# 7.12 SILTUXIMAB, Powder for injection 100 mg, Powder for injection 400 mg, Sylvant®, EUSA Pharma (UK) Ltd.

## 1 Purpose

1.1 The early re-entry resubmission sought to list siltuximab with a Section 100 Efficient Funding of Chemotherapy (EFC) listing for the treatment of idiopathic multicentric Castleman disease (iMCD).

1.2 The resubmission was based on the PBAC advice from July 2021. This resubmission partially addressed the issues raised by the PBAC (see Table 1), further discussion is provided in the economic and financial sections and in the PBAC Outcome section.

**Table 1: Summary of key matters to be addressed**

| Matter of concern | Resubmission |
|---|---|
| **Economic model** | |
| Notwithstanding the remaining uncertainties with the economic model, but noting the high unmet clinical need, the PBAC foreshadowed that use of the respecified model would be appropriate in a resubmission if (i) the utility values were adequately justified, (ii) the mortality adjustment was removed (i.e. return to base case setting, where HR=1.75; from Dong 2018), and (iii) the ICER was in the range $75,000-$85,000/QALY. | The resubmission:<br>(i) Provided additional justification for the proposed utility values.<br>(ii) Used the base case setting for the mortality adjustment as requested.<br>(iii) Presented an ICER of [redacted][1]/QALY. However, this was using a 20-year time horizon, which was a change that was not requested by the PBAC. Using a 15-year model duration, the ICER would be [redacted][1]/QALY. |
| **Financial estimates** | |
| Revision of the financial estimates to use the prevalence-based approach and recalculation of the financial implications using the revised siltuximab price. | The resubmission presented revised financial estimates using a prevalence-based approach and using the proposed effective price as requested. |

Source: Paragraphs 7.9 to 7.12 of the July 2021 PBAC Public Summary Document (PSD).
*The redacted values correspond to the following ranges:*
*[1] $75,000 to < $95,000*

## 2 Background

2.1 Siltuximab was approved by the TGA on 31 August 2015 for the treatment of patients with multicentric Castleman disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpes virus-8 (HHV-8) negative.

2.2 This is the second PBAC consideration for siltuximab for the treatment of iMCD.

2.3 In July 2021, the PBAC noted that iMCD is a rare disease and considered there was a high clinical need for effective treatments for these patients. Placebo was considered an acceptable comparator for siltuximab in iMCD. The PBAC considered that a claim of superior efficacy compared to placebo was reasonable, and that the safety of siltuximab was inferior to placebo. The PBAC noted that a revised economic model was submitted with the pre-PBAC response, which addressed some of the concerns raised in the evaluation and ESC advice. However, in July 2021 the PBAC considered the ICER remained high and uncertain at the proposed price. Furthermore, at that time the PBAC considered the proposed number of patients to be treated with siltuximab was uncertain (paragraph 7.1, siltuximab Public Summary Document (PSD), July 2021 PBAC meeting).

*For more detail on PBAC's view, see section 5 PBAC outcome.*

# 3 Requested listing

3.1 The resubmission requested a special pricing arrangement, with an effective approved ex-manufacturer price (AEMP) of $[redacted] per 100 mg vial and $[redacted] per 400 mg vial and a published AEMP of $[redacted] per 100 mg vial and $[redacted] per 400 mg vial. The proposed effective AEMP was reduced by [redacted]% compared to that offered in the July 2021 pre-PBAC response. The November 2021 pre-PBAC response proposed a further price reduction with effective AEMPs of $[redacted] per 100 mg vial and $[redacted] per 400 mg vial.

3.2 The resubmission accepted the July 2021 Secretariat suggestions regarding the restriction, including the addition of detailed clinical criteria for the initial treatment restriction based on the international consensus diagnostic criteria (Fajgenbaum et al. 2017[1]) (paragraph 3.1, siltuximab PSD, July 2021 PBAC meeting).

3.3 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

[1] Fajgenbaum DC et al. (2017). "International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease." Blood 129(12): 1646-1657.

| **MEDICINAL PRODUCT Form** | **PBS item code** | **Max. Amount** | **Dispensed price for maximum quantity** | **№.of Rpts** |
|---|---|---|---|---|
| SILTUXIMAB<br>Injection | NEW (Public)<br>NEW (Private) | 1200 mg | Published<br>$[redacted] (Public)<br>$[redacted] (Private) | 4 |
| **Available brands** | | | | |
| Sylvant<br>(siltuximab 100 mg injection, 1 vial) | | | | |
| Sylvant<br>(siltuximab 400 mg injection, 1 vial) | | | | |
| | | | | |
| **Category / Program:**<br>Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals | | | | |
| **Prescriber type:** ☒ Medical Practitioners | | | | |
| **Restriction type:** ☒ Authority Required ~~(telephone/online PBS Authorities system)~~ *(in writing only via post/HPOS upload)* | | | | |
| **Episodicity:** Idiopathic | | | | |
| **Severity:** multicentric | | | | |
| **Condition:** Castleman disease | | | | |
| **Indication:** Idiopathic multicentric Castleman disease (iMCD) | | | | |
| **Treatment Phase:** Initial treatment | | | | |
| **Clinical criteria:** | | | | |
| The condition must have histopathologic lymph node features consistent with the iMCD spectrum specified below. | | | | |
| **AND** | | | | |
| **Clinical criteria:** | | | | |
| Patient must have enlarged lymph nodes (at least 1 cm in short-axis diameter) in at least 2 lymph node stations | | | | |
| **AND** | | | | |
| **Clinical criteria:** | | | | |
| Patient must have at least 1 finding as described in the laboratory iMCD diagnostic criteria described below – state each number that applies to this patient in this authority application | | | | |
| **AND** | | | | |
| **Clinical criteria:** | | | | |
| Patient must have at least 2 findings as described in either of: (i) laboratory iMCD diagnostic criteria, (ii) clinical iMCD diagnostic criteria – state each number that applies to this patient in this authority application | | | | |
| **AND** | | | | |
| **Clinical criteria:** | | | | |
| ~~Patient must be negative for each of: (i) human herpes virus-8 infection, (ii) human immunodeficiency virus infection~~<br>*The condition must not be any of the following diseases that can mimic iMCD: (i) human herpes virus-8 infection, (ii) an Epstein-Barr virus-lymphoproliferative disorder, (iii) an acute/uncontrolled infection (e.g. cytomegalovirus, toxoplasmosis, human immunodeficiency virus, tuberculosis) leading to inflammation with adenopathy, (iv) an autoimmune/autoinflammatory disease, (v) a malignant/lymphoproliferative disorder.* | | | | |
| **AND** | | | | |
| **Prescribing Instructions:**<br>iMCD spectrum of diagnostic criteria:<br>Declare the presence of at least 1 of the following histopathologic lymph node features of the iMCD spectrum by stating in this authority application which letter(s) apply to the patient's condition. Features along the iMCD spectrum are:<br>(a) Regressed/atrophic/atretic germinal centers, with/without expanded mantle zones composed of concentric rings of lymphocytes in an 'onion skin' like appearance;<br>(b) Follicular dendritic cell prominence<br>(c)Vascularity, with/without prominent endothelium in the interfollicular space, and, vessels penetrating into the germinal centers with a 'lollipop' like appearance<br>(d) Sheet-like, polytypic plasmacytosis in the interfollicular space | | | | |

| |
|---|
| (e)Hyperplastic germinal centres.<br>Regressive germinal centers or plasmacytosis ~~should be~~ *are* classified as ~~at least~~ grade 2 *or grade* 3. |
| **Prescribing Instructions:**<br>Declare which iMCD *diagnostic* criteria apply by stating in this application which corresponding numerical figure(s) apply to the patient *(at least 1 laboratory finding must be present and at least 2 findings from the combined list of 11 must be present)*:<br>Laboratory iMCD *diagnostic* criteria are *(at least 1)*:<br>(1) Elevated CRP (>10 mg/L) or ESR (>15 mm/h)<br>(2) Anaemia (haemoglobin <12.5 g/dL for males, haemoglobin <11.5 g/dL for females)<br>(3) Thrombocytopenia (platelet count <150 k/microlitres) or thrombocytosis (platelet count >400 k/microlitres)<br>(4) Hypoalbuminemia (albumin <3.5 g/dL)<br>(5) Renal dysfunction (eGFR <60 mL/min/1.73m$^2$) or proteinuria (total protein 150 mg/24 h or 10 mg/100 ml)<br>(6) Polyclonal hypergammaglobulinemia (total gamma globulin or immunoglobulin G >1700 mg/dL).<br><br>Clinical iMCD *diagnostic* criteria are:<br>(7) Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (with a score of at least 2 for this symptom using the Common Terminology Criteria for Adverse Events)<br>(8) Large spleen and/or liver<br>(9) Fluid accumulation: oedema, anasarca, ascites, or pleural effusion<br>(10) Eruptive cherry hemangiomatosis or violaceous papules<br>(11) Lymphocytic interstitial pneumonitis. |
| ~~**Administrative advice:**~~<br>~~Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.~~ |
| **Administrative advice:**<br>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).<br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au<br>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos<br>Or mailed to:<br>Services Australia<br>Complex Drugs<br>Reply Paid 9826<br>HOBART TAS 7001 |
| **Administrative advice:**<br>The iMCD diagnostic criteria mentioned in this restriction represent the consensus of an international working group of clinical experts in iMCD as described in the following literature article:<br>Fajgenbaum DC et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood*. 2017 March 23;129(12):1646-1657. |

| |
|---|
| **Restriction type:** ☒ Authority Required (immediate/real-time assessment by Services Australia) |
| **Indication:** Idiopathic multicentric Castleman disease (iMCD) |
| **Treatment Phase:** Continuing treatment |
| **Clinical criteria:** |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition. |
| **AND** |
| **Clinical criteria:** |
| Patient must not have developed progressive disease while being treated with this drug for this condition. |
| ~~**Administrative advice:**~~ |

| |
|---|
| ~~Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.~~ |
| **Administrative advice:**<br>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). |

| |
|---|
| **Restriction type:** ☒ Authority Required (~~immediate/real-time assessment by Services Australia~~ in writing only via post/HPOS upload) |
| **Indication:** Idiopathic multicentric Castleman disease (iMCD) |
| **Treatment Phase:** Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements |
| *As per Initial treatment criteria, plus treatment commenced prior to effective listing date and patient's disease has not progressed.* |
| ***Administrative advice:***<br>*Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*<br>*Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au*<br>*Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos*<br>*Or mailed to:*<br>*Services Australia*<br>*Complex Drugs*<br>*Reply Paid 9826*<br>*HOBART TAS 7001* |

3.4 A Section 100 (Efficient Funding of Chemotherapy (EFC) Program) listing was proposed for siltuximab in the resubmission. However, the pre-PBAC response stated that the sponsor is amenable to listing in either EFC or the Highly Specialised Drugs (HSD) program. Siltuximab requires reconstitution using aseptic technique. Administration is via intravenous infusion over a period of about 1 hour. Appropriate personnel and medicinal treatment should be available to treat anaphylaxis if it occurs. The PBAC noted that aspects of both intravenous infusion (chemotherapy) and 'Highly Specialised Drugs Program' listings are present for siltuximab stemming from the indication (iMCD) being cancer-like, but not a true cancer, and therefore it may be suitable for listing under either the Efficient Funding of Chemotherapy program, or the Highly Specialised Drugs Program. Given the present formulation of siltuximab proposed for listing is not suitable for patient self-administration and is highly specialised for the aforementioned reasons, but that the indication is not a 'cancer' indication, the Department advised that it would be more consistent to list the proposed siltuximab IV presentation as a Section 100 Highly Specialised Drugs Program.

3.5 The resubmission requested listing of both vial strengths, namely 100 mg and 400 mg. The pre-PBAC response stated that the sponsor would be willing to list only the 100 mg vial if the PBAC considered this to be appropriate. The PBAC noted that the average adult in the supporting clinical trial was 72 kg, meaning that the typical prescribed dose would be approximately 800 mg. From a dispensing/drug

preparation viewpoint, it would be inefficient to prepare an IV infusion from approximately 8 x 100 mg vials compared to 2 x 400 mg vials. Listing of the 400 mg vial would be appropriate. An appropriate maximum quantity appeared to be 2 x 400 mg vials and 2 x 100 mg vials based on the average weight of trial subjects.

3.6 The resubmission noted that there were 10 patients enrolled into the siltuximab Product Familiarisation Program (PFP). These patients were appropriately considered part of the prevalent population in the financial estimates. Under the recommended restriction for initial treatment, it was noted that patients initiated on non-PBS subsidised treatment would not be excluded from transitioning to PBS-subsidised supply and therefore dedicated transitioning arrangements would not be needed for such patients.

3.7 Reproduction of consensus diagnostic criteria in the initial treatment restriction introduced a high degree of complexity in terms of Service Australia administering the restriction. Instead, given the rarity of the condition and lengthy number of investigations required to form a diagnosis, the PBAC considered that the specialist diagnosing the condition could be referred to the consensus diagnostic criteria in the first instance rather than requiring Services Australia to check eligibility to each consensus criteria. The onus would be on the prescriber to declare that their patient has a diagnosis of iMCD. This would in turn make the listing more amenable to a telephone/online Authority Required listing as opposed to a written-only Authority Required listing.

*For more detail on PBAC's view, see section 5 PBAC outcome.*

# 4 Consideration of the evidence

## *Sponsor hearing*

4.1 There was no hearing for this item.

## *Consumer comments*

4.2 The PBAC noted and welcomed the input from two individuals via the Consumer Comments facility on the PBS website. The comments from individuals described improved health and wellbeing while on treatment with siltuximab, and expressed concern about affordability if the drug is not PBS listed.

4.3 The PBAC also noted that in July 2021 input was received from 11 individuals, 6 health care professionals and 1 organisation (paragraph 6.2, siltuximab PSD, July 2021 PBAC Meeting).

## *Comparative effectiveness*

4.4 The July 2021 consideration of siltuximab was based on one head-to-head randomised trial comparing siltuximab to placebo in patients with HIV/HHV-8 negative MCD (MCD2001), additional data from an untreated follow-up period (MCD2001 addendum) and an open-label extension study of patients previously enrolled in the

key clinical trials for siltuximab (MCD2002). No additional clinical data were presented in the resubmission.

## *Economic analysis*

4.5 A summary of the key matters to be addressed is presented in Table 2.

**Table 2: Summary of key matters to be addressed – economic model**

| Matter of concern | Resubmission |
|---|---|
| **Utility values**<br>The PBAC considered that the reliability of the model was improved by using more conservative assumptions in the respecified model provided with the pre-PBAC response. However, the PBAC noted that the respecified model had used unpublished EQ-5D values from the CADTH model rather than the published values from Vernon 2016. The PBAC considered that the selection of utility values was inadequately justified (para 7.9, July 2021 PSD). | The resubmission provided additional justification for the proposed utility values. |
| **Mortality adjustment**<br>The PBAC noted that the respecified model provided with the pre-PBAC response had removed the mortality adjustment that had been applied in the base case in the submission. The PBAC considered that the approach taken in the base case in the submission was more plausible than that used in the respecified model provided with the pre-PBAC response. The PBAC considered that the mortality adjustment should be returned to the base case setting (where HR=1.75; from Dong 2018) (para 7.09 and 7.10, July 2021 PSD). | The resubmission used the base case setting as requested. |
| **ICER**<br>The PBAC considered that the ICER should be in the range of $75,000 to $85,000/QALY (para 7.10, July 2021 PSD). | The resubmission presented an ICER of [redacted][1]/QALY. However, the resubmission model used a 20-year time horizon, which was a change that was not requested by the PBAC. Using a 15-year model duration, the ICER would be [redacted][1]/QALY. The time horizon proposed in the original submission was 50 years, and the ESC had advised that a time horizon of 10 to 15 years would be more appropriate given the data available (para 6.68, July 2021 PSD). |

Source: Compiled during the evaluation.
*The redacted values correspond to the following ranges:*
*[1] $75,000 to < $95,000*

4.6 The resubmission presented a cost-utility analysis of siltuximab versus placebo for the treatment of patients with iMCD. The comparison was based on individual patient data from the MCD2001 trial, MCD2001 addendum and MCD2002 extension studies and other modelled inputs. The results of the economic evaluation are presented in Table 3.

**Table 3: Results of the resubmission economic evaluation (discounted)**

| Resubmission base case | Siltuximab | Placebo | Increment |
|---|---|---|---|
| Costs ($) | [redacted] | $120,689 | [redacted] |
| LYs | 10.12 | 5.62 | 4.50 |
| QALYs | 6.37 | 3.19 | 3.18 |
| **Incremental cost per QALY gained** | | | [redacted][1] |

Source: Table 4 (p 10) of the submission
Abbreviations: QALYs, quality adjusted life years; LYs, life years.
*The redacted values correspond to the following ranges:*
*[1] $75,000 to < $95,000*

4.7 Additional justification of utility values was provided in the resubmission. In summary, the resubmission used the same utility values as the pre-PBAC response model that was considered by the PBAC at the July 2021 meeting, referred to as the "CADTH model utilities". The resubmission correctly noted the previous ESC advice that it would be appropriate to use trial-based utility values rather than values derived from the ACCELERATE database as had been proposed in the original submission. The resubmission stated that CADTH EQ-5D utility estimates were derived directly from the trial patients (i.e., the same source for TTF, OS and for utilities) and were specifically developed for a model with the same health states as used in the current PBAC model. The PBAC noted that use of the CADTH utilities was not the most conservative approach, and considered that use of the values published by Vernon 2016 would have been preferable. However, the PBAC considered the CADTH EQ-5D inputs acceptable, in light of sensitivity analyses indicating that alternative inputs would have a modest impact.

4.8 With regard to mortality adjustment, the resubmission applied the HR adjustment of 1.75 from Dong 2018 for the post-treatment failure overall survival. The PBAC noted this was consistent with the Committee's July 2021 advice.

4.9 The resubmission argued that a 20-year time horizon would be appropriate. The resubmission claimed that the inclusion of a paediatric population would warrant an extension of the duration of the model from 15 years to 20 years. The longer time horizon was not consistent with the July 2021 PBAC advice. The time horizon proposed in the original submission was 50 years, and the ESC had advised that a time horizon of 10 to 15 years would be more appropriate given the data available (paragraph 6.68, siltuximab PBAC PSD, July 2021 PBAC meeting).

4.10 The pre-PBAC response included a revised base case using a 15-year time horizon, and revised price (see paragraph 3.1), as presented in Table 4.

**Table 4: Results of the revised base case with 15-year time horizon provided in pre-PBAC response (discounted)**

| Sensitivity analysis with 15 year time horizon | Siltuximab | Placebo | Increment |
|---|---|---|---|
| Costs ($) | [redacted] | $115,667 | [redacted] |
| LYs | 8.90 | 5.39 | 3.51 |
| QALYs | 5.67 | 3.07 | 2.60 |
| **Incremental cost per QALY gained** | | | [redacted][1] |

Source: Section 3 workbook, modify the time horizon to 15 years, and effective price as stated in pre-PBAC response.
Abbreviations: QALYs, quality adjusted life years; LYs, life years.
*The redacted values correspond to the following ranges:*
*[1] $75,000 to < $95,000*

## *Drug cost/patient/year*

4.11 The estimated drug cost per patient per year for siltuximab used in the economic and financial estimates were calculated assuming the most efficient vial combinations. There is potential for greater wastage than estimated in the submission, should combinations other than the most efficient combination of vials be provided.

4.12 The pre-PBAC response proposed a further price reduction with the effective ex-manufacturer price reducing to $[redacted] per 100 mg vial and $[redacted] per 400 mg vial (see paragraph 3.1).

4.13 Based on the effective price offered in the pre-PBAC response, the estimated drug cost per patient per year of siltuximab was $[redacted] (average drug cost per administration as calculated in the economic model: $[redacted], which assumes 1.49 x 100 mg vials and 1.73 x 400 mg vials) and the recommended dosage regimen (11 mg/kg given every three weeks).

## *Estimated PBS utilisation and financial implications*

4.14 A summary of the key matters to be addressed is presented in Table 5.

**Table 5: Summary of key matters to be addressed – financial implications**

| Matter of concern | Resubmission |
|---|---|
| Revision of the financial estimates to use the prevalence-based approach and recalculation of the financial implications using the revised siltuximab price (para 7.12, July 2021 PBAC PSD). | The resubmission presented revised financial estimates using a prevalence-based approach and using the proposed effective price as requested. |

Source: Complied during the evaluation

4.15 The resubmission assumed 100% compliance with the 3-weekly treatment regimen, in contrast to the initial submission which assumed that some patients would switch to the off-label 6-weekly regimen, and others would cease treatment altogether. The resubmission estimates may be overestimated if as proposed by the July 2021 submission 66% of patients extend their treatment cycle from 3-weekly to 6-weekly after 12 months of therapy. Both the July 2021 submission and the resubmission assumed a treatment duration of 17.33 months. In July 2021, DUSC commented that the modelling of patient persistence was overly complex and that if a prevalence-

based approach was taken, the sponsor would only need to account for treatment discontinuation (siltuximab DUSC Advice, July 2021 PBAC meeting). The PBAC considered it appropriate for the estimated utilisation to be based on the 3-weekly dosing regimen, consistent with the approved product information.

4.16 The estimated utilisation and cost of siltuximab is outlined in Table 6.

**Table 6: Estimated utilisation and cost of siltuximab (effective price)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| Prevalent patients | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| Script volume | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| **November 2021 resubmission effective price** | | | | | | |
| Cost to PBS/RPBS | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| Less Patient Co-Payments | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] |
| **Net Cost to PBS/RPBS** | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| **November 2021 pre-PBAC response effective price** | | | | | | |
| Cost to PBS/RPBS | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| Less Patient Co-Payments | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] |
| **Net Cost to PBS/RPBS** | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| **July 2021 submission estimated utilisation and cost of siltuximab (effective price)[a]** | | | | | | |
| Treated patients | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| Script volume | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| Total cost | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| Patient co-payment | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] | -[redacted][3] |
| Net cost to PBS | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |

Source: 'Siltuximab SYLVANT - Section 4 - 27 August 2021 - (For HPP).xlsx with effective price as stated in pre-PBAC response, Table 4 (p 11) of the resubmission and Table 15, July 2021 PSD.

[a] The costs of siltuximab do not take into account the [redacted]% price reduction offered in the July 2021 pre-PBAC response. The July 2021 submission assumed Year 1 of the financial estimates to be 2021 whereas the resubmission assumed Year 1 would be 2022.

*The redacted values correspond to the following ranges:*

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

4.17 The resubmission estimated between 52 and 84 patients on treatment over the period of the estimates (Table 6). The revised estimates are consistent with the PBAC's request for the financial estimates to use a prevalence-based approach (paragraph 7.12, siltuximab PSD, July 2021 PBAC meeting), noting that the resubmission reasonably assumed a listing date in 2022, rather than 2021 as was assumed previously.

4.18 The estimated net financial impact to the PBS/RPBS for the listing of siltuximab based on the proposed effective price in the pre-PBAC response is $20 million to < $30 million over six years (Table 6).

4.19 The resubmission also estimated increased MBS costs of $0 to < $10 million over six years due to treatment administration (cost of infusion based on MBS item 13950).

*For more detail on PBAC's view, see section 5 PBAC outcome.*

# 5 PBAC Outcome

5.1 The PBAC recommended the Authority Required (immediate assessment) listing of siltuximab for the treatment of idiopathic Multicentric Castleman disease (iMCD). The resubmission provided a revised economic model and financial estimates in response to previous concerns raised by the PBAC. The PBAC considered the revised incremental cost-effectiveness ratio (ICER) was acceptable for the proposed indication, given the high clinical need for effective treatments for these patients. In addition, the PBAC considered the revised financial estimates addressed previous concerns. Overall, the PBAC considered that the concerns raised at the July 2021 meeting had been sufficiently addressed.

5.2 The PBAC is satisfied that siltuximab provides, for some patients, a significant improvement in efficacy over placebo. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of siltuximab would be acceptable at the price proposed in the pre-PBAC response.

5.3 With regard to the requested listing and restriction, the PBAC advised that:

- A Section 100 Highly Specialised Drugs Program listing is appropriate (see paragraph 3.4).
- The eligible PBS population should be defined according to the international, evidence-based consensus diagnostic criteria for this condition (see paragraph 3.2) with the relevant diagnostic findings under the major and minor criteria documented in the patient's medical records. The recommended restriction (see paragraph 6.1) is simplified and references the published diagnostic criteria. An Authority Required (telephone/online) listing is appropriate in this context.
- Listing of both vial sizes, namely 100 mg and 400 mg, was acceptable.
- Prescribing should be limited to haematologists or under the direction of a haematologist.
- Patients will require regular ongoing follow-up care, and therefore a maximum of 4 repeats would be appropriate for the initial and continuing restrictions.

5.4 The PBAC noted the input from individuals highlighted the high clinical need for treatment options. In addition, the PBAC noted the comments from Myeloma Australia's Medical and Scientific Advisory Group that were submitted in support of the proposed listing prior to the July 2021 meeting (see paragraph 4.3).

5.5 The PBAC recalled that in its July 2021 consideration of siltuximab it had previously considered the claim of superior effectiveness compared with placebo was reasonable (paragraph 7.1, siltuximab PSD, July 2021 PBAC meeting). The PBAC also recalled that it had considered that the claim of non-inferior comparative safety was not adequately supported by the data presented in July 2021 but that siltuximab had an

inferior safety profile compared with placebo (paragraph 7.1, siltuximab PSD, July 2021 PBAC meeting).

5.6 The PBAC recalled that in July 2021 the Committee had considered a price reduction to achieve an ICER in the range of $75,000-$85,000/QALY would be appropriate (see Table 1). The PBAC noted the pre-PBAC response provided a price reduction resulting in an ICER of $75,000 to < $95,000/QALY using the revised economic model with a 15-year time horizon, consistent with PBAC advice. The PBAC considered that the ICER presented in the pre-PBAC response was acceptable in the context of iMCD being a rare condition with an unmet need for effective treatment.

5.7 The PBAC considered that its previous concerns about the financial estimates had been addressed with the prevalence-based approach provided in the resubmission.

5.8 The PBAC recommended that siltuximab should not be treated as interchangeable with any drugs.

5.9 The PBAC advised that siltuximab is not suitable for prescribing by nurse practitioners.

5.10 The PBAC recommended that the Early Supply Rule should not apply.

5.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for siltuximab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies on the basis of the clinical evidence considered at the July 2021 meeting (see paragraph 4.4).

b) The treatment is not expected to address an urgent unmet clinical need, as while the PBAC considered there to be a high unmet need, other treatments are used in clinical practice in Australia currently (see paragraph 4.13, siltuximab PSD, July 2021 PBAC meeting).

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

5.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**
Recommended

# 6 Recommended listing

## 6.1 Add new medicinal product as follows:

| MEDICINAL PRODUCT<br>medicinal product pack | PBS item code | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| SILTUXIMAB | | | | | |
| siltuximab 100 mg injection, 1 vial | New (Public) / New (Private) | 2 | 2 | 4 | Sylvant |
| siltuximab 400 mg injection, 1 vial | New (Public) / New (Private) | 2 | 2 | 4 | Sylvant |

| | |
|---|---|
| **Restriction Summary / Treatment of Concept [New 1]** | |
| | **Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private Hospital codes) |
| | **Prescriber type:** ☒ Medical Practitioners |
| | **Restriction type:** ☒ Authority Required (telephone/online PBS Authorities system) |
| | |
| | **Administrative advice:**<br>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. |
| | **Administrative advice:** Special Pricing Arrangements apply. |
| | |
| | **Episodicity:** Idiopathic |
| | **Severity:** multicentric |
| | **Condition:** Castleman disease (iMCD) |
| | **Indication:** Idiopathic multicentric Castleman disease (iMCD) |
| | **Treatment Phase:** Initial treatment |
| | |
| | **Clinical criteria:** |
| | Patient must have a diagnosis of iMCD consistent with the latest international, evidence-based consensus diagnostic criteria for this condition with the relevant diagnostic findings documented in the patient's medical records. |
| | **AND** |
| | **Clinical criteria:** |
| | The condition must not be, to the prescriber's best knowledge, any of the following diseases that can mimic iMCD: (i) human herpes virus-8 infection, (ii) an Epstein-Barr virus-lymphoproliferative disorder, (iii) an acute/uncontrolled infection (e.g. cytomegalovirus, toxoplasmosis, human immunodeficiency virus, tuberculosis) leading to inflammation with adenopathy, (iv) an autoimmune/autoinflammatory disease, (v) a malignant/lymphoproliferative disorder. |
| | |
| | **Treatment criteria:** |
| | Must be treated by a haematologist; or |
| | Must be treated by a medical physician working under the supervision of a haematologist |
| | **AND** |
| | **Treatment criteria:** |
| | Patient must be undergoing treatment through this treatment phase either: (i) once only in a lifetime, where the full number of repeats are prescribed, (ii) for up to the first 5 doses in a lifetime, where the full number of repeats was not prescribed with the first prescription |
| | |
| | **Prescribing Instructions:**<br>Prescribe the most efficient combination of vials/strengths based on the patient's body weight to keep any amount of unused drug to a minimum. |
| | |
| | **Administrative advice:**<br>The international, evidence-based consensus iMCD diagnostic criteria developed by an international working group of clinical experts lists various findings under 'Major' and 'Minor' diagnostic criteria that constitute a diagnosis of iMCD. At the time of |

| | |
|---|---|
| | writing, under these consensus criteria, diagnostic findings that meet: (i) both Major criteria and (ii) at least 2 of 11 Minor criteria including at least 1 laboratory abnormality and (iii) exclude various differential diagnoses, form a diagnosis of iMCD.<br><br>Details of these criteria are presented in Table 2 of the following literature article:<br><br>Fajgenbaum DC, Uldrick TS, Bagg A, Frank D et. al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood* 2017; 129: 1646-1657.<br><br>Where updates to these diagnostic criteria have occurred since the publication, refer to the latest version.<br><br>Do not contact the PBS-administrator to discuss whether an individual patient meets these consensus criteria. |
| | |
| **Restriction Summary / Treatment of Concept [New 2]** | |
| | **Indication:** Idiopathic multicentric Castleman disease (iMCD) |
| | **Treatment Phase:** Continuing treatment |
| | |
| | **Clinical criteria:** |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition. |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must not have developed disease progression while receiving treatment with this drug for this condition. |
| | |
| | **Treatment criteria:** |
| | Must be treated by a haematologist; or |
| | Must be treated by a medical physician working under the supervision of a haematologist |
| | |
| | **Prescribing Instructions:**<br>Prescribe the most efficient combination of vials/strengths based on the patient's body weight to keep any amount of unused drug to a minimum. |

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

# 7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

# 8 Sponsor's Comment

The Sponsor thanks the PBAC for its deliberations and is pleased that iMCD patients will finally have access to treatment.