PUBLIC SUMMARY DOCUMENT

Product: Exenatide, powder for injection, 2 mg, Bydureon®
Sponsor: Bristol-Myers Squibb Australia Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The major re-submission requested listing of a 2 mg once weekly formulation for the treatment of Type 2 diabetes as:

1) Dual combination therapy with metformin or a sulfonylurea in a patient who meets certain criteria; and
2) Triple combination therapy with metformin and a sulfonylurea in a patient who meets certain criteria.

2. Background

This was the third consideration by the PBAC of the once weekly formulation. Exenatide 5 mcg and 10 mcg (twice daily) have been PBS listed since 1 August 2010.

The Public Summary Document for a submission rejected by the PBAC in July 2011 is available on the PBS website.

At the July 2013 meeting, the PBAC rejected a minor submission for exenatide once weekly injection on the basis of no new data presented to support the claims of comparative effectiveness and safety and unclear cost-offsets.

3. Registration Status

Exenatide 2 mg powder for injection was registered by the TGA on 20 December 2012 for:

- The treatment of type 2 diabetes mellitus in combination with metformin; or sulfonylureas; or metformin and a sulfonylurea in patients who have not achieved adequate glycaemic control.

4. Listing Requested and PBAC's View

The requested listing was unchanged from the previous submission:

Authority required (STREAMLINED)
Dual combination therapy with metformin or a sulfonylurea.

Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

Triple combination therapy with metformin and a sulfonylurea.

Type 2 diabetes, in combination with metformin and a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.

5. Clinical Place for the Proposed Therapy

Exenatide once weekly was proposed for use in type 2 diabetes mellitus in dual or triple therapy with metformin and/or sulfonylurea.

The re-submission assumed that exenatide weekly would substitute for exenatide twice daily and thus would not change the current management algorithms.

6. Comparator

The re-submission nominated exenatide 10mcg twice daily as the main comparator. This was the appropriate comparator and had been previously accepted by the PBAC in July 2011.

The re-submission nominated liraglutide 1.2mg once daily as a secondary comparator.

7. Clinical Trials

The re-submission was based on two head-to-head randomised trials comparing exenatide once weekly with exenatide twice daily (Study 105 and Study 108). The PBAC noted that these studies were included in the July 2011 submission. The re-submission presented new single-arm long term data for Study 105.

The re-submission also presented data from two supportive head-to-head trials comparing exenatide weekly to sitagliptin, pioglitazone and insulin glargine (Study 106 and Study GWBR). The PBAC noted that these studies were also previously included in the July 2011 submission. The re-submission presented new long-term data for both of these studies (single arm for Study 106 and comparative data for Study GWBR).

The re-submission also presented indirect comparisons of exenatide weekly versus liraglutide 1.2 mg once daily using either sitagliptin (Study 106, Study 1860) or liraglutide 1.8mg once daily (DURATION-6, Study 1860, LEAD-1, LEAD-2) as the common comparator. These indirect analyses were new to the current re-submission.

A direct comparison of exenatide once weekly versus liraglutide 1.8mg once daily was also presented based on head-to-head results from the DURATION-6 trial.

Details of the studies presented in the submission are shown in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
Exenatide weekly vs. exenatide twice daily		
Study 105 (DURATION-1)	Amylin Study Report (2008). A randomized, open-label, multicenter 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 anti-diabetic medications	Internal study report
	MacConell et al (2013b). Exenatide Once Weekly Resulted in Sustained Improvement in Glycemic Control With Weight Loss Through 4 Years	48th Annual Meeting of the European Association for the Study of Diabetes
	MacConell et al (2013a). Exenatide once weekly: sustained improvement in glycemic control and cardiometabolic measures through 3 years	Diabetes, Metabolic Syndrome and Obesity Targets and Therapy 6: 31-41
	Chiquette et al (2012). Treatment with exenatide once weekly or twice daily for 30 weeks is associated with changes in several cardiovascular risk markers	Vascular Health and Risk Management 8: 621-629
	Taylor et al (2011). Exenatide once weekly treatment maintained improvements in glycemic control and weight loss over 2 years	BMC Endocrine Disorders 11: 9
	Buse et al (2010). Exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks	Diabetes Care 33: 1255-1261
	Best et al (2009). Improved treatment satisfaction and weight-related quality of life with exenatide once weekly or twice daily	Diabetic Medicine 26: 722-728
	Drucker et al (2008). Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study.	Lancet 372: 1240-1250
Study 108 (DURATION-5)	Amylin Study Report (2010). A randomized, open-label, parallel-group, comparator controlled, multicenter study to evaluate the glycaemic effects, safety and tolerability of exenatide once weekly in subjects with type 2 diabetes mellitus	Internal study report
	Blevins et al (2011). Duration 5: Exenatide once weekly resulted in greater improvements in glycaemic control compared to exenatide twice daily in patients with type 2 diabetes	Journal of Clinical Endocrinology and Metabolism 96: 1-10
Exenatide weekly vs. non GLP-1 analogue		
Study 106 (DURATION-2)	Amylin Study Report (2009). A randomized, double-blind, parallel-group, multicenter study to compare the glycaemic effects, safety and tolerability of exenatide once weekly to those of	Internal study report

Trial ID	Protocol title/ Publication title	Publication citation
	sitagliptin and pioglitazone in subjects with type 2 diabetes mellitus treated with metformin	
	Amylin Study Report (2012). Study 106 Clinical Study Report (2.5 year treatment period)	Internal study report
	Best et al (2011). Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment	Diabetes Care 34: 314-319
	Wysham et al (2011). DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide	Diabetic Medicine 28: 705-714
	Bergenstal et al (2010). Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION 2): a randomised trial	Lancet 376: 431-439
Study GWBR (DURATION-3)	Eli Lilly Study Report (2009). Efficacy of once-weekly exenatide long-acting release and once-daily insulin glargine in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylurea	Internal study report
	Eli Lilly Study Report (2012). GWBR Clinical Study Report (156-week treatment period)	Internal study report
	Diamant et al (2010). Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION 3): an open-label randomised trial	Lancet 375: 2234-2243
Exenatide weekly vs. liraglutide (1.8mg)		
Study GWDE (DURATION-6)	Eli Lilly Study Report (2012). Safety and Efficacy of Exenatide Once Weekly versus Liraglutide in Subjects with Type 2 Diabetes and Inadequate Glycemic Control Treated with Lifestyle Modification and Oral Anti-diabetic Medications	Internal study report
	Buse et al (2013). Exenatide once-weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study.	Lancet 381: 117-124
Liraglutide (1.2mg) vs. non GLP-1 analogue		
Study 1860	Pratley et al (2011). One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2	International Journal of Clinical Practice 65: 397-407

Trial ID	Protocol title/ Publication title	Publication citation
	diabetes: A randomised, parallel-group, open-label trial	
	Pratley et al (2010). Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: A 26-week, randomised, parallel-group, open-label trial	Lancet 375: 1447-1456
LEAD-1	Marre et al (2009). Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1)	Diabetic Medicine 26: 268-278
LEAD-2	Nauck et al (2013). Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study.	Diabetes, Obesity and Metabolism 15: 204-212
	Nauck et al (2009). Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes	Diabetes Care 32: 84-90
Systematic reviews/meta-analyses		
Fineman (2012)	Fineman et al (2012). Clinical relevance of anti-exenatide antibodies: safety, efficacy and cross-reactivity with long-term treatment	Diabetes, Obesity and Metabolism 14: 456-554
Ridge (2013)	Ridge et al (2012). Comparison of safety and tolerability with continuous (exenatide once weekly) or intermittent (exenatide twice daily) GLP-1 receptor agonism in patients with type 2 diabetes	Diabetes, Obesity and Metabolism 14: 1097-1103
Scott (2012)	Scott et al (2012). A network meta-analysis to compare glycaemic control in patients with type 2 diabetes related with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily and placebo	Diabetes, Obesity and Metabolism 15: 213-223
Shyangdan (2010)	Shyangdan et al (2010). Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis	BMC Endocrine Disorders 10: 20

8. Results of Trials

With regards to comparative effectiveness, the PBAC noted that at the July 2011 meeting the Committee had agreed that the difference in HbA1c between exenatide once weekly and exenatide twice daily from the pooled results of Studies 105 and 108 would represent a clinically meaningful difference favouring exenatide once weekly. However this was not sufficient to support a claim of superiority as there was uncertainty regarding the appropriateness of pooling data from these two trials given the differences in results.

The PBAC agreed that the clinical data presented in Study 105 and Study 108 supported exenatide once weekly being at least non-inferior to exenatide twice daily.

With regards to comparative harms, the PBAC recalled that the Committee had previously raised concerns about the differences in dose between exenatide twice daily and exenatide once weekly (140 mcg vs. 2000 mcg per week). In response, the re-submission presented a biological plausibility argument claiming that the exenatide weekly dose of 2000mcg was chosen to provide a sustained steady-state concentration at the same level as the average peak concentration of exenatide 10mcg twice daily to ensure that most patients experience optimal glycaemic effects with minimal toxicity.

The PBAC noted that exenatide once weekly has a similar short-term safety profile to both exenatide twice daily and liraglutide, and no new safety concerns were identified by new safety data (up to 4 years) from long-term extensions of Study 105 (4 years), Study 106 (2.5 years) and Study GWBR (3 years) or by the Periodic Safety Update reports covering the period from April 2012 to March 2013.

9. Clinical Claim

The re-submission described exenatide once weekly as superior in terms of efficacy and equivalent in terms of safety compared to exenatide twice daily.

The PBAC considered that the issues around pooling of the data used to support the superiority claim remained, but noted that the claim of superiority was not material to the economic analysis presented, as the price proposed was ‘equivalent’ to exenatide twice daily. The data presented supported exenatide once weekly being at least non-inferior to exenatide twice daily.

The PBAC noted the additional safety data that had been presented in the re-submission, and considered that based on this information the claim of equivalent safety was reasonable.

The re-submission described exenatide once weekly as non-inferior in terms of efficacy and equivalent in terms of safety compared to liraglutide 1.2mg once daily.

10. Economic Analysis

The re-submission presented a modelled cost utility analysis of exenatide once weekly vs. exenatide twice daily for dual and triple therapy.

The PBAC noted the issues raised in the Commentary and Economic Sub committe (ESC) advice about the structure and inputs of the model. In particular, the Committee noted that the re-submission continued to apply side effect/injection frequency disutility values and UK Prospective Diabetes Study (UKPDS) risk equations in the model, despite these assumptions being raised as concerns by the Committee previously.

The PBAC agreed with the ESC that the economic model remained highly uncertain and was of limited value considering that the underlying assumption of the model was that both drugs would have ‘equivalent’ prices.

The PBAC noted that, as in the July 2013 minor re-submission, the pricing calculation was based on price parity to exenatide twice daily plus cost-offsets to PBS. The re-submission claimed that the cost-offsets to PBS were associated with the reduced number of needles required for patients on exenatide once weekly and an increase in patient co-payments received with exenatide once weekly supply for 28 days compared to exenatide twice daily supply for 30 days. The re-submission stated that the proposed pricing was intended to provide the same cost to PBS as exenatide twice daily.

The Pre-PBAC response also stated that the proposed price for exenatide weekly would be exactly equivalent to the price of exenatide twice daily plus the cost of needles required to administer exenatide and additional co-payments. The re-submission stated that there would be a cost to the Government for the needles for exenatide twice daily whereas there would be no cost with exenatide once weekly as the pack provides the administration needle with the drug in a prefilled syringe.

The PBAC recalled that cost-offsets for reduced needle use had not been accepted in the Committee's consideration of the listing of liraglutide for type 2 diabetes, but that in the case of exenatide once weekly the required needles were provided with the product, compared to liraglutide still requiring some needles be provided through the National Diabetes Services Scheme (NDSS), and as such the savings were more likely to be realised, although not to the extent claimed.

The PBAC agreed that it was appropriate to include some cost-offset to account for the Government costs for needles but not to the extent requested by the submission. Given that PBAC had not previously accepted the cost-offset claimed for differential needle use for liraglutide, and noting that the total cost offset claimed in the case of exenatide (based on the assumption of 100% compliance with twice daily exenatide dosing and use of a new needle for each dose) was not substantiated by any data, the Committee considered approximately 50% of that use would be a reasonable basis for a claimed offset. The PBAC considered that a majority of patients using exenatide weekly, through the proposed restriction, would not access needles on the NDSS for other purposes. However, the PBAC did not accept the submission's claim of cost-offsets associated with the increase in co-payments.

11. Estimated PBS Usage and Financial Implications

The re-submission presented a market share approach, based on the exenatide 10mcg twice daily market share data. The likely number of prescriptions dispensed over the first five years of listing was estimated in the submission to be greater than 1 million.

The re-submission claimed that the net cost to Government would be approximately zero, with additional cost to the PBS being offset by the reduction in cost of needles and an additional co-payment. The PBAC did not accept this claim as it relied on offsets that were not accepted by the Committee.

12. Recommendation and Reasons

The PBAC recommended listing of 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 10mcg twice daily.

The PBAC noted the previous issues about the appropriateness of pooling of the data used to support the superiority claim, but considered that the claim of superiority was not material to the economic analysis presented, as the price proposed was 'equivalent' to exenatide twice daily. The Committee considered that the data presented supported exenatide once weekly being at least non-inferior to exenatide twice daily.

The PBAC noted that additional safety data had been provided in the current re-submission, and considered that on the basis of this additional information a claim of non-inferior safety between exenatide 2mg once weekly and exenatide 10mcg twice daily was reasonable.

The Committee agreed that some cost-offsets for reduced needle use would be appropriate, and that the price for exenatide 2mg once weekly should be calculated on this basis. Given that PBAC had not previous accepted the cost-offset claimed for differential needle use for liraglutide, and noting that the total cost offset claimed in the case of exenatide (based on the assumption of 100% compliance with twice daily exenatide dosing and use of a new needle for each dose) was not substantiated by any data, the Committee considered approximately 50% of that use would be a reasonable basis for a claimed offset.

The PBAC considered that exenatide 2 mg once weekly is suitable for inclusion in the list of medicines for prescribing by nurse practitioners within collaborative arrangements.

In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to it at its November 2013 meeting, exenatide should not be treated as interchangeable on an individual patient basis with liraglutide.

Outcome:
Recommended

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

Condition:	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 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.
Prescriber Instructions	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. 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. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: 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 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.
Administrative Advice	Note: This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1, an insulin or an SGLT2 inhibitor. Note: Special Pricing Arrangements apply.

Condition:	Type 2 diabetes mellitus
Restriction:	Authority required (STREAMLINED)
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% 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.
Prescriber Instructions	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. 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. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: 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 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.
Administrative Advice	Note: This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1, an insulin or an SGLT2 inhibitor. Note: Special Pricing Arrangements apply.

13. 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.

14. Sponsor's Comment

The sponsor had no comment.