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PBS Post-Market
Department of Health and Ageing
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Re: Post Market Review of Products Used in the Management of Diabetes
Stage 3: Drug Utilisation and Listing Review

To Whom It May Concern,

Thank you for providing Eli Lilly Australia with the opportunity to contribute to the post market review of products used in the management of diabetes.

Eli Lilly is the Sponsor of several diabetes products available on the Pharmaceutical Benefits Scheme. These include human insulin products, insulin analogue products, and pioglitazone. Eli Lilly, in partnership with Boehringer Ingelheim, also co-markets the DPP-4 inhibitor linagliptin.

Prior to providing our response to the terms of reference, Eli Lilly wishes to note its significant concerns relating to the process governing the Post-Market Review of Products Used in the Management of Diabetes. These concerns extend to the adequacy of the guidelines issued for the review, the level of engagement with relevant stakeholders, the identification of the relevant decision maker and the intent as to the outcome of the review. Eli Lilly has joined with a number of other Sponsors of diabetes products to discuss these process concerns and we endorse the substance of the submission to this review made by Medicines Australia.

Eli Lilly notes the statement from the Pharmaceutical Benefits Division that insulin "is not the specific focus of this Review" and has accordingly not addressed the comparative effectiveness of insulin products in this submission. Furthermore, Eli Lilly has previously responded in detail to the findings of the DUSC review of diabetes medicines. Therefore this submission is, as requested by the Pharmaceutical Benefits Division, a comment on access and utilisation of medicines for the treatment of type 2 diabetes mellitus (T2DM) and the clinical place in therapy of these medicines.

Eli Lilly has two key points that we feel should be integral to this review, as fundamental to the care of patients with diabetes:

1. Access to a range of treatment options for T2DM is critical for individualisation of patient care.
2. Attributes of antidiabetic medications beyond glucose-lowering activity, such as weight control and reduced risk of hypoglycaemia, are valued by physicians and patients.

1. Access to a range of treatment options for T2DM is critical for individualisation of patient care

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Position Statement for Management of Hyperglycaemia in Type 2 Diabetes proposes that, beyond metformin as initial pharmacotherapy, there are limited comparative effectiveness data to guide clinical decision-making.[1] For this reason the ADA and EASD do not recommend (and in fact have actively moved away from) one prescriptive algorithm for intensifying antihyperglycaemic therapy, but rather that individual patients' needs and preferences guide treatment selection. The *Diabetes Care* Editors' Expert Forum subsequently stated that the availability of multiple pharmacological options should be instrumental to early, appropriate treatment to target, which is the only recognised strategy for the prevention of complications.[2]

In comparison, the NHMRC-endorsed Australian treatment guidelines for T2DM include a relatively restrictive clinical algorithm to reflect the PBS criteria for reimbursement.[3] Notably, of the 23 regimens (including monotherapy, two-drug and three-drug combinations) recommended within the ADA and EASD Position Statement, only 7 regimens would be PBS reimbursed in Australia, with an additional 3 regimens PBS reimbursed in the restricted population of patients who cannot tolerate combination therapy with metformin and a sulfonylurea (Appendix, Table 1).

The recent DUSC review of medicines to treat T2DM found that in the first 3.5 years of therapy the majority of prescribing is in accordance with PBS restrictions.[4] However, additional analyses of "third-line" therapies (glitazones, gliptins and GLP-1 analogues) using a prevalent population found prescribing of therapies outside of the PBS restrictions, in particular for the gliptins.[5] It is possible that such prescribing is unintentional, for example due to misunderstanding of the PBS restrictions, or deliberate, for example based on clinical judgement and consideration of the health outcomes most valued by the physician and patient. Of note, DUSC considered that the PBS restrictions do not align with recent clinical guidelines and the perceived place of newer medicines for T2DM in practice.[5]

Eli Lilly appreciates the importance of using health care resources efficiently, and supports the PBAC's evidence-based approach to decision-making. However, evidence-based medicine integrates the best available evidence with individual clinical expertise and patient values.[6] Access to a range of treatment options is essential for the practice of evidence-based medicine and the attainment of optimal patient outcomes. For example, delayed intensification of therapy due to patient reluctance to accept the limited treatment combinations available to them may result in poor glycaemic control and increased risk of microvascular and macrovascular complications.

2. Attributes of antidiabetic medications beyond glucose-lowering activity, such as weight control and reduced risk of hypoglycaemia, are valued by physicians and patients.

A recent review of the comparative effectiveness and safety of antidiabetic medication published by the Agency for Healthcare Research and Quality found similar HbA1c reductions across two-drug combinations, suggesting little differentiation in HbA1c-lowering efficacy.[7] However, clear differentiation between medications was observed for the endpoints of body weight, frequency of hypoglycaemia and other side effects such as congestive heart failure, fractures and GI adverse effects.[7]

Eli Lilly acknowledges that the fundamental action of an antidiabetic medication is to control blood glucose levels. However, the importance of overall tolerability of anti-diabetic medications is reflected in current national and international treatment guidelines which emphasise weight control and minimisation of hypoglycaemia as cornerstones of diabetes care.[1,3]

The recent DUSC Review indicates that physicians are prescribing third-line agents, in particular the gliptins, more broadly than is considered cost-effective by the PBAC.[5] This suggests that physicians and/or patients perceive the value of treatment outcomes differently to the PBAC.

For example, the Australian treatment guidelines state that "*Direct benefits of weight loss include an increase in insulin sensitivity, improvement in glycaemic control, improved lipid profiles, decreased triglycerides and LDL cholesterol and improved blood pressure, mental health and quality of life*".[3] However, the inclusion of weight control in the initial cost-utility model for exenatide was considered invalid by the PBAC, based on uncertainty of the durability of effect and translation into morbidity and mortality outcomes.[8]

Similarly, the recent ADA and EASD Workgroup report on hypoglycaemia[9] presented evidence and consensus expert opinion on the adverse short and long-term consequences of hypoglycaemia, including an increased risk of subsequent mortality. The recommended medication adjustments for patients experiencing troublesome hypoglycaemia include replacing sulfonylureas with other oral agents or GLP-1 analogues, and replacing regular human insulin and NPH with rapid-acting and basal insulin analogues, respectively.[9] Despite the importance of minimising hypoglycaemia in the management of diabetes, PBAC acceptance of insulin glargine cost-effectiveness (based on reduced risk of hypoglycaemia) required 5 submissions by the Sponsor.[10]

Conclusion

Eli Lilly supports broad access to antidiabetic medications to enable individualisation of therapy and optimisation of patient outcomes. Importantly, antidiabetic medications differentiate on tolerability and ease of use to a greater extent than they differentiate on glucose-lowering efficacy. Eli Lilly hopes that the value physicians and patients perceive in new antidiabetic medicines is appropriately considered in determination of pricing consequences of this review.

We look forward to receiving a copy of the Stage 3 Draft Report prepared by the Department, and providing comment prior to its consideration by PBAC.

Yours sincerely,

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Appendix

Table 1. Antidiabetic medication regimens recommended by the ADA and EASD, and PBS reimbursement status in Australia.

ADA/EASD Recommended Regimens				**PBS Reimbursed**
	1st Drug	2nd Drug	3rd Drug	
Monotherapy				
1	Met			Yes
Dual therapy				
2	Met	+ SU		Yes
7		+ TZD		Restricted*
12		+ DPP-4i		Restricted*
16		+ GLP-1		Restricted*
20		+ Insulin		Yes
Triple Therapy				
3	Met	+ SU	+ TZD	Yes
4			+ DPP-4i	No
5			+ GLP-1	Yes
6			+ Insulin	Yes
8		+ TZD	+ SU	No
9			+ DPP-4i	No
10			+ GLP-1	No
11			+ Insulin	No
13		+ DPP-4i	+ SU	No
14			+ TZD	No
15			+ Insulin	No
17		+ GLP-1	+ SU	No
18			+ TZD	No
19			+ Insulin	No
21		+ Insulin	+ TZD	Yes
22			+ DPP-4i	No
23			+ GLP-1	No

* Reimbursement restricted to patients who cannot tolerate combination therapy with metformin and a sulfonylurea.