BRISTOL MYERS SQUIBB AUSTRALIA AND ASTRAZENECA AUSTRALIA

Submission to the Department of Health and Ageing

on

Post-Market Review of Products Used in the Management of Diabetes: Stage 3 – Medicines Used in the Treatment of Type 2 Diabetes

July 2013

Contents

1. Executive Summary

Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) ("the alliance") welcome the opportunity to provide input into Stage 3 of the Post-Market Review of Products Used in the Management of Diabetes (*The Review*). *The Review* should fully examine the clinical management of diabetes and the value clinicians and patients place on treatment selection.

The alliance have a broad portfolio of medicines currently available and in development for the treatment of type 2 diabetes mellitus (T2DM), each with a distinct clinical profile that will provide appropriate treatment choices for a range of patients with varying risk-profiles.

A majority of the current best-practice guidelines for the management of T2DM contain recommendations where the individual's risk profile is central to treatment choice. For example, the joint American Diabetes Association (ADA) / European Association for the Study of Diabetes (EASD) guidelines state that HbA1c treatment targets and choice of medicine should be determined for an individual patient taking into account factors such as:

- time since diagnosis
- diabetes symptoms
- cardiovascular profile
- weight
- risk and consequence of hypoglycaemia
- presence and severity of co-morbidities such as renal or hepatic impairment

The Australian treatment guidelines for T2DM are outdated and in contrast to many of the International guidelines, are restrictive and based on historical PBAC decisions rather than an evidence-based, best-practice approach.

The current PBS process inadequately recognises how important it is that clinicians have a number of treatment options available by failing to appropriately value issues important to individual patients such as weight loss, reduction in incidence and severity of hypoglycaemia and cardiovascular benefits such as lowering blood pressure. *The Review*, done properly, provides the PBAC with a timely opportunity to (i) acknowledge the value of having a range of therapeutic options available for treating patients based on their individual risk profile and (ii) to evolve the current PBS restrictions accordingly.

The alliance recommends that outcomes and future actions arising from *The Review* focus on:

i) **acknowledging** and **valuing** the need for clinicians to make treatment choices specific to an individual's risk profile (e.g. consequence of hypoglycaemia, time since diagnosis, treatment target, cardiovascular profile, weight, symptoms etc), and

ii) **updating** the Australian clinical guidelines to reflect best-practice, evidence-based medicine and recognising the need to select treatment based on an individual's risk-profile

iii) **simplifying** PBS restrictions, consistent with TGA indications, to allow for the safe and appropriate utilisation of T2DM medications in the context of this individualised therapy framework.

The alliance acknowledges that there is a low level of use of the newer T2DM medications outside of the current PBS criteria. However, the two DUSC reports cannot be seen as sufficiently aligned, nor quantitatively accurate, to deliver a true estimation of the percentage of use outside PBS criteria. Importantly, the alliance reiterates that the vast majority of T2DM medication use is clinically appropriate and in accordance with recently updated International diabetes guidelines.

2. Background

BMS and AZ ("the alliance") are two companies with an expanding role and responsibility as stakeholders in diabetes management in Australia. This alliance continues to conduct substantial research, in Australia and globally, on the pharmacological management of T2DM, with studies ongoing involving:

- Saxagliptin (Onglyza): a PBS listed dipeptidyl peptidase-4 (DPP4) inhibitor;
- Exenatide: Byetta, a PBS listed glucagon-like peptide-1 (GLP1) receptor agonist and Bydureon, a new extended release formulation of exenatide;
- Dapagliflozin (Forxiga): a sodium/glucose co-transporter 2 (SGLT-2) inhibitor;

These research efforts are focussed on the best ways to use these medicines to secure a meaningful improvement in the health and long term outcomes for people with T2DM. The alliance is able to offer a range of medicines, with different modes of action and clinical profiles that add to the treatment armamentarium available to clinicians. Having a range of accessible treatment options is key to the ethos of individualised therapy.

Novel, safe and effective therapies, such as those being studied by the alliance, will deliver improved health outcomes for people already diagnosed with T2DM and address underlying disease pathophysiology. The increasing value that clinicians and patients place on these newer medicines is heightened by the growing concern with the effectiveness and tolerability of a number of older medicines including sulfonylureas (SUs) and thiazolidinediones (TZDs). This is exemplified through the data presented in the second utilisation report considered by DUSC which demonstrated that a small proportion of clinicians are using medicines outside of PBS restrictions to best meet the needs of their patients and to avoid perceived safety and long-term efficacy concerns around older medicines.

Notwithstanding concerns regarding process issues as outlined in the Medicines Australia submission, the Alliance supports *The Review*. *The Review* should fully examine the clinical management of diabetes and the value clinicians and patients place on treatment selection.

The alliance recommends that outcomes and future actions arising from *The Review* focus on:

i) **acknowledging** and **valuing** the need for clinicians to make treatment choices specific to an individual's risk profile (e.g. consequence of hypoglycaemia, time since diagnosis, treatment target, cardiovascular profile, weight, symptoms etc),

ii) **updating** the Australian clinical guidelines to reflect best-practice, evidence-based medicine and recognising the need to select treatment based on an individual's risk-profile, and

iii) **simplifying** PBS restrictions, consistent with TGA indications, to allow for the safe and appropriate utilisation of T2DM medications in the context of this individualised therapy framework.

Submission to Stage 3 of the post market review of products used in the management of diabetes are required to address terms of reference 1-4 as detailed on the PBS reviews website[1]. The layout of this submission and how it addresses each of the terms of reference is outlined in **Table 1.**

Table 1: Stage 3 of the Post-Market Review of Products Used in the Management of Diabetes

Term of Reference	How addressed in Submission
1. Describe the utilisation and patterns of treatment of PBS listed drugs for T2DM, and compare these with PBS restrictions	**Section 6** discusses the DUSC analysis of utilisation and raises some concerns about the quantitative interpretation of the report.
2. Consider if the utilisation of PBS listed drugs in current clinical practice represents expected cost effective use;	**Section 6** provides comment on aspects related to the cost of usage of DPP4s outside the current PBS restrictions
3. Consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002	**Section 4** and the **Appendix 1** summarises the clinical evidence that has previously been considered by the PBAC
4. Collate and evaluate any additional clinical studies or meta-analyses for drugs currently PBS listed for T2DM that the Pharmaceutical Benefits Advisory Committee (PBAC) has not seen and that would inform their consideration;	**Section 4** and the **Appendix 1** summarises the pivotal clinical evidence not previously considered by the PBAC. There is a substantial amount of clinical data available for both saxagliptin and exenatide. **Section 5** briefly discusses clinical data for two new diabetes medicines – Bydureon, an extended release formulation of exenatide and dapagliflozin (Forxiga)

Following a review of local and International T2DM treatment guidelines (**Section 3**), **Section 4** of this submission will detail the clinical evidence base that supports the efficacy

[1] http://pbs.gov.au/info/reviews/diabetes

and safety of the alliance's PBS listed medicines, namely saxagliptin (Onglyza) and exenatide (Byetta) for use across a broad range of patients with T2DM.

While currently not PBS listed, Bydureon (an extended release formulation of exenatide) and dapagliflozin (Forxiga) are currently under evaluation by the PBAC for PBS listing for the treatment of patients with T2DM. As these two novel therapies will be key to future potential treatment options for Australian patients with T2DM, the sponsor will briefly summarise relevant data specific to these two medicines in **Section 5** of this submission.

Section 6 will provide comment on the two recent DUSC analyses which, while demonstrating that the vast majority of Australian T2DM patients are treated according to current PBS restrictions, also concluded that some use utilisation occurs outside PBS listing. Uncertainties associated with the DUSC analyses will also be examined in this section.

3. Treatment Guidelines

Most current treatment guidelines contain flexible pharmacological recommendations, recognising that medicine choice and treatment target (i.e. HbA1c level) is dependent upon many factors including individual patient characteristics. Treatment decisions should be based on factors such as treatment target, efficacy of the medicine, cardiovascular risk profile and other co-morbidities, likelihood and implications of hypoglycaemia, weight and side-effects. Any value consideration of new diabetes medicines needs to take into account these factors. The Australian treatment guidelines for T2DM and PBS listings for medicines to treat T2DM need to be updated.

The treatment of T2DM is complex and treatment pathways are dependent upon individual risks, lifestyle factors and the ability to tolerate different medications. Most current treatment guidelines contain flexible pharmacological recommendations, recognising medicine choice is dependent on many factors including individual patient characteristics. A summary of pharmacological recommendations from key local and international treatment guidelines is provided in **Table 2.**

The joint ADA and EASD guidelines are representative of many of the treatment guidelines. They recommend adding a second oral agent, a GLP1 agonist or insulin to metformin if glycaemic targets aren't achieved within approximately 3 months (Inzucchi, 2012). Treatment decisions are based on factors such as efficacy (i.e. better HbA1c lowering ability if high glucose levels), cardiovascular risk profile, likelihood and implications of hypoglycaemia (i.e. in elderly patients at risk of a fall), weight, side-effects and cost. If a third agent is required, a medicine with a different mechanism of action should be added with strong recommendation to consider whether insulin maybe the best option, especially if a high blood glucose (as measured by HbA1c) is present.

Table 2 Pharmacological recommendations from T2DM treatment guidelines

Guideline	First-line	Second line	Third line	Treatment target
NHMRC and Australian Diabetes Handbook (NHMRC, 2005)	Metformin	Add SU Newer agents may be an option	Add insulin Newer agents may be an option	General HbA1c target in people with type 2 diabetes is ≤ 7%. An HbA1c target above 7% may be appropriate in people with type 2 diabetes who have a history of severe hypoglycaemia, a limited life expectancy, co-morbidities or who are elderly.
National Prescribing Service (NPS, 2012)	Metformin	Add SU Newer agents may be an option	Add insulin Newer agents may be an option	≤6.5% for patients with short duration of disease and no clinical cardiovascular disease ≤7.0% if longer duration of disease, any cardiovascular disease ≤8.0% if recurrent severe hyoglycaemia
American Diabetes Association and European Association for the Study of Diabetes (Inzucchi, 2012)	Metformin	Add a second oral agent, a GLP1 agonist or basal insulin. choice is based on advantages and disadvantages of specific drugs for each patient. Factors considered include efficacy, hypoglycaemia, weight, side effects and cost. If no response, agent should be withdrawn and substituted with an alternative that has a different mechanism of action.	Add a third oral agent, GLP1 agonist or insulin. Insulin may be best option.	HbA1c < 7% appropriate in most patients. Consider 6% to 6.5% in patients with short disease duration, long life expectancy, no significant CVD. Consider 7.5% to 8% if patient has history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and in those that struggle with self-management.
Canadian Diabetes	Metformin	Add an agent best suited to the individual based on patient and	Add an agent from a different class or add/ intensify insulin	-

Guideline	First-line	Second line	Third line	Treatment target
Association (Harper, 2013)	Insulin ± metformin in symptomatic patients	agent characteristics. Patient characteristics include: degree of hyperglycaemia, risk of hypoglycaemia, overweight or obese, comorbidities (renal, cardiac, hepatic) and preference. Agent characteristics include blood glucose lowering efficacy and durability, risk of hypoglycaemia, effect on weight, contraindications and side effects, cost and access.		
American College of Physicians (Qaseem, 2012)	Metformin	Add a second agent. While SUs are cheapest second-line agent, adverse events are generally worse with combination therapies that include an SU	Not included in scope of guideline	-
National Institute for Health and care Excellence (NICE)	Metformin SU is alternative if not overweight, metformin not tolerated or is contraindicated or rapid response required.	SU DPP4 or TZD (pio) if significant risk of hypoglycaemia (or its consequences) or SU is contraindicated or not tolerated. Continue only if HbA1c reduction of ≥0.5% in 6 months GLP1 agonist only if intolerant or contraindicated to either SU or MET and intolerant or contraindicated to DPP4, TZD. Continue only if HbA1c reduction of ≥1.0% in 6 months	Insulin Sitagliptin or pioglitazone if insulin is unacceptable because of employment, social, recreational or other personal issues or obesity. Some guidance provided on when one might be preferable to other. Continue only if HbA1c reduction of ≥1.0% in 6 months GLP1 agonist if BMI ≥ 35kg/m2 or BMI < 35kg/m2 but insulin unacceptable or weight loss would benefit other comorbidities. Continue only if HbA1c reduction of ≥1.0% and weight loss of at least 3 % in 6 months	Individualised target - HbA1c equal to or more than 6.5%

Guideline	First-line	Second line	Third line	Treatment target
American Association of Clinical Endocrinologists (Garber, 2013)	Metformin Dual therapy if HbA1c > 7.5%. Triple therapy if HbA1c >9.0%	Add GLP1 agonist, DPP4	Add GLP1 agonist, DPP4. Add insulin if still no resolution	HbA1c ≤ 6.5% for health patients without concurrent illness and at low hypoglycaemia risk HbA1c > 6.5% individualise goals for patients with concurrent illness and at risk of hypoglycaemia

Of note, many of the International treatment guidelines are less than 2 years old, with the exception of the Australian guidelines which were published in 2009. Also in contrast to many of the International guidelines, the Australian treatment guidelines are restrictive and based on historical PBAC decisions rather than an evidence-based, best-practice approach. It is clear that evolution of the Australian treatment guidelines and, subsequently, the PBS restrictions for the T2DM medicines is required and the alliance recommends this be a key outcome arising from *The Review.*

In addition to medicine choice being individualised, it is increasingly recognised that HbA1c targets need to be individualised too. The HbA1c target recommendations from clinical guidelines are presented in **Table 2**. The ADA recommend individualised HbA1c goals based on age, presence of co-morbidities, duration of diabetes, presence of cardiovascular disease or microvascular manifestations (ADA, 2013). A younger patient with newly diagnosed diabetes may aim for an HbA1c less than 6.5% while a target of less than 8% may be more appropriate for an older patient with long-standing disease. This requires a flexible approach to treatment options including access to medicines based on individual risk profile. For example, using an SU in an overweight, newly-diagnosed, young long-haul truck driver to achieve an HbA1c target of 6.5% may not be appropriate for a number of reasons. For example, SU causes weight gain and a number of factors may increase the risk (i.e. erratic meals due to occupation, aggressive HbA1c target) and consequence (i.e. truck accident) of hypoglycaemia.

This broad change from a prescriptive, defined treatment algorithm to a more flexible approach based on individual patient risk has evolved at least partly because of concerns regarding the incidence and consequences of hypoglycaemia (Oyer, 2013). The objectives and risks of therapy should be individualised and this requires a good understanding of the risk factors and the interventions that can improve hyperglycaemia without an unacceptable risk of hypoglycaemia.

The DUSC report indicates that SU is still an appropriate treatment choice for a majority of patients. However, SUs are seen by Australian clinicians as an inappropriate treatment option for some patients for a range of reasons beyond contraindication or intolerance to SU. As discussed below, these reasons include higher risk of hypoglycaemia, lack of durability of response and weight gain. Consequently, the extent of use of the newer agents such as the DPP4s is higher than would be expected simply based on the rate of contraindication/ intolerance to SU. SU is clearly not appropriate for all patients, as the extent of use of the

newer agents such at the DPP4s is higher than would be expected by the rate of contraindication/ intolerance to SU.

The SUs disadvantage in terms of durability is related to the fact they promote insulin secretion by pancreatic beta cells and hence, are dependent on beta cell activity. The effects of SU treatment diminishes over time and is dubbed “sulfonylurea failure” (Melander, 1990) . There a number of different causes postulated for this sulfonylurea failure, including the diminishing beta cell activity over time (Melander, 1990) and the densensitisation to insulin secretagogues over time (Rustenbeck, 2002).

Hypoglycaemia is a major issue for patients treated with SUs. The incidence of hypoglycaemia for the second generation SUs is lower than the older agents; however, as stated in the ADA/ EASD guidelines “even occasional hypoglycaemia may be devastating, if severe”. A number of factors may disincline prescribers from using SUs in their patients:

- the NHMRC Guidelines state that “people taking sulfonylureas, repaglinide or insulin may need to notify motor vehicle licensing authorities and their insurance company as these medications can affect driving performance”.
- the AusRoad “Assessing Fitness to Drive” publication states that if a ‘severe hypoglycaemic event’ occurs, the person should not drive for a minimum of 6 weeks. This may have a significant impact on a person’s quality of life.
- the presence of a note in the PBS listing for SUs, warning of the risk of hypoglycemia is also likely to compel clinicians to avoid SUs even in the absence of a clear contraindication or intolerance.
- the Australian PI for SUs notes patients who may be particularly sensitive to anti-diabetic agents include those who are elderly, undernourished or who have poor general health, and patients with adrenal insufficiency or hypopituitarism. Hypoglycaemia may be difficult to recognise in elderly patients and those receiving beta-blockers.
- the NPS[2] lists other medicines that may interact with SUs, including a number of agents that are likely to be taken in an older, T2DM patient population including blood thinners, ACE inhibitors and some medicines for depression.

[2] http://www.nps.org.au/conditions-and-topics/conditions/hormones-metabolism-and-nutritional-problems/diabetes-type-2/for-individuals/medicines-and-treatments/sulfonylureas, accessed January 2013

Whilst risk of hypoglycaemia may not be considered a contraindication to treatment with SU (Item 7.4 DUSC Agenda February 2013, page 6), it is a practical reason that clinicians may be hesitant to prescribe SU for some patients.

In conclusion:

1. Australian treatment guidelines and the PBS treatment algorithm are out of step with International guidelines and clinician practice.

2. There has been a shift in the management of T2DM towards individualisation of patient treatment, at least in part due to concerns around the effects of the older medicines (i.e. weight gain, hypoglycaemia) and the availability of newer medicines with positive clinical attributes (i.e. weight neutral or loss, less hypoglycaemia).

3. A collaborative approach involving all stakeholders, including Australian clinicians, other health care professionals, the pharmaceutical industry and the PBAC is an effective and robust way to bring about the evolution and alignment of treatment guidelines and the PBS listings of T2DM medicines to maximise patient outcomes.

4. Clinical data for PBS listed medicines

Saxagliptin and exenatide are safe and effective medicines that are supported by an extensive clinical evidence base for use as appropriate treatment options for a broad range of patients with T2DM at various stages of their disease.

The BMS/ AZ alliance currently have two PBS listed medicines for the management of T2DM: saxagliptin (Onglyza) and exenatide (Byetta). The information presented in this section addresses two of *The Reviews* Terms of Reference, namely:

- Consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002 (TOR 3), and
- Collate and evaluate any additional clinical studies or meta-analyses for drugs currently PBS listed for T2DM that the PBAC has not seen and that would inform their consideration (TOR 4)

A summary of the TGA indications, PBS listings and a brief discussion of the body of clinical evidence for saxagliptin and exenatide is provided in **Section 4.1** and **Section 4.2**, respectively. Detailed information on the clinical trial data used to support PBS listings (TOR 3) and the pivotal published evidence not considered previously by PBAC (TOR 4) for saxagliptin and exenatide is provided in the **Appendix 1.**

4.1 Saxagliptin (Onglyza)

Saxagliptin (Onglyza), a DPP4 inhibitor, is TGA registered for use in patients with T2DM as initial combination therapy, dual therapy, triple therapy and as an add-on to insulin. A summary of the TGA approved indications is provided in **Table 3**.

The PBS listing for all the DPP4s, including saxagliptin, is narrow, centred on a subset of patients in the dual oral therapy setting (restricted dual oral therapy, see **Table 4**). Restricted dual oral therapy refers to use in combination with metformin or SU in patients that cannot be treated with metformin and SU due to a contraindication or intolerance to one or both of the agents.

An immediate-release fixed dose combination of saxagliptin plus metformin (Kombiglyze) is TGA indicated for the same patient population as the saxagliptin monocomponent. The PBAC recommended Kombiglyze IR for listing in April 2013 as an unrestricted dual oral therapy.

Table 3 TGA approved indications for saxagliptin

DPP4 Inhibitor	Monotherapy	Initial combination	Dual Oral Therapy	Triple Oral Therapy	Add-on to Insulin
Saxagliptin	X	✓ With MET	✓ With MET, SU or TZD	✓ With MET and SU	✓ With or without MET

Source: Australian Register of Therapeutic Goods, accessed 19 June 2013

SU: sulfonylurea MET: metformin TZD: thiazolidinediones

Table 4 PBS reimbursed indications for saxagliptin

DPP4 Inhibitor	Monotherapy	Initial combination	Dual Oral Therapy	Restricted Dual Oral therapy	Triple Oral Therapy	Add-on to Insulin
Saxagliptin	X	X	X	✓	X	X

Source: PBS Schedule, accessed 19 June 2013

A number of other DPP4s, including saxagliptin, have previously tried unsuccessfully to broaden their PBS listing beyond that of restricted dual therapy. One of the hurdles that these previous submissions were unable to clear was convincing the PBAC of the clinical, economic and patient value of positive attributes related to weight neutrality/ weight loss and/ or reduction in hypoglycaemic events. These are key factors acknowledged in current International Guidelines as integral to the assessment of treatment options based upon individual risk profile.

A list of the pivotal published saxagliptin clinical trials and additional information for each trial is provided in the **Appendix 1**. In summary, there are a total of 14 trials, with 4 as monotherapy in treatment-naïve patients, 7 in dual oral therapy, 1 in triple oral therapy, 1 as add-on to insulin, 1 in initial combination with metformin, and 1 in renally impaired patients. Three of the dual oral therapy trials and the add-on to insulin trial have been evaluated by

the PBAC during consideration of submissions for these indications. The following section provides a broad overview of the clinical profile of saxagliptin.

Summary of clinical data

A number of clinical review papers provide a comprehensive overview of the saxagliptin clinical data (Kania, 2011, Yang, 2012, Gerrald, 2012).

When used as monotherapy or as a combination therapy (add-on to metformin, SU, TZD and insulin), saxagliptin reduces mean baseline HbA1c by a range of -0.52 to -0.9 (Kania, 2011, Yang, 2012). A meta-analysis of five placebo-controlled trials (with baseline HbA1c 7.7 to 8.5) found the mean incremental reduction in HbA1c from baseline of saxagliptin 5mg relative to placebo was -0.710 (95%CI: -0.805, -0.614) (Gerrald, 2012).

Saxagliptin is well- tolerated as both a monotherapy and a combination therapy (Kania, 2011). Adverse reactions reported in ≥ 5% of patients treated with saxagliptin 5mg and more commonly than in patients treated with placebo include upper respiratory tract infection (8.8% vs. 11.6%), urinary tract infection (6.9% vs. 4.2%), headache (8.2% vs. 7.4%) and sinusitis (5.6% and 3.2%). Saxagliptin is considered to be weight neutral (Kania, 2011). A pooled analysis of 6 randomised controlled trials found symptomatic hypoglycaemia in patients treated with saxagliptin 5mg to be comparable to placebo in monotherapy trials (5.6% saxagliptin 5mg vs. 4.1% placebo), in initial combination trials (3.4% saxagliptin 5mg plus metformin vs. 4.0% metformin) and for pooled add-on therapy trials (8.3% saxagliptin 5mg vs. 6.8% for placebo) (Chen R., 2009). None of the hypoglycaemic events across the 6 trials required medical assistance. In the add-on to insulin study, the overall incidence of reported hypoglycaemia was 18.4% for saxagliptin 5mg and 19.9% for placebo (Saxagliptin Product Information). In the triple therapy study (i.e. as add-on to metformin plus SU), the overall incidence of hypoglycaemia was 10.1% for saxagliptin 5mg and 6.3% for placebo (Saxagliptin Product Information).

Conclusion

The evidence base for saxagliptin is both robust and broad and provides clinicians with an effective tool with which to individualise treatment for their patients.

While the recent DUSC report on utilisation of diabetes medicines in Australia asserts that a small proportion of DPP4 use is outside their current PBS restriction, it can be clearly seen from the evidence and data presented that use of saxagliptin is clinically appropriate, within the bounds of TGA indications and most likely in accordance with recently evolved International diabetes guidelines.

The sponsor proposes that as a result of the Commonwealth's Stage 3 Review of Diabetes medicines, a broad, simplified PBS listing be assigned to saxagliptin that is reflective of its current TGA indications i.e. initial combination, dual oral therapy, triple oral therapy and add-on to insulin. This will allow Australian clinicians to take into account each patient's risk profile when deciding upon the most appropriate management options.

Any outcomes from *The Review*, will be more readily implemented if the PBAC process recognises the value of factors important to individual patients such as weight loss/ neutrality, reduction in incidence and severity of hypoglycaemia and cardiovascular benefits such as lowering blood pressure.

4.2 Exenatide (Byetta)

Exenatide (Byetta), a GLP-1 agonist, is administered as a subcutaneous injection (under the skin) to the abdomen, thigh, or arm before the first and last meal of the day. Given the unique mode of administration in non insulin T2DM patients, Byetta is distinct from the other currently reimbursed treatments for T2DM. Sponsorship of the exenatide products in Australia transferred from Eli Lilly to BMS on 1 April 2013.

Exenatide is TGA registered for use in the dual therapy, triple therapy and the add-on to insulin settings. A summary of the TGA approved indications for exenatide is provided in **Table 5.**

Exenatide is currently the only GLP1 agonist on the PBS. As with the DPP4s, the PBS listing for exenatide is centred on a subset of patients in the dual therapy setting (restricted dual therapy) and in the triple therapy setting (**Table 6**).

Table 5 TGA indications for exenatide

GLP-1 agonists	Monotherapy	Initial combination	Dual Therapy	Triple Therapy	Add-on to Insulin
Exenatide	X	X	✓	✓	✓

Source: Australian Register of Therapeutic Goods, accessed 19 June 2013

Table 6 PBS reimbursed indications for exenatide

GLP-1 agonists	Monotherapy	Initial combination	Dual Therapy	Restricted Dual therapy	Triple Therapy	Add-on to Insulin
Exenatide	X	X	X	✓	✓	X

Source: PBS Schedule, accessed 19 June 2013

A list of the pivotal published exenatide twice daily clinical trials and additional information for each trial is provided in the **Appendix 1**. In summary, there are a total of 11 trials, with 5 in dual therapy, 3 in triple oral therapy, 1 in add-on to insulin and 2 in mixed dual and triple therapy trials. Three of the dual therapy trials and the three triple therapy trials have been evaluated by the PBAC during consideration of submissions. The following section provides a broad overview of the clinical profile of exenatide twice daily formulation.

Summary of clinical data

Two clinical review papers provide a comprehensive overview of the clinical data for exenatide twice daily. (Balena, 2013, Gentilella, 2009).

Across 7 clinical trials in almost 3,000 patients treated for between 16 and 52 weeks, exenatide (5 µg or 10 µg twice daily) reduced HbA1c by a range of -0.40 to -1.43 (Gentilella, 2009). Exenatide reduced body-weight significantly more than both placebo and active comparators. Exenatide was generally well-tolerated and dose-dependent with affects on the gastrointestinal (GI) tract most common. Commonly reported adverse events included nausea (33 – 57%), vomiting (12 – 17.4%), diarrhoea (5.8 – 17.4%) and headache (4.7 – 8.9%). The nausea was mild to moderate in intensity and its incidence tended to decrease over time. Discontinuation of therapy because of the GI adverse events was low (~3 – 9% in 10 µg arm).

The incidence of hypoglycaemia in patients treated with exenatide in combination with an SU (14.4% and 35.7% for exenatide 5 µg bd and 10 µg bd, respectively) is higher than the incidence in patients treated with an SU plus placebo (3.3%). In contrast, when exenatide was used in combination with metformin, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin (5.3% for placebo, 4.5% and 5.3% for exenatide 5 µg bd and 10 µg bd, respectively). (Byetta Product Information)

Patients from three placebo-controlled studies entered a long-term open-label extension (Klonoff, 2008). The long-term extension trials demonstrated the therapeutic effect of exenatide on blood glucose as measured by HbA1c is fully maintained over 3 years with a mean HbA1c reduction of -1.0%. A progressive weight loss of -5.3 (±0.4) kg from baseline was also observed.

Pancreatitis has been reported in patients treated with the DPP4s and GLP1 agonists including exenatide; however, a causal relationship has not been established (Nauck, 2013).

Conclusion

The evidence base for exenatide is both robust and broad and provides clinicians and patients alike with confidence of its effectiveness in the treatment of T2DM.

While the recent DUSC report on utilisation of diabetes medicines in Australia asserts that a small proportion of exenatide use is outside its current PBS restriction, it can be clearly seen

from the evidence and data presented that the current use of exenatide is clinically appropriate, within the bounds of the TGA indications for this medicine and most likely in accordance with recent international diabetes guidelines.

Any outcomes from *The Review*, will be more readily implemented if the PBAC process recognises the value of factors important to individual patients such as weight loss/ neutrality, reduction in incidence and severity of hypoglycaemia and cardiovascular benefits such as lowering blood pressure.

5. New diabetes medicines

The two new medicines discussed here, exenatide extended-release formulation (Bydureon) and dapagliflozin (Forxiga), have unique clinical profiles and are currently under evaluation by the PBAC. They will provide additional opportunities for clinicians to tailor treatments to their patients individual risk profile.

5.1 Exenatide (Bydureon)

Bydureon is an extended release formulation of exenatide, requiring administration once a week. It is TGA registered for the treatment of T2DM for dual therapy (with metformin or a SU) and triple therapy (with metformin and a SU).

In three short-term, open-label trials exenatide extended-release formulation provided significantly better glycaemic control than exenatide twice daily. (Scott, 2012) In patients inadequately controlled on metformin, the addition of exenatide 2mg weekly was significantly better than the addition of sitagliptin [treatment difference -0.6% (95C%I: -0.9%, -0.4%] and pioglitazone [treatment difference -0.3% (95%CI: -0.6%, -0.1%) at 26 weeks (Bergenstal, 2010). These results were maintained to 52 weeks for exenatide treated patients and glycaemic control was significantly improved for patients that switched to exenatide from sitagliptin (Scott, 2012).

Weight-loss for exenatide once weekly is similar to that observed for exenatide twice daily. Overall, there was no difference in the general safety profile between exenatide twice daily and exenatide once weekly. The once weekly formulation is better tolerated in terms of gastrointestinal tract adverse events. Data presented recently show that the efficacy and safety profile of Bydureon is consistent over 3 years (Trautmann, 2013).

5.2 Dapagliflozin (Forxiga)

Dapagliflozin (Forxiga) is an oral SGLT-2 inhibitor that improves glycaemic control by reducing renal glucose absorption leading to urinary glucose excretion. Dapagliflozin is indicated as restricted monotherapy (when metformin is contraindicated or not tolerated), initial combination therapy with metformin and add-on combination therapy with metformin, SU or insulin (with or with metformin and/ or SU).

Five published randomised double-blind, placebo-controlled Phase III trials demonstrate that dapagliflozin 10mg/ day as monotherapy in previously untreated patients, or as add-on combination therapy with metformin, SU, pioglitazone or insulin significantly improved glycaemic control compared with placebo as assessed by mean changes from baseline to week 24 in HbA1c. (Plosker, 2012) Additionally, in all of the combination trials, dapagliflozin was associated with a significantly greater reduction in body weight compared to placebo.

Dapagliflozin was generally well tolerated in clinical trials of 24 or 52 weeks duration and in extension studies up to 2 years. Dapagliflozin is associated with a relatively low incidence of hypoglycaemia, with incidence dependant on which background therapy a patient is on (Plosker, 2012). Genital and urinary tract infections are reported more frequently with dapagliflozin than placebo (4.8% vs. 0.9% for genital infections, 4.3% vs. 3.7% for urinary tract infections) (Dapagliflozin Product Information). Events of genital and urinary tract infections were generally mild to moderate and rarely resulted in discontinuation from the studies.

6. Utilisation of PBS listed medicines

The information presented in this section examines the current utilisation pattern of medicines used in the treatment of Australian patients with T2DM and in doing so, addressed two of the Reviews Terms of Reference:

- Describe the utilisation and patterns of treatment of PBS listed drugs for T2DM, and compare these with PBS restrictions (TOR 1)
- Consider if the utilisation of PBS listed drugs in current clinical practice represents expected cost effective use (TOR 2)

The alliance acknowledges that some clinicians will use the newer diabetes agents outside of the strict PBS conditions. However, this practise is very likely in response to specific patient level considerations and is certainly in line with the approved indications and International clinical guidelines. Importantly, the magnitude of this usage, while small, is not discernible from the DUSC analyses alone.

As part of *The Review,* the DUSC undertook two separate analyses.

The first analysis conducted for the DUSC (discussed at Agenda Item 7.2.1 DUSC October 2012 meeting) concluded that there was little use outside PBS indications. Specifically, data from the first analysis indicated that:

- Over 88% of diabetes patients initiated on therapy in a two year time period were commenced on metformin (~75%) or SU (13%)
- Over the course of 3.5 years, 63% of patients had no change in therapy
- Of the patients that had a change in therapy, a majority did so within PBS restrictions

However, the DUSC believed there were issues with the methodology of this original analysis, and as such, initiated a second review. The second report to the DUSC (discussed at Agenda Item 7.4 DUSC February 2013 meeting) on utilisation of T2DM medicines in Australia provided data which showed that the majority of T2DM patients (95%) are being treated within PBS criteria:

- Only a small proportion (14%) of T2DM patients require a third line agent and a majority (72.1%) do so according to PBS criteria on the basis of the analysis presented.

However, the DUSC minutes pertaining to the second report conclude that:

- The rate of use beyond the PBS restrictions is high. Gliptins (DPP4s) have the most extensive use outside restrictions.

As with the first report commissioned by DUSC, the alliance believes that the analyses produced within the second report for DUSC need to be interpreted with caution. The following section highlights two of the uncertainties associated with the report that lead to this conclusion.

Methodological Issues with the second DUSC report

(i) Limitations of extrapolation from a concessional patient cohort

As part of *The Review* the DUSC undertook analyses that utilised a Concessional Patient Cohort. The reason for using a Concessional Patient Cohort was that two key products included in the analyses (metformin and SU) are priced below the General Benefit Co-payment of $36.10. However, in reviewing the methodology outlined in the DUSC review, Decision Health (who conducted a review of the DUSC report for the Alliance, **Appendix 2**) identified potential shortcomings in how the Concessional Patient Cohort was created and handled at the analysis stage.

Specifically, because of the long duration of treatment and the fact that patients will transition into the concessional cohort over time, the use of this cohort will overestimate the magnitude of use outside PBS restriction. T2DM is a chronic and progressive disease, with first diagnosis often made when the patient is younger and not eligible for the age pension. Consequently many patients on early regimens of T2DM medicines (consisting of oral agents such as metformin and SU) are still of working age, employed and thus not eligible to receive any subsidies for these medications. Additionally, since the price of metformin and SU fall below the general co-payment, any information on oral agent use in this group of patients is completely missing in the PBS claims database.

The second analysis conducted for the DUSC illustrates how significant numbers of T2DM patients are excluded from examination, leaving behind a cohort of older, less healthy patients. Specifically, during a 6 month period, between July and December 2011 and with no history of one of these agents being dispensed in the preceding 24 months, 29,433 patients were initiated one either a gliptin (i.e. DDP4), glitazone (i.e. TZD) or exenatide. Of these, 12,186 patients had a least one General or general Safety Net prescription in the 2 years prior to their initiation date and consequently were excluded from the analysis as there

was potential for their prescription history to be incomplete. This resulted in 17,247 concessional only patients remaining in the second analysis, thereby excluding 41% of potential patients.

While it is potentially useful to use a concessional cohort to undertake a patient study on the basis of dealing with complete prescription histories, this is counterbalanced by significant weaknesses in extrapolating any findings to the general population. On this basis alone, results arising from the second report for DUSC cannot be relied on as quantitative estimates of inappropriate usage

(ii) Proportion of patients on a gliptin (DPP4), glitazone (TZD) or GLP-1 agonist who have not used an SU

Analysis from the second DUSC report into T2DM utilisation in the Australian setting presented data illustrating that 47.7% of patients who were prescribed a gliptin, glitazone or exenatide had not had prior exposure to metformin and SU, a pre-requisite for accessing these agents on the PBS (unless contraindicated to metformin or SU). The figure of 47.7% was derived from an analysis of medicines supplied 2 years prior to the initiation of a gliptin, glitazone or exenatide in a sample cohort of patients recorded via the Medicare PBS Claims Database.

An analysis conducted for the alliance by Decision Health (refer to **Appendix 2**) set out to i) validate the data in the second DUSC report, and ii) extending the analysis to review a patients history back 9 years and thereby establish a more credible estimate of the proportion of patients who were currently taking a gliptin, glitazone or exenatide and who had not had prior exposure to metformin and SU

The results of the analysis conducted for the alliance demonstrates that the 2 year cohort produced in the second DUSC report significantly overestimates the proportion of patients who are prescribed a gliptin, glitazone or exenatide outside of the current PBS restrictions. When the same analysis is conducted for a 5 year cohort, the proportion of patients decreases to 43.6%, with further reductions seen at 7 years (41.8%) and 9 years (40.6%) (**Table 7** and **Appendix 2**). This represents a difference of 15% relative to the DUSC analysis (i.e. 47.7% to 40.6%).

Table 7 Metformin and Sulfonylurea exposure prior to 3rd Line Agent Initiation*

Pre-Initiation treatment regimen	2 years prior	5 years prior	7 years prior	9 years prior
Number of Patients				
Met & SU	**5,080**	**5,710**	**5,900**	**6,020**
Met only	3860	3520	3440	3350
SU only	660	460	380	370
Neither Met nor SU	530	440	410	390
Total regimens not containing Met and SU	**5,050**	**4,420**	**4,230**	**4,110**
TOTAL	**10,130**	**10,130**	**10,130**	**10,130**
Percentage of Patients				
Met & SU	**50.1**	**56.4**	**58.2**	**59.4**
Met only	38.1	34.7	34.0	33.1
SU only	6.5	4.5	3.8	3.7
Neither Met nor SU	5.2	4.3	4.0	3.8
Total regimens not containing Met and SU	**49.9**	**43.6**	**41.8**	**40.6**
TOTAL	**100**	**100**	**100**	**100**

* Construction of the cohort is slightly different to the DUSC cohort. Therefore, 2 year analysis is slightly higher than the DUSC analysis (49.9% vs. 47.7%).

Clearly there is uncertainty with regards to the true number of patients who are prescribed a gliptin, glitazone or exenatide outside of the current PBS restrictions. Adding to this uncertainty is the dearth of evidence pertaining to the proportion of patients who are truly contraindicated and/or intolerant to metformin and/ or SU.

In conclusion, the alliance acknowledges that there is likely to be a low level of gliptin, glitazone and exenatide use outside of the current PBS criteria. However, the two DUSC reports cannot be seen as sufficiently quantitative to deliver an accurate estimation of what the percentage of use outside PBS criteria is, and importantly, the alliance reiterates that much of this use is clinically appropriate and in accordance with recently updated International diabetes guidelines.

7. Discussion and Conclusion

The alliance agrees with the following DUSC statement included in the minutes from the February 2013 meeting:

"DUSC proposed that differences between clinical guidelines, perceived place in clinical practice and the PBS criteria could be the main factor contributing to use outside of PBS restrictions".

It is clear that evolution of the Australian treatment guidelines and PBS restrictions for the T2DM medicines is required and the BMS/ AZ alliance recommends this be a key outcome arising from *The Review.*

The Australian treatment guidelines need to be updated to reflect an evidence-based approach and the general move towards treating patients based on their individual risk profile. In the minutes from their October 2012 meeting, DUSC suggested an approach to listing similar to the 'general statement for lipid lowering drugs prescribed as pharmaceutical benefits' may be an appropriate way to list PBS medicines for diabetes. The BMS/AZ alliance agrees this may represent a useful model but it may require, as a pre-requisite, a revision to local treatment guidelines. Such a revision would most efficiently be undertaken via abroad stakeholder consultation process, including, at a minimum, specialist physicians, general practitioners, patients groups, pharmaceutical companies and diabetes educators.

The alliance is willing to work with the PBAC and the Department to support the value of such a proposal. The process needs to value important additional benefits such as effect on weight, reduced incidence and severity of hypoglycaemia, cardiovascular profile and the provision of clinician choice.

The alliance recommends that outcomes and future actions arising from *The Review* focus on

i) **acknowledging** and **valuing** the need for clinicians to make treatment choices specific to an individual's risk profile (e.g. consequence of hypoglycaemia, time since diagnosis, treatment target, cardiovascular profile, weight, symptoms etc),

ii) **updating** the Australian clinical guidelines to reflect best-practice, evidence-based medicine and recognising the need to select treatment based on an individual's risk-profile and

iii) **simplifying** PBS restrictions, consistent with TGA indications, to allow for the safe and appropriate utilisation of T2DM medications in the context of this individualised therapy framework.

Additionally, the alliance supports the Diabetes Australia recommendations as outlined in the National Diabetes Strategy and Action Plan[3], regarding improved access to diabetes treatments and the establishment of diabetes management guidelines reflecting best clinical practice.

In conclusion, the alliance acknowledges that there is likely to be a low level of gliptin, glitazone and exenatide use outside of the current PBS criteria. However, the two DUSC reports cannot be seen as sufficiently aligned nor quantitatively accurate to deliver an estimation of outside PBS criteria utilisation. Importantly, the alliance reiterates that much of this use is clinically appropriate and in accordance with recently updated International diabetes guidelines.

The Review provides a timely opportunity to evolve the PBS listing for T2DM medicines, in line with best-practice treatment guidelines and thereby improving the care of Australian T2DM patients.

3 http://www.diabetesaustralia.com.au/PageFiles/3/National%20Diabetes%20Strategy%20and%20Action%20Plan.pdf

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** All references are available on request**

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