

## 5.03 EXENATIDE, Injection 2 mg in 0.85 mL single dose autoinjector, Bydureon BCise<sup>®</sup>, AstraZeneca

### 1 Purpose of Application

- 1.1 The submission requested an Authority Required (Streamlined) listing for exenatide 2 mg once weekly autoinjector (exenatide autoinjector) for the treatment of type 2 diabetes mellitus (T2DM). Exenatide autoinjector had not been considered by the PBAC previously.
- 1.2 The requested listing was based on a cost-minimisation analysis against exenatide 2 mg once weekly dual chamber pen (exenatide DCP).
- 1.3 The key components of the clinical issue addressed by the submission are presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control on metformin and/or a sulfonylurea.
Intervention	Exenatide 2 mg once weekly suspension in an autoinjector
Comparator	Exenatide 2 mg once weekly dual chamber pen
Outcomes	Change in HbA1c per cent from baseline to Week 28; safety outcomes
Clinical claim	In patients with T2DM who have inadequate glycaemic control on metformin and/or a sulfonylurea, exenatide autoinjector is non inferior to exenatide DCP in terms of reduction of HbA1c, and similar safety.

Source: Table 1-1, p10 of the submission

### 2 Requested listing

- 2.1 The requested listing is presented below.

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Name, Restriction, Manner of administration and form	Max quantity (packs)	Max. quantity (units)	No. of Repeats	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
EXENATIDE 2 mg modified release injection, 4 x 0.85 mL injection devices	1	4	5	\$131.15 (published)	BYDUREON BCise AstraZeneca Pty Ltd
Category/Program:	GENERAL – General Schedule (Code GE)				
PBS indication:	Diabetes mellitus type 2				
Restriction:	Streamlined				
Clinical criteria:	<p>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 metformin or a sulfonylurea.</p>		<p>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% 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 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>		
Prescribing information	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: <ul style="list-style-type: none"> <li>• a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</li> <li>• b) Had red cell transfusion within the previous 3 months.</li> </ul> </li> </ul> <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>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> <p><i>Special Pricing Arrangements Apply.</i></p>				

- 2.2 The submission requested that the special pricing arrangement (SPA) for exenatide DCP be extended to the exenatide autoinjector. Extension of the SPA would result in an effective price of \$ [REDACTED] per pack of exenatide autoinjector compared to a published DPMQ of \$131.15.
- 2.3 The requested restriction for exenatide autoinjector was identical to the exenatide DCP.

### **3 Background**

#### ***Registration status***

- 3.1 TGA status at time of PBAC consideration: Exenatide autoinjector was included in the Australian Register of Therapeutic Goods on 7 February 2019.
- 3.2 The submission was made under TGA/PBAC Parallel Process. The second round clinical evaluation report and TGA Delegate's Overview were available to the PBAC.
- 3.3 The Delegate's Overview was supportive of the registration of exenatide autoinjector, noted the ease of administration, and recommended changes to the Product Information. The Delegate's Overview also noted there was no comparative data to the existing formulations.

### **4 Population and disease**

- 4.1 Diabetes is a chronic disease associated with hyperglycaemia and an increased risk of microvascular and macrovascular complications. Type 2 diabetes mellitus (T2DM) is associated with comorbid overweight/obesity, dyslipidaemia, and hypertension. The consequences of uncontrolled diabetes include vascular damage, which may lead to blindness, neuropathy, amputation, kidney failure, heart disease, or stroke.
- 4.2 Exenatide and other glucagon-like peptide-1 (GLP-1) agonists may be added to existing therapy (metformin and/or sulphonylurea, plus other oral antidiabetic therapies and/or insulin if appropriate) if HbA1c goals were not achieved and are considered as third line therapy in T2DM. Importantly, exenatide is not recommended as monotherapy in patients with T2DM. The proposed restrictions did not allow monotherapy and this was considered appropriate.

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

### **5 Comparator**

- 5.1 The submission nominated exenatide DCP as the main comparator. The submission noted that dulaglutide, despite not being a pharmacological analogue, could take market share from exenatide autoinjector. However, dulaglutide was only recently PBS listed in June 2018 and therefore the impact on the market for exenatide is unclear. The ESC agreed with the submission nominated comparator. The ESC noted the Pre-Sub-Committee Response (PSCR) and the [REDACTED]. The ESC noted that weekly dosing is increasing in utilisation and

considered that dulaglutide, another once weekly injection, may be a relevant comparator.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 The sponsor requested a hearing for this item. The clinician stated that the new presentation was easier to use resulting in improved compliance due to ease of administration. The clinician discussed the clinical data submitted in the submission claiming that there was no significant difference in efficacy between the two formulations and presenting further pharmacodynamic and pharmacokinetic modelling to demonstrate similarity of exenatide blood plasma concentration across the forms, stating blood plasma concentration varied in limited amounts that were not clinically significant, across the clinical trials. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

### ***Consumer comments***

6.2 No consumer comments were received for this submission.

### ***Clinical trials***

6.3 The submission was based on:

- one head-to-head randomised trial comparing exenatide once weekly autoinjector to exenatide twice daily (NEO-1); and
- two head-to-head randomised trials comparing exenatide once weekly DCP to exenatide twice daily (DURATION-1 and DURATION-5).

6.4 A claim of non-inferiority was made on the outcome of change in HbA1c from baseline at week 24/26/30 derived from an indirect treatment comparison (ITC) using Bucher's method between exenatide autoinjector with exenatide DCP using exenatide twice daily as the common comparator.

6.5 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Exenatide once weekly autoinjector versus exenatide twice daily - included</b>		
NEO-1	<p>A randomised, open label, long term, parallel group, comparator controlled, multicentre study to compare the glycemic effects, safety, and tolerability of exenatide once weekly suspension to exenatide twice daily in subjects with type 2 diabetes mellitus.</p> <p>Wysham C et al: Efficacy and tolerability of the new autoinjected suspension of exenatide once weekly versus exenatide twice daily in patients with type 2 diabetes.</p> <p>Wysham C et al: DURATION NEO 1: Greater HbA(1c) reductions with exenatide suspension once weekly by autoinjector pen versus exenatide twice daily in inadequately controlled type 2 diabetes.</p> <p>Wysham C et al: Duration neo 1: Greater A1C reductions with exenatide suspension once weekly by autoinjector pen versus exenatide twice daily in inadequately controlled type 2 diabetes.</p> <p>Wysham C et al: Patient reported treatment satisfaction with exenatide once weekly suspension for autoinjection (EQW SAI) versus exenatide twice daily (EBID) in patients with inadequately controlled type 2 diabetes mellitus (T2DM).</p>	<p>Final Clinical Study Report for Study MB001 003/BCB118. Report date: 26 March 2015.</p> <p>Diabetes, Obesity and Metabolism 2018; 20:165 72.</p> <p>Diabetologia 2014; 57 SUPPL. 1 (S109). Date of Publication: September 2014</p> <p>Endocrine Reviews. 2014; 35 SUPPL. 3. Date of Publication: 2014</p> <p>Endocrine Reviews (2015) 36 Supplement 2. Date of Publication: 2015</p>
<b>Exenatide once weekly dual chamber pen versus exenatide twice daily - included</b>		
DURATION-1 (study 105)	<p>Clinical Study Report BCB105: A randomised, open label, multicentre, comparator controlled study to examine the effects of exenatide long acting release on glucose control (HBA1c) and safety in subjects with type 2 diabetes mellitus managed with diet modification and exercise and/or oral antidiabetic medications.</p> <p>Drucker D et al: Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open label, non-inferiority study.</p> <p>Buse J et al: DURATION 1: Exenatide once weekly produces sustained glycaemic control and weight loss over 52 weeks.</p> <p>Wysham C et al: Five Year Efficacy and Safety Data of Exenatide Once Weekly: Long term Results from the DURATION 1 Randomized Clinical Trial.</p> <p>Macconell L et al: Exenatide once weekly: Sustained improvement in glycemc control and cardiometabolic measures through 3 years.</p> <p>Macconell L et al: Exenatide once weekly resulted in sustained improvement in glycemc control with weight loss through 4 years.</p> <p>Maggs D et al: Exenatide once weekly resulted in sustained improvement in glycaemic control with weight loss through four years.</p> <p>Henry R et al: Efficacy and Tolerability of Exenatide Once Weekly over 6 Years in Patients with Type 2 Diabetes: An Uncontrolled Open Label Extension of the DURATION 1 Study.</p>	<p>07 July 2008.</p> <p>Lancet. 2008; 372:1240 50.</p> <p>Diabetes Care. 2010; 33:1255 61.</p> <p>Mayo Clinic Proceedings. 2015; 90:356 65.</p> <p>Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2013; 6:31 41.</p> <p>Diabetes. 2012; 61 SUPPL. 1 (A298). Date of Publication: June 2012</p> <p>Diabetologia. 2012. 55 SUPPL. 1 (S8). Date of Publication: October 2012</p> <p>Diabetes Technology and Therapeutics 2016; 18:677 86.</p>
DURATION-5 (study 108)	<p>Clinical Study Report BCB108: A randomised, open label, parallel group, comparator controlled, multicentre study to evaluate glycemc effects, safety, and tolerability of exenatide weekly in subjects with type 2 diabetes mellitus.</p> <p>Blevins T et al: DURATION 5: Exenatide once weekly resulted in greater improvements in glycaemic control compared with exenatide twice daily in patients with type 2 diabetes.</p>	<p>22 January 2010.</p> <p>J Clin Endocrinol Metab. 2011; 96:1301 10.</p>

Source: table 2-6, pp32-33 of the submission, Wysham et al 2017, Blevins et al 2011 and Drucker et al 2018.

6.6 The key features of the direct randomised trials included in the indirect comparison (with exenatide twice daily as the common comparator) are summarised in Table 3.

**Table 3: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Exenatide autoinjector vs exenatide twice daily</b>					
NEO-1	377	R, OL, 28 weeks	High	T2DM with HbA1c 7.1%-11.00%	Change in HbA1c% from baseline, incidence of adverse events
<b>Exenatide DCP vs exenatide twice daily</b>					
DURATION-1	293	R, OL, 30 weeks	High	T2DM with HbA1c 7.1%-11.00%	Change in HbA1c% from baseline, incidence of adverse events
DURATION-5	253	R, OL, 24 weeks	High	T2DM with HbA1c 7.1%-11.00%	Change in HbA1c% from baseline, incidence of adverse events
Meta-analysis	546	Included DURATION-1 and DURATION-5, assessed change in HbA1c% from baseline			

R=randomised; OL=open label

Source: Table 2-6, pp32-33 of the submission , Figure 1, Wysham et al 2017, Figure 1, Blevins et al 2011 and Figure 1, Drucker et al 2018.

6.7 The proposed PBS population (exenatide as a second- or third-line agent, in addition to at least one other oral antidiabetic agent) does not align with the whole trial population in NEO-1, DURATION-1 and DURATION-5 (where exenatide could be used as monotherapy alongside diet and exercise). Patients enrolled in the trials who were treated with diet and exercise alone are not representative of the proposed PBS population. However, it is unclear if the efficacy of exenatide once weekly differs as monotherapy or in combination therapy.

6.8 The rules for concomitant medication differed between trials. In NEO-1, patients were to continue their antidiabetic medications from baseline with no changes in doses unless patients experienced a loss in glucose control (2 consecutive visits with fasting blood glucose >15.0 mmol/L in week 4-16 or >13.3 mmol/L from week 16-28). Similarly, in DURATION-5, patients were to refrain from changing their baseline antidiabetic medications during the study unless otherwise instructed. However, in DURATION-1, all patients who were treated with sulphonylurea had their dose re-titrated during the study. This decreased the sulphonylurea dose to the minimum labelled dose until week 10 and then up titrated based on daily glucose measurements to reach a fasting plasma glucose of <6 mmol/L. DURATION-1 should be excluded from the indirect comparison given the differences in the administration of concomitant antidiabetic medications compared to NEO-1. The ESC considered that the comparison of NEO-1 and DURATION-5 was the most appropriate indirect comparison as the trial designs were similar in relation to background use of oral anti-diabetic medication.

### **Comparative effectiveness**

6.9 The results for least squares (LS) mean change from baseline HbA1c per cent from NEO-1, DURATION-1 and DURATION-5 are summarised in Table 4.

**Table 4: Least squares mean change from baseline HbA1c per cent across the trials**

	NEO-1 (28 weeks)		DURATION-1 (30 weeks)		DURATION-5 (24 weeks)	
	Exenatide QWS-AI (N=229)	Exenatide 10mcg BD (N=146)	Exenatide QW-DCP (N=148)	Exenatide 10mcg BD (N=147)	Exenatide QW-DCP (N=129)	Exenatide 10mcg BD (N=123)
Baseline mean (SE)	8.47 (0.07)	8.51 (0.08)	8.3 (0.08)	8.3 (0.08)	8.5 (0.10)	8.4 (0.10)
Mean Δ HbA1c (SE)	-1.44 (0.09)	-1.08 (0.12)	-1.6 (0.09)	-1.3 (0.08)	-1.4 (0.10)	-0.7 (0.10)
LS mean Δ HbA1c (SE)	-1.39 (0.09)	-1.02 (0.11)	-1.9 (0.08)	-1.5 (0.08)	-1.6 (0.10)	-0.9 (0.10)
LS mean difference (95% CI)	-0.37 (-0.63, -0.10) p=0.0072		-0.33 (-0.54, -0.12) p=0.0023		-0.7 (-0.9, -0.4) p<0.0001	

Abbreviations: Δ, change; AI, autoinjector; DCP, dual-chamber pen; BD, twice daily; CI, confidence interval; HbA1c, glycosylated haemoglobin; LS, least squares; SE, standard error

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

Source: CSR for NEO-1: Table 7.2.1-1 (page 77); CSR for DURATION-1: Table 8 (page 49); CSR for DURATION-5: Table 7 (page 42)

6.10 Both exenatide autoinjector and exenatide DCP resulted in statistically significantly lower HbA1c per cent after 24-30 weeks of treatment compared to exenatide twice daily.

6.11 The results of the indirect comparison between exenatide autoinjector and exenatide DCP (using exenatide twice daily as the common comparator) are presented in Table 5.

**Table 5: Results of the indirect comparison of exenatide QWS-AI and the main comparator exenatide QW-DCP**

Trial	Change from baseline in HbA1c at endpoint LSM (SE)			LSM difference (95% CI)
	Exenatide QWS-AI	Common reference (Exenatide BD)	Exenatide QW-DCP	
<b>Exenatide once weekly autoinjector versus exenatide twice daily</b>				
NEO-1 (28 weeks)	-1.39 (0.09)	-1.02 (0.11)	-	-0.37 (-0.63, -0.10)
<b>Comparator versus common reference trials</b>				
DURATION-1 (26 weeks)	-	NR	NR	NR
DURATION-5 (24 weeks)	-	-0.9 (0.10)	-1.6 (0.10)	-0.7 (-0.9, -0.4)
Pooled (DURATION-1 and DURATION-5)	-	-1.18 (0.07)	-1.71 (0.07)	-0.53 (-0.70, -0.36)
Ji et al 2013 (week 26)	-	NR	NR	-0.31 (-0.49, -0.14)
Pooled (DURATION-1, DURATION-5 and Ji et al 2013)	-	NR	NR	-0.42 (-0.64, -0.20)
Indirect estimate of effect adjusted for the common reference				<i>0.16 (-0.16, 0.48)<sup>1</sup></i>
Indirect estimate of effect including Ji et al 2013				<i>0.05 (-0.29, 0.39)</i>
Indirect estimate of effect excluding DURATION-1 and Ji et al 2013				<i>0.33 (-0.03, 0.69)</i>

Abbreviations: LSM = least square means; QWS = once weekly suspension; QW = once weekly; AI = autoinjector; DCP = dual-chamber pen; SE = standard error, NR = not reported

Text in italics indicate values calculated during evaluation.

<sup>1</sup> Calculated during evaluation. Submission reported estimate of -0.16 (-0.48, 0.16) in error.

Source: Table 2-22, p58 of the submission

6.12 The indirect estimate of effect of change from baseline HbA1c per cent adjusted for the common reference was 0.16% (95% CI: -0.16, 0.48). The sponsor noted that the point estimate of 0.16% was below the non-inferiority margin of 0.4% indicating no statistically significant difference between exenatide autoinjector and exenatide DCP.

6.13 The submission suggested that a non-inferiority margin of 0.4% should apply based on the previous PBAC decision for dulaglutide (November 2017) and that the 0.4% margin was also applied in the clinical trials. The ESC noted that the upper limit of the

confidence interval exceeded the non-inferiority margin of 0.4% previously accepted by the PBAC and therefore advised that the data did not support the non-inferiority claim for exenatide autoinjector versus exenatide DCP. This might be explained by the lower bioavailability of exenatide in the autoinjector formulation compared to the DCP formulation. The ESC also considered that based on the ITC results, the exenatide autoinjector could be considered inferior to DCP. The Pre-PBAC Response argued that application of the 95% confidence interval to the base case result of 0.48 should be interpreted with caution due to uncertainty associated with an ITC and provided calculations to justify variance.

- 6.14 The PSCR sought to include Ji et al (2013) as the base case analysis. The study was originally excluded as it was conducted in Asian patients only, however as Australia has a significant Asian population and no ethnic differences had been observed, there was no reason to exclude this study. Inclusion of this study changed the ITC result to 0.05 (95% CI: -0.29, 0.39). Accordingly, the PSCR claimed that applying the 0.4% non-inferiority margin, the exenatide autoinjector is non-inferior to exenatide DCP. The ESC considered that the results of this comparison were not appropriate, as there was no evidence to support inclusion of the trial, no comment on the applicability to the PBS population or comparability of this trial to the others in the ITC. The ESC noted that the sponsor had also excluded Ji et al (2013) from the analysis of its submission to the November 2013 meeting due to the trial population not matching the likely Australian PBS population. The Pre-PBAC Response (p3) reiterated that the exclusion of Ji et al (2013) in the comparison was conservative and stated that the study had been reviewed to determine applicability and inclusion and exclusion criteria were consistent with NEO-1, DURATION-1 and DURATION-5, with a variation in baseline characteristics and background sulphonylurea use.
- 6.15 A sensitivity analysis excluding DURATION-1 from the indirect comparison was conducted during the evaluation. The indirect estimate of effect in this sensitivity analysis was 0.33% (95% CI: -0.03, 0.69), which also did not meet the nominated non-inferiority margin. The ESC noted that the indirect comparison of only the NEO-1 and DURATION-5 trials yielded a less favourable point estimate, as well as a higher upper CI limit.
- 6.16 The ESC noted that only the indirect comparison including Ji et al (2013) provided an upper limit under the 0.4% margin, and that inclusion of Ji et al (2013) and DURATION-1 introduced significant uncertainty.
- 6.17 The PSCR presented data from a range of exenatide DCP studies that demonstrated a statistically significant reduction in HbA1c from baseline, claiming that this should be considered therapeutically equivalent to exenatide autoinjector as the reductions were in line with those reported in NEO-1 and NEO-2 for exenatide autoinjector. The PSCR also included pharmacokinetic and pharmacodynamic modelling which it claimed supported therapeutic equivalence. The ESC did not consider that these data were sufficiently relevant to consideration of non-inferiority of exenatide autoinjector, particularly given the results of the indirect comparison. The Pre-PBAC Response (p2) reiterated the value of these additional data, stating there is inevitable

variability across the DURATION studies and these data enable a more reliable comparison than an ITC, demonstrating therapeutic equivalence of exenatide autoinjector and DCP.

### **Comparative harms**

- 6.18 The submission presented an indirect comparison of the incidence of adverse events. None of the adverse events in the indirect comparison showed statistically significant differences between exenatide autoinjector and exenatide DCP. No non-inferiority margin for safety outcomes was nominated. The ESC noted that there were no significant differences in the indirect comparison and considered it uncertain, but likely that the claim of non-inferior safety was reasonable.

### **Benefits/harms**

- 6.19 The indirect comparison presented in the submission did not result in statistically significant differences in benefits and harms of exenatide autoinjector and exenatide DCP. Accordingly, a benefits/harms table was not presented.

### **Clinical claim**

- 6.20 The submission described exenatide 2mg once weekly autoinjector as non-inferior in terms of effectiveness and safety compared with exenatide 2mg once weekly DCP.
- 6.21 The therapeutic conclusion presented in the submission was not adequately supported by the evidence presented in the submission because the upper 95% confidence interval for the change from baseline in HbA1c per cent from the indirect comparison did not meet the non-inferiority margin of 0.4%. No non-inferiority margin for safety outcomes were proposed so it was not possible to conclude that non-inferiority was demonstrated; however, it is likely that there were no differences in safety between the exenatide autoinjector and exenatide DCP. The PSCR claimed exenatide autoinjector shows statistically lower HbA1c compared to exenatide twice daily ( $p=0.0072$ ). The PSCR added that exenatide autoinjector and exenatide DCP are therapeutically equivalent, based on population pharmacokinetic and pharmacodynamic modelling provided in the PSCR. The population analysis showed that the average steady-state plasma concentration of both exenatide forms was similar (within ■%). The HbA1c analysis also yielded no therapeutic difference between the two forms. The ESC considered that the submission's non-inferiority claim was not adequately supported based on the base-case comparison exceeding the non-inferiority margin of 0.4% previously considered by the PBAC. Moreover, the ESC advised that best indirect comparison would be using the NEO-1 and DURATION-5 trials; however, this comparison resulted in a worse point estimate and a higher upper limit of the CI for exenatide autoinjector.
- 6.22 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.
- 6.23 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

## Economic analysis

6.24 The submission presented a cost-minimisation analysis of exenatide autoinjector versus the exenatide DCP. The result of the cost minimisation analysis is presented in Table 6.

**Table 6: Results of the cost minimisation analysis**

	Exenatide once weekly autoinjector	Exenatide once weekly DCP
Equi-effective dose	2 mg	2 mg
Administration frequency	Once weekly	Once weekly
Drug cost (pack of 4 injections) (DPMQ)	\$131.15	\$131.15
Drug cost (pack of 4 injections) (AEMP)	\$111.44	\$111.44 <sup>a</sup>
Drug cost (pack of 4 injections) (Effective AEMP)	\$ [REDACTED]	\$ [REDACTED] <sup>b</sup>
Doses per year	52	52
Annual drug cost per patient	\$1448.72	\$1,448.72
Annual incremental drug cost per patient		\$0

<sup>a</sup> PBS ex-manufacturer excel sheet (<http://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price>)

<sup>b</sup> Effective AEMP as per the current exenatide once weekly-DCP (BYDUREON) special pricing arrangement\

Source: Table 3-4, p66 of the submission

6.25 The equi-effective doses were estimated as exenatide autoinjector 2 mg administered once weekly and exenatide DCP 2 mg administered once weekly, based on the results of an indirect comparison. This may not be an appropriate equi-effective dose, as the submission did not adequately demonstrate that exenatide autoinjector 2 mg once weekly was non-inferior to exenatide DCP 2 mg once weekly. The ESC considered that the equi-effective dose was not supported by the ITC results.

6.26 The ESC considered the cost-minimisation should account for the reduced efficacy of exenatide autoinjector compared to exenatide DCP and that offsets to account for the additional costs associated with increased use of other oral hypoglycaemic medicines should be included.

### Drug cost/patient/year

6.27 The cost per patient per year for treatment with exenatide autoinjector would be \$1,704.95 based on 13 packs of 4 injections each year, allowing for 52 weekly doses at the published DPMQ of \$131.15; or \$ [REDACTED] based on 13 packs of 4 injections each year, allowing for 52 weekly doses at the effective DPMQ of \$ [REDACTED]. The patient is expected to continue treatment indefinitely. This is the same cost/patient/year as for exenatide DCP.

### Estimated PBS usage & financial implications

6.28 This submission was not considered by DUSC. The financial estimates for the listing of exenatide autoinjector are presented in Table 7.

6.29 Given that the requested price for exenatide autoinjector was the same as the exenatide DCP, (which the submission expects to be replaced in a 1:1 ratio) and the submission assumed no growth in the market due to the listing of the autoinjector, the result of no overall change is reasonable. However, there may be insufficient evidence to claim that exenatide autoinjector is non-inferior to exenatide DCP

therefore, the 1:1 ratio may not be reasonable, or there may be changes in concomitant medications not captured in the submission. The ESC considered that increased use of oral anti-diabetic medicines was likely given the results of the ITC, and that these have not been adequately factored in to the financial estimates.

**Table 7: Estimated use and financial implications of listing exenatide autoinjector**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed	██████	██████	██████	██████	██████	██████
<b>Estimated financial implications of exenatide autoinjector</b>						
Cost to PBS/RPBS less copayments (published)	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Cost to PBS/RPBS less copayments (effective)	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
<b>Estimated financial implications for exenatide DCP replaced</b>						
Cost to PBS/RPBS less copayments (published)	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Cost to PBS/RPBS less copayments (effective)	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
<b>Net financial implications</b>						
Net change in prescription	0	0	0	0	0	0
Net change in MBS	\$0	\$0	\$0	\$0	\$0	\$0
Net impact for health budget	\$0	\$0	\$0	\$0	\$0	\$0

Source: Table 4-4, p69, table 4-5, p70, table 4-6, p71, table 4-7 and 4-8, p72, table 4-10, p73 of the submission

6.30 Moreover, the submission may have underestimated the annual growth rate of exenatide once weekly, though this may have minimal impact on the net financial implications ██████████

██████████. Further, there may potentially be growth in the exenatide once weekly market if the benefits of the autoinjector formulation (e.g. fewer shakes and less risk of needle stick injury) are relevant to the patient. Overall, the submission’s estimations of the financial impact for the listing of exenatide autoinjector were likely to underestimated, though the magnitude of the underestimate was unclear.

6.31 At year 6, the estimated number of scripts dispensed was over 200,000 and the cost to the PBS was estimated to be \$20 - \$60 million (effective).

**Quality Use of Medicines**

6.32 The submission proposed that the following actions would be undertaken to ensure quality use of medicines, particularly for the period of time where both forms of the medicine will be PBS listed:

- A letter to prescribers communicating key features of the exenatide autoinjector along with the TGA approved PI and PBS prescribing information following PBS-listing;

- Sales representatives and medical personnel will be trained on optimal use of the exenatide autoinjector and will be responsible for educating prescribers and diabetes educators;
- Promotional material in line with Medicines Australia Code of Conduct will be distributed; and
- Sponsored medical education programmes will be updated to include exenatide once weekly autoinjector.

Further, post marketing pharmacovigilance activities will be conducted.

### **Financial Management – Risk Sharing Arrangements**

- 6.33 The sponsor sought a special pricing arrangement (SPA) for exenatide once weekly autoinjector at an effective ex-manufacturer price of \$ [REDACTED], which is the same as current effective ex-manufacturer price for exenatide once weekly DCP. The sponsor advised that after the PBS listing of exenatide once weekly autoinjector, [REDACTED].

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend exenatide 2 mg once weekly autoinjector for the treatment of type 2 diabetes mellitus (T2DM) on the basis that the indirect treatment comparison (ITC) presented in the submission did not support the claim that exenatide autoinjector was non-inferior in effectiveness to the currently PBS-listed exenatide dual chamber pen (DCP). While there may be patient-related benefits of using the autoinjector formulation due to ease of administration, the PBAC noted there was a low clinical need to list a new formulation of exenatide due to the availability of other weekly antidiabetic agents on the Pharmaceutical Benefits Scheme (PBS) for the same patient population.
- 7.2 The PBAC considered that the requested listing was appropriately aligned with exenatide DCP.
- 7.3 The PBAC considered that exenatide DCP was the appropriate comparator. However, the PBAC noted that there was an increased preference for antidiabetic medicines with weekly dosing schedules and therefore considered that dulaglutide, another once weekly injection, was also a relevant comparator.
- 7.4 The PBAC agreed with the ESC that the trials included in the ITC were not comparable, due to differences in the trial design including sulphonylurea usage in the DURATION-1 study. The PBAC considered that the PSCR's request to include Ji et al (2013) in the ITC was inappropriate, as there was no evidence to support inclusion of the trial or applicability to the ITC. The PBAC noted that the Asian population in Australia was

approximately 9% at the 2016 census<sup>1</sup> compared to 100% in Ji et al. The PBAC therefore considered that the most appropriate trials for use in the indirect comparison were NEO-1 and DURATION-5 as they were similar in design and background use of oral anti-diabetic medication.

- 7.5 The PBAC considered that the results of the ITC did not support non-inferiority of exenatide autoinjector to exenatide DCP, with an indirect estimate of effect of change from baseline HbA1c of 0.16% (95% CI: -0.16, 0.48) in the base case and 0.33% (95% CI: -0.03, 0.69) in the revised ITC removing the DURATION-1 trial.
- 7.6 The PBAC noted the pharmacokinetic and pharmacodynamic modelling presented in the PSCR and in the sponsor hearing, however considered that given the results of the indirect treatment comparison, these data were insufficient to demonstrate non-inferiority.
- 7.7 The PBAC considered it likely that reduced bioavailability of exenatide autoinjector explained the results of the indirect treatment comparison not supporting non-inferiority.
- 7.8 The PBAC considered that the claim of non-inferior comparative safety was reasonable, noting that although there was some uncertainty as no non-inferiority margin for safety outcomes was nominated, there were no statistically significant differences observed in adverse events in the ITC.
- 7.9 The PBAC considered that the equi-effective doses were uncertain given the submission had not adequately demonstrated that exenatide autoinjector 2 mg once weekly was non-inferior to exenatide DCP 2 mg once weekly. The PBAC considered that the cost-minimisation analysis should have accounted for the reduced efficacy of exenatide autoinjector and included offsets to account for increased use of other oral hypoglycaemic medicines.
- 7.10 The PBAC considered that the utilisation estimates may be underestimated in annual growth rate, particularly given the stated convenience of the formulation. The PBAC also considered that the submission's estimate of zero net financial implications with the listing of the exenatide once weekly autoinjector was likely underestimated as the use of other hypoglycaemic medicines was likely to increase given the likely non-inferior efficacy compared with the exenatide once weekly DCP.
- 7.11 The PBAC considered that a future resubmission would need to be a major submission if presenting new clinical data to seek the same cost as the currently listed exenatide DCP presentation. A minor resubmission would be appropriate if seeking listing based on the same clinical data at a reduced price to reflect the reduced comparative efficacy

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<sup>1</sup>Australian Bureau of Statistics 2016,

<https://www.abs.gov.au/websitedbs/D3310114.nsf/home/census>, viewed March 2019

of exenatide autoinjector and adequately accounting for the likely increased concomitant usage of other hypoglycaemic medicines.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 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.

## **9 Sponsor's Comment**

The sponsor had no comment.