

4.3 PROPOSED CHANGE TO THE LISTINGS OF THIAZOLIDINEDIONES, GLUCAGON-LIKE PEPTIDE-1, AND SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS FOR TYPE II DIABETES

1 Purpose of Application

- 1.1 To inform the Pharmaceutical Benefits Advisory Committee (PBAC) of responses from the sponsors of thiazolidinediones (glitazones), glucagon-like peptide-1 (GLP-1) and sodium-glucose co-transporter 2 (SGLT2) inhibitors (gliflozins) regarding the Department's proposed changes to the restriction wordings (listings/circumstances) of PBS-subsidised third line treatment options for type 2 diabetes mellitus to take into account the change in the PBS availability of the dipeptidyl peptidase 4 inhibitors (gliptins).
- 1.2 To request PBAC give advice on a series of options with respect to the Department's proposed changes to these restrictions.

2 Background

- 2.1 The glitazones, glucagon-like peptide-1, and gliflozin currently subsidised on the PBS have circumstances restricting their PBS subsidised use for type 2 diabetes mellitus to the third-line setting (i.e. after first and second line treatment options for type 2 diabetes have been exhausted). The Department reviewed the current restrictions for these PBS-subsidised third-line treatment options to take into account the change in the PBS availability of the gliptins.
- 2.2 The Department initially prepared draft revised restrictions such that, for third-line therapy:
 - Patients must try all three dual second-line combinations before being eligible for third-line treatment.
 - Patients are able to switch from one third-line combination therapy to another without having to re-qualify, i.e. patients are able to move sideways.
- 2.3 Drafts of the relevant revised restrictions were provided to sponsors with PBS listings, or positive PBAC recommendations not yet implemented for glitazones, glucagon-like peptide-1, and gliflozins for comment. Sponsors who had an application for a PBS-subsidised third-line treatment for type 2 diabetes mellitus before the July 2014 PBAC were included in this consultation process. Seventeen sponsors were invited to comment, and responses were received from seven sponsors and two other stakeholders.
- 2.4 Subsequent to the circulation of the draft restrictions to sponsors, the Department undertook further consultation internally and with members of PBAC. As a result, the draft restrictions were further revised prior to PBAC consideration so that patients must fail treatment with only two of the three second line combination therapies, as follows:

Metformin and a sulfonylurea
AND

Metformin and a gliptin
OR
A sulfonylurea and a gliptin

This amendment was proposed based on advice that it is clinically inappropriate for a patient stabilised on maximally tolerated doses of metformin to have to cease that treatment and trial a sulfonylurea before being eligible for third-line treatment. This revision was not provided to sponsors.

3 PBAC Outcome

- 3.1 The PBAC considered the comments received from all seven sponsors and other stakeholders and noted that, overall, the main concern expressed by sponsors is the inconsistency of the proposed restrictions with both local (eg. Diabetes Australia/NHMRC) and international (eg. US and Europe) treatment guidelines.
- 3.2 The PBAC also acknowledged the comment made by some sponsors that the proposed restrictions, in the version circulated to sponsors, are inconsistent with the current PBS treatment algorithm as it requires patients to have tried a DPP-4 inhibitor in combination with metformin, and separately with a sulfonylurea, whereas the current second line restrictions only require a patient to have tried either metformin or a sulfonylurea.
- 3.3 The PBAC also noted several sponsors concerns that the proposed restrictions are unsupported by clinical evidence and have the potential to lead to additional HbA1c tests and general practitioner (GP) visits which will result in additional costs to patients and the MBS.
- 3.4 The proposed restrictions have been developed to take account of the cost differences in treatment in the absence of evidence showing difference in effectiveness. They require that patients exhaust all the less expensive second-line options before moving to more expensive treatments. The PBAC agreed that this approach represents the most cost effective use of these PBS subsidised medicines.
- 3.5 The PBAC further acknowledged that the differences in the restrictions for the second and third line agents may be clinically inappropriate and may cause confusion amongst prescribers.
- 3.6 The PBAC indicated that it was of a mind to recommend second line listings consistent with those for the gliptins, for all agents in the gliflozin class and potentially the GLP-1 class, at prices consistent with the gliptin prices (taking into account the cost-offsets for individual gliflozins) should the sponsors of those drugs seek such a listing. The PBAC recommended the Minister offer sponsors the opportunity to consider this option before implementing any changes to the current restrictions for these agents.
- 3.7 In forming this view, the PBAC recalled that it had previously concluded dapagliflozin and canagliflozin to be non-inferior to sitagliptin in terms of comparative effectiveness, but to be associated with higher rates of adverse events compared with sitagliptin. The PBAC further recalled that sitagliptin was initially recommended for listing on a cost-minimisation basis with rosiglitazone, and that exenatide was recommended for listing on the basis of a comparison with rosiglitazone and insulin glargine. In other words, the evidence PBAC has seen to date supports this approach for the gliflozins, and indicates that it may also be appropriate for drugs in the GLP-1 class. The PBAC acknowledged that further consideration may need to be

given to the place in therapy of the glitazone class, noting the evolving diabetes treatment algorithm.

- 3.8 If, on the other hand, sponsors choose not to request a second line listing at the lower price, or, in the event a request is made but the PBAC does not recommend a second line listing, then PBAC considered it would be appropriate that the current third line restrictions be amended to articulate that patients must try metformin plus a sulfonylurea AND metformin plus a gliptin OR a gliptin with a sulfonylurea before being eligible for third line treatment, in line with the revised restriction proposed by the Department (see Background above).
- 3.9 The PBAC agreed that it is clinically inappropriate for a patient stabilised on maximally tolerated doses of metformin to have to cease that treatment and trial a sulfonylurea before being eligible for third-line treatment. However the PBAC considered it is appropriate for patients to have to fail two second line dual therapy treatments before being eligible for access to PBS subsidised third line treatments.
- 3.10 The PBAC noted that two of the sponsors who responded to the Department's invitations for comment had indicated their support for such a restriction. The PBAC acknowledged that some sponsors had proposed patients need only fail one second line therapy before being eligible for third line treatment, but did not consider this appropriate.
- 3.11 The PBAC further recommended that gliflozins which remain subsidised only in the third line setting have their risk share arrangements (RSA) reviewed. This is because the shift of the gliptins to the second-line setting for subsidy purposes is expected to reduce the potential number of patients eligible for treatment with PBS subsidised third line treatments and therefore requires a re-negotiation of the caps in the existing RSA.
- 3.12 The PBAC also noted the comments regarding the ambiguity in the current clinical criteria of the term 'inadequately controlled'. The PBAC acknowledged that the current diabetes restrictions could lead to confusion amongst prescribers and requested the Department investigate the feasibility of a general statement for PBS subsidy for drugs for type 2 diabetes, similar to the general statement for lipid-lowering drugs and under the auspices of the diabetes review.
- 3.13 Lastly, the PBAC noted that the Post-Market Diabetes Review is currently underway and considered that, although the findings of this review may impact the PBS restrictions for medicines for the treatment of Type 2 diabetes, it remains appropriate to progress the current review of the restrictions for the third line agents.

Outcome:
Deferred

4 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.