Not to target: the Diabetes Review misses the mark

Medicines Australia’s submission to the PBAC on the draft report of the post-market review of products used in the management of diabetes - Stage 3: Type 2 Diabetes Medicines

Medicines Australia represents the research-based pharmaceutical industry in Australia. Our members make an important contribution to improving better health outcomes for Australians and supply over 80% of the prescription medicines market, including some of the medicines considered under the Post-Market Review of Products Used in the Management of Diabetes, Stage 3 (herein, “the review”). Medicines Australia welcomes the opportunity to comment on the draft report of the review (“the report”).

Medicines Australia has raised many concerns about review over the past two years. Our July ‘13 submission notes that the review “could represent a lost opportunity to improve the management of diabetes”\(^1\). From reading the report, we remain concerned this fear may be realised.

The fundamental limitation of the report is that it falls well short of the evidentiary and methodological standards required of routine PBAC submissions. While the report has no recommendations, it includes statements that are not supported by the analysis provided. It overlooks important information that Medicines Australia and other stakeholders have raised repeatedly in the course of the review. It is Medicines Australia’s view that the report cannot support decision making in its current form.

The Department of Health’s approach to this review has been narrow in its focus. Prescribers still face complex PBS restrictions for diabetes medicines which compromise patients’ access, from both a timeliness and equity perspective, to the best possible treatment. While the Department has already derived savings from the lower medicines prices secured in parallel to the review, this report leaves the diabetes community in the dark about whether patients will gain better access to medicines in the future.

In the longer term, this approach to determining access to medicine will reduce the incentive for pharmaceutical companies to develop much needed new therapies in diabetes, which will ultimately have enormous negative consequences for people with diabetes, families and treating clinicians. The lesson in this regard from antibiotics and vaccines is very clear: if you commoditise medicines, it can be to the detriment of innovation.

The key points for PBAC’s consideration from this submission are:

1. The draft report’s statements on triple therapy are not evidence-based
2. The report overlooks the broader benefits of diabetes medicines
3. The report fails to contribute to Australia’s broader diabetes goals
4. The process followed in completing the report was flawed

These are outlined in greater detail below.

1. The draft report's statements on triple therapy are not evidence-based

The report presents new analysis on triple therapy which finds that these regimens produce clinically meaningful reductions in HbA\textsubscript{1c}. It is important that the report recognizes the clinical value of triple therapy, however it includes no analysis on the cost-effectiveness of these regimens. Therefore, it is surprising that the Reference Group queries "whether the use of DPP-4 inhibitors and SGLT2 inhibitors in triple therapy would be cost-effective at the current prices".

This statement appears without any justification. In addition, the value of patient relevant outcomes beyond HbA\textsubscript{1c} such as hypoglycaemia and weight reduction does not appear to have been considered.

It is also of concern that this statement may have been informed by the 2012 DUSC analysis which identified use of PBS medicines outside of restriction in a triple therapy setting. The PBS restrictions on diabetes medicines have changed significantly since the DUSC analysis was conducted. Specifically, DPP-4 medicines can now be used in a second line setting, whereas previously they could only be used in patients contraindicated or intolerant to sulfonylurea. In addition, the analysis pre-dates the listing of the SGLT2s.

The clinical pathway followed in treating diabetes patients would have changed with these new restrictions. A significant proportion of patients would now receive second line treatment with newer therapies. Given that sulphonylureas are an unrestricted general benefit, it could be asked whether a specific recommendation for triple therapy is even necessary.

Medicines Australia has expressed grave concerns in the past where reviews have identified utilization outside of restriction which has then been addressed through price cuts. There remains no evaluation of the benefits in the broader population, nor of the reasons for why the use is outside the estimates determined as appropriate at the time these medicines were made available. Indeed, one of the most significant gaps in this analysis is there has been no attempt to assess if, in fact, the use is appropriate and the initial estimate of patient numbers was the incorrect parameter in this approach. This undermines the evidence-based assessment process which forms the foundation of the PBS. Recommendations on cost-effectiveness should be informed by cost-effectiveness analysis. In addition, there are policy responses that can improve the health outcomes and quality use of medicines that could arise from PBS reviews that do not require price changes – including patient and prescriber education.

2. The report overlooks the broader benefits of diabetes medicines

The review requested broad input through submissions and a stakeholder forum. This showed a clear consensus across the stakeholder community (patients, healthcare professionals and industry) that diabetes outcomes should not be measured by HbA\textsubscript{1c} levels alone. Especially for patients, the avoidance of both severe and non-severe hypoglycaemia was critical, not only for the immediate and direct impact that such events can have on health outcomes but also for the more long term and indirect effects such as lost productivity.

Stakeholders also stated that the avoidance of weight gain and reduced side effect profiles were important when considering optimal therapy options. Furthermore, stakeholders strongly considered that patient
centric outcomes such as convenience, ease of use and quality of life measures were important parameters when reviewing the treatment options for type 2 diabetes.

Although the report mentions this feedback, it ultimately fails to include the value and/or the benefits beyond HbA1c in the Reference Group’s statements or in the core analysis of the report. This is inconsistent with the outcomes from the review Stakeholder Forum which agreed that considerations other HbA1c should be incorporated into decision making where it is available².

In the report’s meta-analysis of triple therapy trials, results were generated for HbA1c, hypoglycaemia and body weight, however, only the significant improvements in HbA1c of 0.7-1.1% were regarded as clinically meaningful. The analysis of hypoglycaemia did not include a definition as to the type of hypoglycaemia measured (severe or non-severe, daytime or nocturnal) and there was no mention of the clinical importance of these findings. Furthermore, there were significant improvements in body weight with some triple therapies but again there was no mention of the clinical importance or relevance of these outcomes. It is unknown whether patient quality of life or patient satisfaction was reported in any of the trials and there is no mention of these parameters in the analysis. There is clear evidence that hypoglycaemia, weight gain and tolerability all contribute significantly to the ability to use a medicine in a way deemed to be Quality Use of Medicine.

The report states that the Reference Group members supported a ‘stopping rule’. Although the concept of a stopping rule (whereby therapy may be stopped if a patient is not receiving any benefit) is highly appropriate, the suggested stopping rule is based solely on HbA1c reduction (in this case a 0.5% reduction in a specified time frame). If a stopping rule is to be implemented, then the considerations for stopping therapy must include those parameters identified by stakeholders as important to diabetes management beyond HbA1c, e.g. reduced hypoglycaemia, weight loss, patient QoL and tolerability. A stopping rule in a disease area such as diabetes, a chronic degenerative condition, must be necessarily complex to reflect the complexities facing clinicians and their patients in identifying and maintaining optimal therapy.

In the hypothetical example outlined below, based on the proposed HbA1c centric stopping rule, the patient would have to stop their new treatment because their HbA1c has not decreased sufficiently. However, there is no consideration of the other additional patient benefits associated with the new treatment. This is in direct contradiction to the stakeholder inputs.

<table>
<thead>
<tr>
<th>Previous Treatment</th>
<th>New Treatment</th>
<th>Stopping Rule (≤0.5% HbA1c reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c 7.5%</td>
<td>HbA1c 7.2%</td>
<td>STOP</td>
</tr>
<tr>
<td>Weight gain 3kg over 6 months</td>
<td>Weight loss 4kg</td>
<td>Not Considered</td>
</tr>
<tr>
<td>Non-severe hypoglycaemia daily</td>
<td>No reports of hypoglycaemia</td>
<td>Not Considered</td>
</tr>
<tr>
<td>Patient frustrated</td>
<td>Patient positive about treatment</td>
<td>Not Considered</td>
</tr>
</tbody>
</table>

Another key outcome from the stakeholder meeting was the request that the clinical guidelines be updated to take into account best clinical practice and not be based solely on reimbursement requirements. It is therefore encouraging to see that the local RACGP guidelines clearly articulate the additional features of a medicine (hypo risk, weight etc), however, it appears that the use of a sulphonylurea (SU) as the preferred 2nd line therapy is based entirely on cost. Sulphonylureas carry a high risk of weight gain and an increased hypoglycaemic risk – two key side effects of diabetes treatment which should be minimized rather than promoted as a preferred therapy.

3. The report fails to contribute to Australia’s broader diabetes goals

There is compelling evidence that glycaemic control of people living with Type 2 Diabetes (T2D) is less than optimal. Potentially half of Australians with T2D fail to meet their HbA1c target\(^3\). The need for action is clear, not only with diabetes as a National Health Priority but also more recently with government announcing the development of a new National Diabetes Strategy.

The focus of the report is on the less than 5% of patients who may have received therapy outside the cost-effectiveness guidelines of the PBS over 3.5 years\(^4\). The report says nothing about whether the patients that stayed on existing therapy remained well managed, let alone about the substantial proportion of diabetes patients that are not being treated at all. In the context of T2D being a chronic degenerative disease, the question has to be asked as to whether the attention paid through this review to marginal changes in the medication of currently treated patients could not have been better spent on patients that are currently treated sub-optimally, either because they have not been identified or because they are not receiving the care that they require.

In its 2 July 2013 submission, the Consumer Health Forum\(^5\) recommended that the findings of the review include a statement of how its outcomes will benefit consumers. It is telling that this recommendation has not been taken up in this report. Moreover, it is unclear what such a statement could say given the narrow focus this review has taken.

4. The process followed in completing the report was flawed

Medicines Australia continues to support initiatives to ensure that medicines are prescribed, dispensed and used in a responsible, appropriate and ethical manner. However, any post-market review should have a clear focus on Quality Use of Medicines, value for money and not be focused primarily on cost.

Last year, while the diabetes review was underway, the PBAC recommended the listing of a new diabetes medicine on the PBS using preliminary utilization information that was under the review’s consideration. This led to major changes in the listing conditions of a number of other diabetes medicines which are not reflected in the findings of the Diabetes review report. Again, this focus on utilization as the critical determinant of value for money is not good practice in a HTA system such as Australia.


Medicines Australia and the Department are consistent in saying that normal PBAC process should continue alongside a review. However, Medicines Australia’s concern with these diabetes listings was that preliminary utilization data was allowed to inform PBAC recommendations before the review had assessed the clinical or economic significance of this data in conjunction with broader evidence. There was nothing preventing the Department from listing the new medicines under existing conditions. If this had occurred, it is quite possible that the review could have reached a different recommendation to improve the quality use of these medicines.

Additional confusion has been raised by the PBAC’s more recent consideration of changes to the PBS restrictions for anti-diabetic medicines including glitazones, GLP-1 and SGLT2 inhibitors. Again, these deliberations have taken place outside of the remit of the review.

Medicines Australia is further concerned that:

- The draft diabetes review report does not provide any clear outcomes or recommendations; it is therefore hard for stakeholders and sponsors to provide an informed or targeted response.
- Given the vagueness of the report, any actions arising would need further consultation with stakeholders. This is particularly the case for any consideration for the implementation of a stopping rule and a general statement on diabetes medicines. Medicines Australia was surprised that the vague recommendation for a general statement was not accompanied by draft text, particularly given the length of time the review took to be conducted.
- Medicines Australia was surprised that the membership of the External Reference Group was not published as part of the draft report. Medicines Australia expects that this membership list will be published as part of the final report.
- The objective of the diabetes review is to systematically evaluate the body of clinical evidence to ensure that patients are treated with the most appropriate medicines and products, effectively and safely, to achieve optimal health outcomes and support quality use of medicines. It is therefore necessary that any proposed recommendations following PBAC consideration of the draft report are made with this aim in mind.

Medicines Australia acknowledges that important steps have been taken towards improving the post-market review process, in addition to working towards producing an appropriate framework for their initiation and conduct through the Access to Medicines Working Group (AMWG). With this framework, Medicines Australia hopes that the duplication, confusion and mis-alignment evident through the diabetes review can be avoided in future reviews.

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