

11.01 Programmed cell death-1/ programmed death ligand-1 (PD-(L)1) inhibitors

1 Background

- 1.1 At the December 2023 meeting, the PBAC considered and deferred proposals for nivolumab and pembrolizumab for broad Pharmaceutical Benefits Scheme (PBS) listings which would allow expanded access to all current and future indications registered by the Therapeutic Goods Administration (TGA) without review of the clinical effectiveness and cost-effectiveness of each indication by the Pharmaceutical Benefits Advisory Committee (PBAC). At their September 2024 meeting, the PBAC discussed parameters that need to be considered for future broad PBS listing proposals for programmed cell death-1/ programmed death ligand-1 (PD-(L)1) inhibitors.
- 1.2 As of 1 August 2024 there were seven PD-(L)1 inhibitors listed on the PBS:
- atezolizumab (Tecentriq[®]) sponsored by Roche Products Pty Ltd.
 - avelumab (Bavencio[®]) sponsored by Merck Healthcare Pty Ltd.
 - cemiplimab (Libtayo[®]) sponsored by Medison Pharma Australia Pty Ltd.
 - dostarlimab (Jemperli[®]) sponsored by GlaxoSmithKline Australia Pty Ltd.
 - durvalumab (Imfinzi[®]) sponsored by AstraZeneca Pty Ltd.
 - nivolumab (Opdivo[®]) sponsored by Bristol-Myers Squibb Australia Pty Ltd
 - pembrolizumab (Keytruda[®]) sponsored by Merck Sharp & Dohme (Australia) Pty Ltd
- 1.3 In addition, tislelizumab (Tevimbra[®], sponsored by BeiGene Pty Ltd¹) and toripalimab (sponsored by AA-Med Pty Ltd²) are under evaluation by the Therapeutic Goods Administration (TGA). The European Medicines Agency (EMA) have approved tislelizumab for advanced oesophageal squamous cell carcinoma and advanced non-small cell lung cancer. Toripalimab has EMA approval for advanced oesophageal squamous cell carcinoma and nasopharyngeal carcinoma.
- 1.4 The PBS listings for PD-(L)1 inhibitors are for a range of tumour types including lung cancer, mesothelioma, melanoma, hepatocellular cancer, bladder cancer, renal cell carcinoma, urothelial cancer, lymphoma, breast cancer, cervical cancer, endometrial cancer, biliary tract cancer, gastro-oesophageal cancers, colorectal cancer, cutaneous squamous cell carcinoma, Merkel cell carcinoma and squamous cell carcinoma of the oral cavity, pharynx or larynx.
- 1.5 Pembrolizumab and nivolumab are PBS listed for a broad range of tumour types (11 and 7, respectively). Atezolizumab, avelumab, cemiplimab, dostarlimab and

¹ <https://www.tga.gov.au/resources/prescription-medicines-under-evaluation?keywords=tislelizumab>

² <https://www.tga.gov.au/resources/prescription-medicines-under-evaluation?keywords=toripalimab>

durvalumab are listed for three or less tumour types, however a number of these listings are for unique tumour types.

- 1.6 The specific criteria for the PBS listings vary in terms of treatment setting (e.g., neoadjuvant, adjuvant, maintenance, locally advanced, metastatic), patient performance status, prior treatments (e.g., specific line of therapy, previous treatments), biomarkers, concomitant treatments, and treatment duration (e.g., maximum duration).

2 Previous reviews and simplifications of PD-(L)1 inhibitor PBS listings

- 2.1 At the August 2018 meeting, at the request of the Minister for Health, the PBAC reviewed the PD-(L)1 inhibitor PBS listings. At this time there were four PD-(L)1 inhibitors TGA registered, and there had been PBAC submissions for seven tumour types. The PBAC advice to the minister is publicly available³. In 2018 the PBAC noted that its assessment processes allow for flexibility in evidentiary requirements including for medicines used to treat less common and rare diseases with a high and unmet clinical need for new treatment options. The PBAC noted its recommendations for PD-(L)1 inhibitors had included rare cancers and confirmed it would continue to review clinical evidence with appropriate consideration of unmet need. The PBAC considered that any change to the PBS process should not disadvantage any other consumer group, disease type or medicine class.
- 2.2 At the August 2019 meeting, as recommended as part of the PD-(L)1 inhibitor review outlined above, the PBAC considered proposals from the sponsors of atezolizumab, durvalumab, nivolumab and pembrolizumab for an approach to a broad PBS subsidy listing for PD-(L)1 inhibitors for non-small cell lung cancer (NSCLC)⁴. The PBAC noted a number of the PD-(L)1 inhibitors demonstrated an overall survival benefit for the treatment of NSCLC. However the available clinical data varied substantially by line of therapy (first-line, second-line), disease stage (Stage III, Stage IV), histology (squamous, non-squamous), targeted mutation status, PD-L1 TPS status and chemotherapy backbone. The PBAC noted listings or recommendations were in place for most patients with Stage IV NSCLC and the only patient cohort with Stage IV disease and without targetable mutations that did not currently have access to first-line treatment with a PD-(L)1 inhibitor were patients with squamous histology and PD-L1 TPS <50%. As part of its consideration of the sponsor proposals, the PBAC noted the pembrolizumab study, KN-407, provided evidence of an overall survival benefit for patients with previously untreated Stage IV squamous NSCLC. The PBAC considered it would be appropriate for pembrolizumab to be available for this patient population on the basis of a high clinical need and to ensure PD-(L)1 inhibitors were available for all patients with Stage IV NSCLC as first line therapy. Additionally, the PBAC considered the listing for pembrolizumab could be consolidated and recommended a listing of pembrolizumab for previously untreated Stage IV NSCLC without targetable

³ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/agenda/august-2018-pbac-special-meeting>

⁴ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-08/broad-pbs-subsidy-listing-for-pd-l-1-checkpoint-inhibitors>

mutations. The PBAC considered it would be reasonable for clinicians to determine whether pembrolizumab was used in combination with chemotherapy or as monotherapy according to its approved TGA indications.

- 2.3 At the November 2021 meeting, as part of its consideration of pembrolizumab⁵ and nivolumab⁶ for a number of upper gastrointestinal cancers, the PBAC noted that the TGA indication and trial population for pembrolizumab and nivolumab reflected a subset of the full patient population likely to be considered clinically appropriate for checkpoint inhibitor treatment. The PBAC indicated its preference for an aligned, simpler restriction for checkpoint inhibitors that reflected likely clinical practice across gastric, gastro-oesophageal junction and oesophageal cancers, while noting the different TGA indications for pembrolizumab and nivolumab. At the March 2022 meeting, the PBAC considered it would be appropriate for nivolumab to be available broadly for the treatment of advanced or metastatic ‘gastro-oesophageal cancers’ as defined in the TGA Product Information (PI) document without reference to the specific location of the tumours or line of therapy in the PBS listing. As a result changes to the PBS restriction were not required when additional gastro-oesophageal cancers were registered by the TGA.
- 2.4 At the December 2023 meeting, the PBAC considered proposals for nivolumab and pembrolizumab for expanded listings to facilitate broad access to indications with current or future TGA registration. The PBAC considered, in the context of the extensive experience with applications for PD-(L)1 inhibitors, that it would be appropriate and desirable to have a simplified process for listing future indications. The PBAC considered a broad listing for nivolumab and pembrolizumab would be appropriate with a Risk Sharing Arrangement (RSA) that provided confidence regarding total cost to Government and cost-effectiveness of a broad listing, and that a substantial price reduction versus the current PBS prices would likely be required. The PBAC considered further consultation was required with the sponsors and the Department regarding the restriction, the price at which nivolumab is likely to be cost-effective, the financial forecasts and parameters for the RSA. The PBAC deferred making a recommendation for both proposals⁷.

3 PBAC outcome

- 3.1 The PBAC considered the parameters for future broad PBS listing proposals for PD-(L)1 inhibitors in the context of the changes and implications for the current process. Outlined below is the current process for PBAC consideration of new listings for PD-(L)1 inhibitors followed by parameters that would need to be considered if this process is to be changed.

⁵ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-11/pembrolizumab-oac-solution-concentrate-for-i-v-infusion>

⁶ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-11/nivolumab-injection-concentrate-for-i-v-infusion-40-mg-in>

⁷ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-december-2023-intracycle>

Current process for PBAC consideration of new listings for PD-(L)1 inhibitors

- 3.2 The PBAC noted that there is extensive experience with PD-(L)1 inhibitors across a broad range of tumour types, and the current process involves the PBAC considering an application for each new indication. The PBAC noted this process allows for:
- Evaluation prior to PBAC consideration of the clinical, economic, and financial information provided to support the applications;
 - Stakeholder input on each new listing;
 - The patient population for each listing to be refined versus the TGA indication. An example of the PBS criteria being narrower than the TGA registered indication is nivolumab for adjuvant melanoma, which is registered for Stage III and IV disease, but the PBS listing excludes Stage IIIA disease due to treatment not being cost-effective in this patient group. An example of the PBS criteria being silent with respect to aspects of the TGA indication is pembrolizumab for cervical cancer where the TGA indication is for patients with PD-L1 tumour proportion score (TPS) $\geq 1\%$ however, the PBS listing does not include criteria for PD-L1 expression;
 - The comparative clinical effectiveness for each listing to be assessed. The PBAC noted there is considerable heterogeneity in the clinical outcomes observed across cancer indications; between lines of therapy within a cancer indication for a specific medicine; and between medicines of the same class within a cancer indication, within the same line of therapy (with there being positive and negative trials for different PD-(L)1 inhibitors for the same indication).
 - The incremental cost-effectiveness for each listing to be assessed. The PBAC noted that the cost-effective price for each listing depends on a number of indication specific factors including the extent of benefits and harms, the PD-(L)1 inhibitor treatment duration, the cost of the comparator, the extent of cost offsets, including for subsequent lines of treatment, the accepted ICER and the level of uncertainty for the estimated ICER. The PBAC noted this has resulted in the cost-effective price across different indications varying substantially;
 - The financial impact of each listing to be estimated at the time of listing. The PBAC noted the current expenditure on PD-(L)1 inhibitors is substantial with Commonwealth expenditure in the 2022-23 financial year over \$1 billion⁸, acknowledging that net expenditure is less due to Special Pricing Arrangement rebates. The PBAC noted the majority of this expenditure is for pembrolizumab and nivolumab.
 - Consideration of the need for an RSA. The PBAC has recommended RSAs for many PD-(L)1 inhibitor listings to manage a range of risks and uncertainties, including in relation to duration of treatment, uptake rates, use outside restriction criteria and total financial impact to Government. For new listings requested on a cost minimisation basis, usual practice is for the new medicine to be included in the existing RSA, if there is one. For new listings requested on a cost-effectiveness basis, it may be appropriate for the new medicine to join an existing RSA for the

⁸ <https://www.pbs.gov.au/info/statistics/expenditure-prescriptions/pbs-expenditure-and-prescriptions-report-1-july-2022-to-30-june-2023>

same tumour type but in a different setting, especially if the cost-effectiveness in the new setting relies on reduced use of PD-(L)1 inhibitors as later line therapy.

- Consistency with previous recommendations. For new listings requested on a cost-minimisation basis versus a PD-(L)1 inhibitor already listed on the PBS, the listing generally requires the cost per patient to be the same as for the listed PD-(L)1 inhibitor, and for there to be no additional cost to the PBS budget. Consistency is also assessed for new listings requested on a cost-effectiveness basis, both in comparison to existing listings for the same tumour type but in a different setting and for different tumour types with similar outcomes.

3.3 The PBAC noted the current process is initiated by sponsor companies with an application for each new listing, and it is the sponsor's decision to list on the PBS following a positive PBAC recommendation.

3.4 The PBAC noted there are 4 positive PBAC recommendations for PD-(L)1 inhibitors that the sponsors have not progressed to a PBS listing:

- pembrolizumab for advanced or metastatic gastro-oesophageal cancer recommended at the same or lower cost per 3 weekly treatment cycle as for nivolumab (May 2022)⁹;
- pembrolizumab for metastatic or locally advanced cutaneous squamous cell carcinoma recommended on a cost-minimisation basis versus cemiplimab (November 2023)¹⁰;
- avelumab in combination with axitinib for renal cell carcinoma (RCC) recommended on a cost-minimisation basis versus nivolumab in combination with ipilimumab (March 2021)¹¹;
- cabozantinib in combination with nivolumab for RCC recommended on a cost-minimisation basis versus pembrolizumab in combination with lenvatinib (March 2024)¹².

The PBAC considered there was a low clinical need for these listings as there are suitable alternatives currently available through the PBS.

3.5 The PBAC noted there are a number of tumour types and populations within tumour types with TGA indications for which a PBAC application has not been lodged. For example, tumour mutational burden-high cancers, microsatellite instability high/mismatch repair deficient cancers, basal cell carcinoma and adjuvant Stage IIB/C melanoma. Additionally, the PBAC noted there may be indications for the PD-(L)1 inhibitors that are approved in overseas countries but not registered in Australia, as well as indications for rare cancers for which regulatory approval is unlikely to be sought. The PBAC considered there was a clinical need for subsidised access to PD-(L)1 inhibitors in some of these circumstances.

⁹ <https://www.pbs.gov.au/medicinesstatus/document/830.html>

¹⁰ <https://www.pbs.gov.au/medicinesstatus/document/1041.html>

¹¹ <https://www.pbs.gov.au/medicinesstatus/document/496.html>

¹² <https://www.pbs.gov.au/medicinesstatus/document/1129.html>

Parameters for applications for broad PD-(L)1 inhibitors listings

- 3.6 The PBAC reaffirmed its December 2023 advice (see paragraph 2.4), that in the context of the extensive experience with applications for PD-(L)1 inhibitors, it would be appropriate and desirable to have a simplified process for listing future indications. The PBAC recalled it considered broad listings would be appropriate with an RSA that provided confidence regarding total cost to Government and cost-effectiveness, and that a substantial price reduction versus the current PBS prices would likely be required.
- 3.7 The PBAC considered the aim of any proposal for a broad or simplified listing for PD-(L)1 inhibitors needs to be clearly stated in the context of the current process and gaps in PBS listings as outlined above. The PBAC noted previously stated aims for a broad listing have included accelerated/earlier access for patients and access for rare conditions including those for which there is not a TGA indication.
- 3.8 The PBAC reiterated advice provided as part of the August 2018 PD-(L)1 inhibitor review that any change to the PBS process for PD-(L)1 inhibitors should not disadvantage any other consumer group, disease type or medicine class (see paragraph 2.1).
- 3.9 The PBAC noted that any broad subsidy proposal would need to address the potential risk of causing harm either directly (forgoing effective current standard treatments, adverse events) or intangibly (false hope, not resolving patient needs, inadequate provision of palliative care). The PBAC considered there are substantive Quality Use of Medicines risks with a PBS listing that is not linked to TGA indications in terms of overtreatment and treating where there are limited or no benefits but risk of adverse events. Broad access may lead to patients wanting to try treatment with PD-(L)1 inhibitors when it is not an appropriate treatment. In this context, the PBAC considered a restriction which limits use to the indications approved by the TGA may be appropriate, noting that a separate arrangement may be required for rare cancers without a TGA indication.
- 3.10 Additional parameters to be considered for broad PBS listing proposals for PD-(L)1 inhibitors in which the PBAC do not consider an application for each new listing include:
- Ensure that TGA approvals continue to be sought for new indications with available evidence within expected timeframes;
 - Include PBAC review of the available clinical evidence to monitor comparative effectiveness;
 - Address the high level of uncertainty in cost-effectiveness when it is not assessed for a specific listing based on clinical trial data for that use. The PBAC noted given the relatively large expenditure on PD-(L)1 inhibitors, it would need to be confident about the cost-effectiveness for future use. In terms of cost-effectiveness:
 - The PBAC noted it cannot support a proposal that includes a higher price for any indication versus what it has already recommended as cost-effective (including for listings not progressed by a sponsor);

- In general, preliminary views of the Committee were that the efficacy of PD-(L)1 inhibitors for future indications is likely to be lower on average versus the existing indications and hence the cost-effective price would also be lower. Further, registered indications for which a PBAC application has not been presented to date, or will not be presented in the future, are expected to have a lower cost-effective price.
- Listings which do not limit use according to patient performance status, and listings which allow re-challenge with PD-(L)1 inhibitors within the same clinical setting, are likely to result in use that is less cost-effective.
- Address the high level of uncertainty with the financial estimates when they are for use across a number of indications. Estimating future utilisation is complex and subject to unresolvable uncertainty, especially when estimated earlier in the process and when market share across the different PD-(L)1 inhibitors is required.
- Ensure that the impact on existing RSAs is accounted for, including if specific medicines are removed from or not added to existing RSAs, that the RSA continues to manage the originally identified risks.
- Consider the potential impact on other medicines (including PD-(L)1 inhibitors) that may already be in the market or may wish to enter the market. Any change to the process should not discourage sponsors of other medicines from seeking a PBS listing and should not limit patient access to PD-(L)1 inhibitors. The PBAC noted five of the seven PBS listed PD-(L)1 inhibitors are currently listed for three or less indications however, as some of these listings are unique (i.e., only one of the PD-(L)1 inhibitors is listed for the indication) access to all currently listed PD-(L)1 inhibitors is required.
- Ensure access to future indications where PD-(L)1 inhibitors are used in combination with other high-cost agents is not affected. The PBAC noted a PBS listing which provided access to one of the components ahead of the other(s) would be problematic.
- Ensure any proposal does not adversely impact biosimilar policies that might be in place, noting that multiple biosimilars for pembrolizumab and nivolumab are in the late phase of clinical development, with patents due to expire in some jurisdictions within the next five years.

Future considerations

- 3.11 The PBAC was supportive of implementing simplified listings for PD-(L)1 inhibitors within a specific tumour type if this would facilitate appropriate and timely access for patients.
- 3.12 The PBAC noted the pembrolizumab NSCLC listing (see paragraph 2.2) and the nivolumab gastro-oesophageal cancer listing (see paragraph 2.3) are examples of the PD-(L)1 inhibitor restrictions being simplified at the tumour level.
- 3.13 The PBAC considered active engagement with stakeholder groups such as Medical Oncology Group of Australia (MOGA) was needed to develop clinically appropriate listings for PD-(L)1 inhibitors which ensured evidenced based, cost-effective clinical

practice. The PBAC noted discussions have commenced between the PBAC and MOGA.

- 3.14 The PBAC encouraged sponsors to make submissions (via the standard process) for simplified PBS listings within tumour types. These submissions should address the parameters outlined in paragraphs 3.6 to 3.10. In this regard, the PBAC noted that, to date, it had not received an acceptable proposal for an expanded listing to facilitate broad access to PD-(L)1 inhibitors.
- 3.15 The PBAC remain concerned about the clinical need for PD-(L)1 inhibitors for some rare cancers for which there is not a registered TGA indication, however acknowledged that a separate arrangement may be required in these circumstances.