus, estimated from a WTP study. The PBAC did not accept that the WTP study provided a sufficient basis for quantifying the potential benefit of exenatide once weekly for patients (see paragraph 6.25). Furthermore, the PBAC recalled that when a price advantage based on a WTP study was accepted for tobramycin (November 2013), the PBAC was more persuaded that the new tobramycin formulation provided significant impacts on quality of life for patients that were likely to lead to health benefits. The PBAC therefore recommended that the price advantage for this exenatide product should be substantially less in absolute and relative terms than applied in the tobramycin precedent.
- 7.6 The PBAC listing exenatide 2 mg once weekly may lead to an improvement in quality use of medicines due to a potential reduction in needle reuse.
- 7.7 The PBAC advised that exenatide was suitable for prescribing by nurse practitioners under collaborative arrangements.
- 7.8 The PBAC recommended that the Safety Net 20 Day Rule should apply.
- 7.9 The PBAC noted that this submission was not eligible for an Independent Review because it was neither a request for a new drug, nor an additional indication for an existing drug.

Outcome:
Recommended

8 Recommended listing

8.1 Amend recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
EXENATIDE			Bydureon®	AstraZeneca
exenatide 2 mg injection [4 x 2 mg vials] (& inert substance diluent [4 x 1.5 mL syringes], 1 pack	1	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with metformin; OR The treatment must be in combination with a sulfonylurea. AND Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR Patient must not have tolerated a combination of metformin and a sulfonylurea. AND Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like-peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with either metformin or a sulfonylurea; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with either metformin or a sulfonylurea.

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Prescriber Instructions:	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>b) Had red cell transfusion within the previous 3 months</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records.</p>
Administrative Advice:	<p>Note:</p> <p>This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin or an SGLT2 inhibitor.</p>

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be in combination with metformin,</p> <p>AND</p> <p>The treatment must be in combination with a sulfonylurea,</p> <p>AND</p> <p>Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like-peptide-1 or a sodium-glucose co- transporter 2 (SGLT2) inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea; OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea.</p>

<p>Prescriber Instructions:</p>	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <ul style="list-style-type: none"> a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or b) Had red cell transfusion within the previous 3 months <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records.</p>
<p>Administrative Advice:</p>	<p>Note: This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin or an SGLT2 inhibitor.</p>

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.