

**11.01 DUPILUMAB,
Injection 200 mg in 1.14 mL single dose
pre-filled syringe,
Injection 300 mg in 2 mL single dose
pre-filled syringe,
Dupixent[®],
Sanofi-Aventis Australia Pty Ltd**

1 Purpose of Submission

- 1.1 The Category 3 resubmission requested the PBAC to revise the previously estimated utilisation of dupilumab in patients aged 12 years or older, with severe atopic dermatitis (AD) to reflect the higher than estimated utilisation of dupilumab for severe chronic atopic dermatitis (AD) since listing on 1 March 2021.
- 1.2 The sponsor proposed a revised risk sharing arrangement (RSA) to reflect these revised estimates. The sponsor proposed a two-tier structured RSA with varying rebate percentages. The sponsor proposed the following RSA structure:
- No rebate for use below the tier 1 caps.
 - Tier 1 caps: An increase in the current RSA caps of approximately $\frac{1}{2}\%$ per year to account for 15% of patients with severe AD of the face/hands only.
 - $\frac{1}{2}\%$ rebate for use between tier 1 and tier 2 caps.
 - Tier 2 caps: A further increase in the current RSA caps to account for (i) the remaining 85% of patients with severe AD of the face/hands, (ii) increasing the proportion of patients being inadequately controlled on topical corticosteroids (from 68% to 100%) and (iii) increasing the uptake rates (in year 6 from $\frac{1}{2}\%$ to $\frac{1}{2}\%$ of the prevalent pool of patients)
 - $\frac{1}{2}\%$ rebate for use exceeding the tier 2 caps.
- 1.3 The current and revised caps are summarised in Table 1. Based on the proposed tier 2 caps, the potential additional PBS/RPBS expenditure associated with the revised RSA versus the existing RSA is \$ $\frac{1}{2}$ million over 3 years.

Table 1: Proposed RSA caps for forward years (years 3, 4 and 5)

	Y3 (Mar 2023-Feb 2024)	Y4 (Mar 2024-Feb 2025)	Y5 (Mar 2025-Feb 2026)
Current caps (with Feb 2022 increase)			
Proposed Tier 1 caps			
% increase from existing caps			
Proposed Tier 2 caps			
% increase from existing caps			
Rebate for expenditure between Tier 1 and Tier 2 caps (█%)			
Maximum PBS/RPBS spend			

Source: RSA proposal calculations. Dupilumab_March 2023.xls/Whole market, values in italics calculated for submission overview.

2 Requested listing

2.1 The resubmission proposed no changes to the existing listing.

3 Background

Previous PBAC consideration

- 3.1 Dupilumab was previously considered for use in this indication by the PBAC in July 2018, July 2019, and was recommended at its March 2020 meeting. In November 2020, the PBAC provided further advice regarding the sponsor’s listing proposal which included a revised economic model and revised financial estimates following the March 2020 recommendation. In March 2022, the PBAC recommended extending the listing of dupilumab to include patients aged less than 12 years with severe AD.
- 3.2 In July 2022, the sponsor requested an increase in the financial caps for the current RSA to reflect the higher than estimated use of dupilumab for severe chronic AD. The sponsor presented revised financial estimates with changes to the proportion of patients uncontrolled on topical corticosteroids (TCS) and proportion of patients engaged with a specialist. The PBAC did not advise that its previous recommendation regarding the RSA subsidisation caps for dupilumab for the treatment of severe AD in adult and adolescent patients be amended. The PBAC considered the proposed revisions to the previously agreed assumptions informing the financial estimates were not adequately supported.
- 3.3 A summary of the March 2020, November 2020, July 2022 PBAC considerations and current proposal is provided in the table below.

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Table 2: Summary of the March 2020, November 2020 PBAC consideration and current proposal

	March 2020 PBAC consideration	November 2020 consideration	July 2022 consideration	July 2023 consideration
Requested effective DPMQ		<p>█████ proposed</p> <p>Revised to █████ following PBAC's recommendation.</p>	<p>█████ (small increase due to mark-ups)</p> <p>█████ used in the financial estimates.</p>	<p>█████ (small increase due to mark-ups)</p> <p>Proposed effective DPMQ of █████ net of Tier 2 rebate.</p>
Key assumptions input for calculating the estimated net cost to PBS/RPBS				
Addition of the hand/face population	<p>The PBAC noted the resubmission proposed an additional initial and continuing restriction for patients with chronic severe AD on the face and hands, which was not considered in the previous submissions. The sponsor argued that these patients would not be eligible for treatment under the original restriction due to the relatively small body surface involved but that severe lesions in these specific areas have a significant impact on patients' quality of life. The PBAC agreed with the ESC that this additional listing may be clinically appropriate and that the listing should include improvement in DLQI as a criterion for continuing treatment (para 7.5, dupilumab PSD, March 2020 PBAC meeting)</p>	<p>Remained unchanged.</p>	<p>The PBAC agreed with the sponsors of both dupilumab and upadacitinib that there may be substantial use of dupilumab in patients with severe AD exclusively of the hand and/or face, who would not otherwise meet the criteria for severe AD. The PBAC recalled it previously considered that it would not be appropriate for the caps to be increased to account for patients with severe AD exclusively of the hands or face as the cost-effectiveness in these patients has not been established. The PBAC considered that if the sponsors of dupilumab and upadacitinib wish to include this population in the financial estimates for the RSA caps, a submission demonstrating the cost-effectiveness in this population would be required (para 5.6, dupilumab PSD, July 2022 PBAC meeting).</p>	<p>Proposed addition of patients with hand/face AD to estimates (15% under tier 1 (no RSA rebate) and 85% under tier 2 (█████% rebate)).</p> <p>No additional data demonstrating cost effectiveness in this population was presented.</p>
Proportion of topical corticosteroid (TCS) therapy patients who have uncontrolled AD	<p>Estimated in the submission to be 68% of severe AD population based on clinician survey (METIS 2019b). The evaluation considered it was inappropriate to have assumed some severe AD patients would be 'adequately controlled' on treatment. It</p>	<p>The PBAC noted that the proposed estimates changed the assumption regarding patients being adequately controlled on topical corticosteroids (from 68% to 100%). The PBAC maintained that this parameter should</p>	<p>The PBAC noted that no data was provided in the submission to support the increase in the proportion of patients uncontrolled on TCS from 68% to 100% (para 5.3, dupilumab PSD, July 2022 PBAC meeting).</p>	<p>Assumes 100% of patients on TCS therapy would have uncontrolled AD.</p> <p>No additional data supporting this assumption were provided.</p>

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	March 2020 PBAC consideration	November 2020 consideration	July 2022 consideration	July 2023 consideration
	was also stated in the evaluation that this is a major source of uncertainty in the financial estimates and may underestimate the eligible patients (Table 19, Dupilumab PSD, March 2020 PBAC Meeting). The PBAC did not recommend revisions to this input.	remain unchanged (para 5.7, dupilumab PSD, November 2020 PBAC meeting).		
Proportion of patients engaged with specialist	<p>For moderate-to-severe population (as proposed by sponsor in Jul 2019), the evaluation considered this assumption could be 100%. However, DUSC disagreed noting that there would be workforce constraints and would not reach 100% (DUSC advice, July 2019).</p> <p>The ESC noted that it was unclear how many patients would re-engage with specialist care if dupilumab is listed (paragraph 6.6, dupilumab PSD, March 2020 PBAC meeting).</p> <p>Yr 1-6 assumptions: 55%, 58%, 61%, 64%, 67%, 70%</p>	Remained unchanged from March 2020.	<p>Assumes 100% patients would be engaged with a specialist.</p> <p>The PBAC noted that the submission argued that the implementation of Authority Required listing with telephone/online approval and access to telehealth consultations had enabled greater access to specialists for prescribing than estimated. The PBAC noted that no evidence was presented to support the claim that availability of telehealth consultations has resulted in additional access to dermatologists, enabling greater access to prescribing of dupilumab than was anticipated. The PBAC considered that the submission did not provide sufficient justification to support changes to these inputs as the basis for an increase to the agreed subsidisation caps (para 5.3, dupilumab PSD, July 2022 PBAC meeting).</p>	<p>Uses estimates from March 2020 submission.</p> <p>Yr 1-6 assumptions: 55%, 58%, 61%, 64%, 67%, 70%</p>
Uptake rates applied to prevalent patient	The PBAC noted that the uptake rates of 5% in year 1, increasing to 7.5% in year 6 were applied to the prevalent pool of	Revised uptake rates based on PBS uptake of biologic therapies for ankylosing spondylitis, psoriasis, and	Agreed uptake rates based on PBAC's Nov 2020 recommendation remain unchanged.	The uptake rates for forward years are revised to reflect the estimated actual uptake rates in the first 2 years

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	March 2020 PBAC consideration	November 2020 consideration	July 2022 consideration	July 2023 consideration
pool	<p>eligible patients each year to calculate the number of patients initiating treatment. The PBAC considered it is not reasonable to assume the uptake rate of new patients from the prevalent pool would increase each year (paragraph 6.56, Dupilumab ratified minutes, March 2020 PBAC Meeting).</p> <p>Yr 1-6 uptake rates as per March 2020 PBAC recommendation: 5%, 4.2%, 2.7%, 2.5%, 2.6%, 2.7% (net eligible population)</p>	<p>Crohn disease.</p> <p>Pricing proposal (as per sponsor's clarification in pre-PBAC response): 5%, 4.5%, 4.0%, 3.5%, 3.5%, 3.5% (total PBS population).</p> <p>The PBAC acknowledged the proposal's claims that the uptake rates were a better estimate of the pattern of uptake. Importantly, the PBAC considered that the uptake rates of patients from the prevalent pool proposed by the sponsor decreased over time and therefore were reasonable (paragraph 5.6, dupilumab PSD, November 2020 PBAC meeting).</p>		of listing (applied to estimates for tier 2 of RSA).
Risk sharing arrangement (RSA)	The PBAC considered the potential for use of dupilumab outside the proposed restriction could be managed through an RSA (paragraph 7.1, Dupilumab PSD, March 2020 PBAC Meeting).	The PBAC restated that an RSA would be required consisting of subsidisation caps based on the financial estimates and █████% rebate for any expenditure exceeding these caps (paragraph 5.8, dupilumab PSD, November 2020 PBAC meeting).	<p>Request to vary current RSA to reflect additional utilisation of dupilumab in the first year of listing.</p> <p>The PBAC considered the proposed revisions to the previously agreed assumptions informing the financial estimates were not adequately supported, and it was not demonstrated that dupilumab would be cost-effective when used in a population that was potentially broader than that previously recommended, where the submission's revised estimates were more than █████ those previously recommended and agreed by the sponsor for listing on the</p>	Proposed a revised RSA with three-tier structure with varying rebates percentages and increased caps.

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	March 2020 PBAC consideration	November 2020 consideration	July 2022 consideration	July 2023 consideration
			<p>PBS. The PBAC further considered that it was premature (less than 18 months since PBS listing) to increase the agreed caps when the available data potentially suggest that, although the initial uptake was more rapid than expected, uptake in new patients is likely to continue to reduce and utilisation over a longer time frame may be considerably less than estimated in the submission's revised estimates.</p>	

Source: DUSC advice, July 2019, Dupilumab Public Summary Document (PSD), March 2020 PBAC meeting; Dupilumab PSD, November 2020 PBAC meeting; Main submission body

Current RSA and expenditure

- 3.4 In March 2020, the PBAC considered there was potential for substantial use beyond the requested restriction to those with less severe AD, those with comorbid conditions such as asthma, those with reduced QoL due to overly complex topical regimens, and to patients who do not have sufficient response according to the continuing criteria (paragraph 7.20, dupilumab Public Summary Document (PSD), March 2020 PBAC meeting). The PBAC considered an RSA was required to address the potential for use outside the intended population, and to address the potential continuing use in patients who do not have adequate response, where use of dupilumab is likely to be less cost-effective (paragraph 7.21, dupilumab PSD, March 2020 PBAC meeting). Under the current RSA, the sponsor is required to rebate $\%$ of Commonwealth expenditure above the agreed caps.
- 3.5 Between its July 2021 and November 2021 meetings, the PBAC recommended the listing of upadacitinib (UPA) for severe AD on the basis that the cost-effectiveness of UPA would be accepted if it were cost-minimised against dupilumab (paragraph 9.1, upadacitinib PSD, July 2021 PBAC Meeting). The PBAC recommended that UPA should join the same RSA as dupilumab, with a modest increase to the caps to account for sequential use (paragraph 9.4, upadacitinib PSD, July 2021 PBAC meeting).
- 3.6 The currently agreed caps are shown in Table 3.

Table 3: Dupilumab and upadacitinib severe AD subsidisation caps

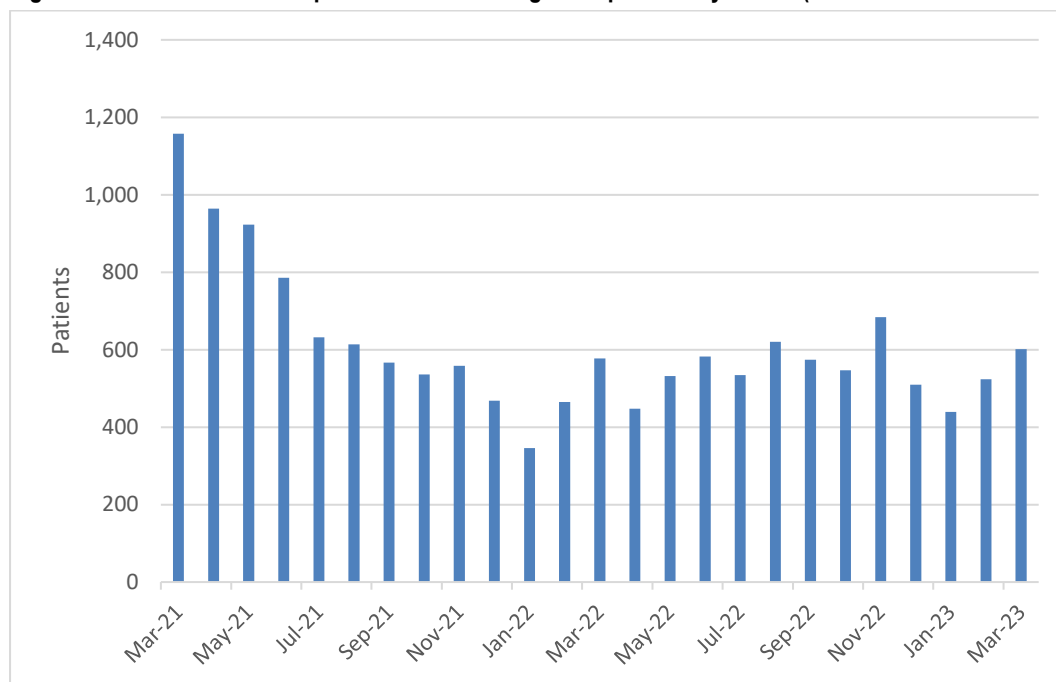
	Year 1 Mar 2021 to Feb 2022	Year 2 Mar 2022 to Feb 2023	Year 3 Mar 2023 to Feb 2024	Year 4 Mar 2024 to Feb 2025	Year 5 Mar 2025 to Feb 2026
Original cap (March 2021) (\$)					
Amended cap (Feb 2022)* (\$)					

*Amended to account for the inclusion of UPA

Source: Attachment 1 – Deed of Agreement, executed 15 Feb 2021; Main submission body; Dupilumab PSD, July 2022 PBAC meeting

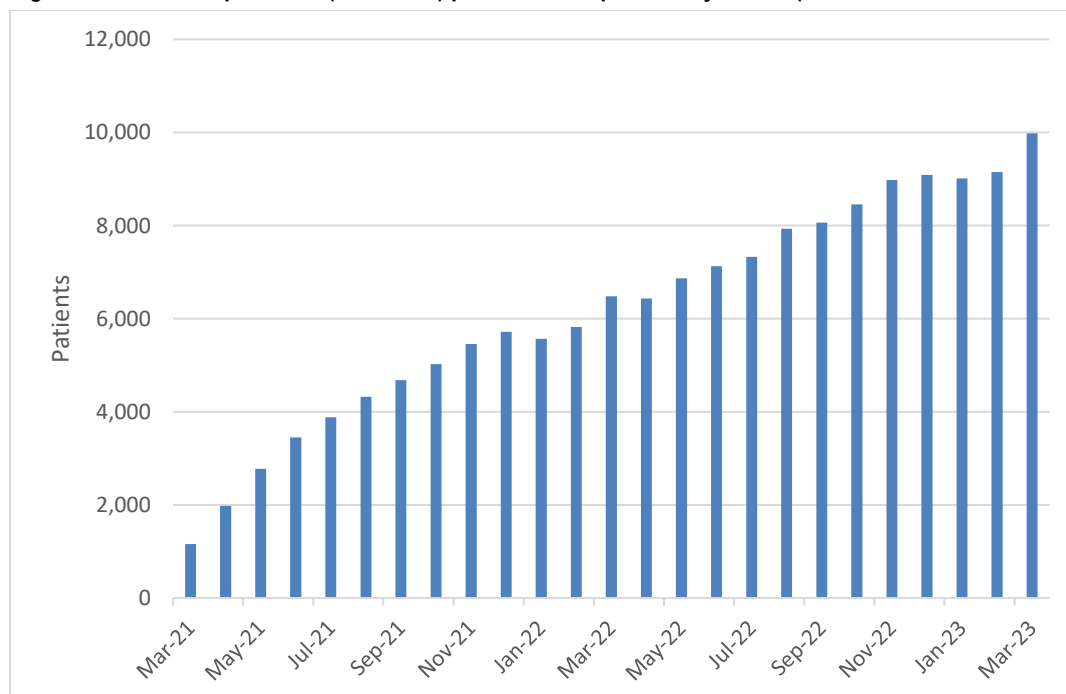
- 3.7 Based on the Streamlined Monthly Rebate Payment (SMRP) data, the submission noted that in the first year of listing (1 March 2021 to 28 February 2022), the actual Commonwealth expenditure exceeded the whole market cap by $\%$. Based on the 11 months of the second year of listing (1 March 2022 to January 2023), expenditure was expected to exceed the whole market year 2 cap by $\%$.
- 3.8 The number of incident patients per month, prevalent (all treated) patients per month and packs per month are shown in Figure 1, Figure 2 and Figure 3. The pre-PBAC response noted that peak initiations tend to occur between Jun-November, reflecting the seasonal variation in exacerbation of symptoms. The pre-PBAC response stated that utilisation patterns have not plateaued to a degree that would result in sustainable listing conditions under the current RSA.

Figure 1: Number of incident patients first initiating on dupilumab by month (PBS items 12291X and 12292Y)



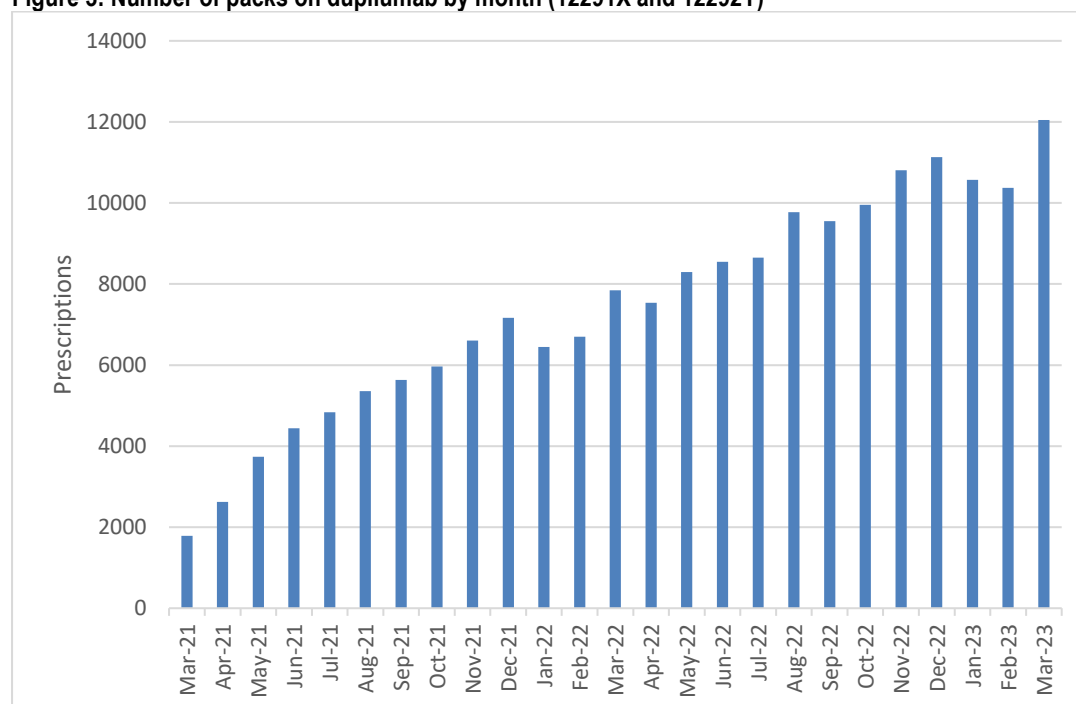
Source: Data extracted from the PBS data maintained by Department of Health, processed by Services Australia. All claims' records for PBS items 12291X and 12292Y were extracted based on the date of supply from 1 March 2021, date of their first listing, to 31 March 2023, the most complete month.

Figure 2: Number of prevalent (all treated) patients on dupilumab by month (PBS items 12291X and 12292Y)



Source: Data extracted from the PBS data maintained by Department of Health, processed by Services Australia. All claims' records for PBS items 12291X and 12292Y were extracted based on the date of supply from 1 March 2021, date of their first listing, to 31 March 2023, the most complete month.

Figure 3: Number of packs on dupilumab by month (12291X and 12292Y)



Source: Data extracted from the PBS data maintained by Department of Health, processed by Services Australia. All claims' records for PBS items 12291X and 12292Y were extracted based on the date of supply from 1 March 2021, date of their first listing, to 31 March 2023, the most complete month.

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 health care professionals (6) and organisations (4) via the Consumer Comments facility on the PBS website.

4.3 The comments from healthcare professionals noted the improvements observed in patients undergoing dupilumab treatment and described the drug as a 'game changer' and 'life changing'. Healthcare professionals also noted that dupilumab has minimal disadvantages with side effects described as being few and manageable. The comments also outlined the significant improvements dupilumab treatment has had on individual quality of life, including improved self-esteem, increased ability to work, study, perform daily tasks, attend social events and dramatic improvements to itch and sleep. There was a comment noting the need for continued affordable access to dupilumab treatment for individuals with severe AD.

4.4 The comments from individuals described a significant improvement in individual symptoms upon dupilumab treatment and noted the need for affordable access to dupilumab treatment, particularly for those under 11 years old.

4.5 The PBAC noted the input received from The Australasian College of Dermatologists (ACD), Allergy and Anaphylaxis Australia (A&AA) and Australasian Society of Clinical Immunology and Allergy (ASCIA) that described the significant improvement in patients who are on dupilumab treatment and the need to continue affordable access to dupilumab treatment for this patient group. The PBAC noted input from Eczema Support Australia (ESA) including reference to their report on the burden and prevalence of atopic dermatitis in Australia. ESA requested that the Committee consider realistic utilisation data to ensure that dupilumab is included on the PBS on a sustainable basis.

Characteristics of the reimbursed cohort of severe AD patients

4.6 The submission presented an analysis of data from Services Australia (SA), provided by DUSC, relating to the population of patients receiving dupilumab treatment on the PBS during the first 18 months of listing (March 2021 to August 2022).

4.7 From 1 March 2021 to 24 August 2022, SA data indicated that 5,000 to < 10,000 (82.4%) patients initiated treatment with dupilumab under the whole-body PBS criteria, whilst 500 to < 5,000 (17.6%) patients initiated therapy under the hand and/or face criteria as shown in Table 4. The PBAC noted that the most recent utilisation data for dupilumab indicated that the proportion of hand/face utilisation has increased to 19% (March 2021 to March 2023).

Table 4: Number of patients initiating therapy by patient type

Body area	Number of initiating patients	Proportion of patients	Mar 2021-Mar 2023
Face and hands	¹	17.6%	¹ (19%)
Whole body	²	82.4%	² (81%)

Source: D1436 dupilumab utilisation_2Sept2022.xls, Analysis 2; Main submission body, DUSC Secretariat

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

4.8 A summary of the baseline PGA, EASI scores for patients qualifying for treatment under the full body criteria is shown in Table 5. PGA and full EASI score at baseline are not recorded for patients treated for AD under the face and/or hands restrictions.

Table 5: Summary of baseline characteristics of treated patients

	N	Mean	Median	Lower 95% CI	Upper 95% CI	Min	Max
PGA	¹	4.0	4	4	4	NA	NA
EASI	¹	34.2	31	33.93	34.39	20	72

Source: D1436 dupilumab utilisation_2SEP2022.xls, Analysis 1; Main submission body

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000,

4.9 The submission noted that all patients who received dupilumab treatment under the whole body criteria fulfilled the PBS requirement of severe AD as defined by the pre-treatment PGA score of 4. The submission further noted that all patients qualifying for therapy under the whole body criteria were above the minimum EASI score required (20). The submission therefore claimed that of those patients qualifying for treatment under the whole body criteria, all patients fulfilled the pre-treatment disease severity

requirements and leakage into a non-reimbursed, less severe patient cohort is not contributing to the higher-than-expected utilisation.

- 4.10 A summary of the baseline DLQI scores for patients qualifying under the whole body and hand and face criteria is provided in Table 6.

Table 6: Baseline DLQI

	N	Mean	Median	Lower 95% CI	Upper 95% CI	Min	Max
Whole body	2	20.5	21	20.35	20.47	0	30
Hand and face	1	19.2	20	18.71	19.6	0	30

Source: D1436 dupilumab utilisation_2SEP2022.xls, Analysis 1; Main submission body

The redacted values correspond to the following ranges:

¹ 500 to 5,000

² 5,000 to < 10,000

- 4.11 Mean DLQI scores for whole body and hand and/or face patients were 20.5 (95% CI: 20.35, 20.47) and 19.2 (95% CI: 18.71, 19.6) respectively and the corresponding median (min:max) scores were 21 (0:30) and 20 (0:30). The submission concluded that the baseline DLQI scores for hand and face patients were similar to those for whole body patients, and therefore there is no reason to assume that the potential benefit, and consequently, the cost-effectiveness of treating patients with AD primarily of the hand and face is lower than that for patients with whole body AD.
- 4.12 At its March 2020 meeting, the PBAC considered that it would not be appropriate for the caps to be increased to account for patients with severe AD exclusively of the hands or face as the cost-effectiveness in these patients is unknown (Paragraph 7.21, dupilumab PSD, March 2020). At its July 2021 meeting the PBAC recalled that cost-effectiveness in this population had not been established as neither the dupilumab nor upadacitinib submissions presented data to inform the efficacy of treatment in patients who exclusively had severe face and/or hand AD (para 3.4, dupilumab PSD, March 2020 PBAC meeting and para 6.19, upadacitinib PSD, July 2021 PBAC meeting).

Continuation rates

- 4.13 The resubmission presented a summary of the proportion of whole body patients qualifying for ongoing treatment following the initial treatment period who initiated treatment with dupilumab over the period 1 March 2021 to 24 August 2022 (see Table 7). Patients who had initiated treatment within 20 weeks of the data cut-off date (25 August 2022) were censored as no applications for continuing treatment would have been captured in the available data.

Table 7: Proportion of patients qualifying for first maintenance cycle

Total patients with approved initial application	■ ²
Number of patients censored	■ ¹
Number of non-censored initial patients	■ ²
Number of non-censored initial patients with an approved continuing treatment application	■ ²
Proportion of patients with an application for Initial to Continue	86.0%

The redacted values correspond to the following ranges:

¹ 500 to 5,000

² 5,000 to < 10,000

- 4.14 Of the 5,000 to < 10,000 patients with sufficient follow-up, 5,000 to < 10,000 (86%) had an application for continuing treatment approved. The submission noted that this is higher than the week 16 response rate assumed in the agreed utilisation estimates based on clinical trial data (59.6%). The submission noted this may explain part of the higher-than-expected utilisation observed. Higher than anticipated continuation rates have not been directly accounted for in the revised estimates. However, the higher continuation rates contribute to the current use and therefore the revised uptake rates. The Pre-PBAC response agreed, noting the utilisation estimates “are anchored on the observed number of packs dispensed in Years 1 and 2 of the listing of dupilumab on the PBS for the treatment of severe AD. As such, whilst the number of packs estimated to be used by continuing patients relative to newly initiating patients may be underestimated, the total number of packs to be used by the full treated population are considered to be reflective of the expected overall use”.
- 4.15 The resubmission presented a summary of the proportion of patients completing the first maintenance cycle and qualifying for continuing treatment into the second maintenance cycle in Table 8. Patients who were eligible for first continuing cycle of treatment within 24 weeks of the data cut-off date (24 August 2022) were excluded from the analysis as these patients would not have completed the first maintenance course prior to the data cut-off date. Consequently, a significant number of patients (83.6%) who were eligible for the first continuing cycle were not included in this analysis and results of this analyses should be interpreted with caution.

Table 8: Proportion of patients qualifying for second maintenance cycle

Total number of patients with an approved application for their first course of continuing treatment	■ ¹
Number of continuing patients who were censored	■ ¹
Number of non-censored continuing patients	■ ²
Number of non-censored continuing patients with an approved further continuing treatment application	■ ²
Proportion of patients meeting continuation criteria for further continuing treatment	99.5%

Source: D1436 dupilumab utilisation_2SEP2022.xls, Analysis 4; Main submission body

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 500 to < 5,000

- 4.16 Out of the 500 to < 5,000 patients who were eligible for a first continuing course of treatment (at least 24 weeks prior to the data cut-off date), 500 to < 5,000 were eligible for a second continuing course, indicating that approximately 99.55% of week 16 responders continued to maintain response at the end of the first continuing course. The submission noted that this is higher than the 78.6% assumed in the agreed utilisation estimates and, whilst these data need to be interpreted with caution, they indicated that a higher proportion are qualifying for subsequent continuing treatment than expected based on clinical trial data. The resubmission noted that the continuation rate of 99.5% for the second continuing cycle is consistent with what was observed during the early access programs run by Sanofi prior to the listing of dupilumab on the PBS. No data were presented for the continuation rates in the face/hands population. The revised financial estimates assumed that the continuation rates for both whole body and face/hand populations are the same. As above, the higher-than-expected continuation rate for the second continuing course of treatment has not been directly applied to the revised estimates.

For more detail on PBAC's view, see section 6 PBAC outcome

5 Estimated PBS usage and financial implications

Revised eligible population estimates

- 5.1 The March 2020 resubmission used market research data to inform the proportion of patients treated by a dermatologist or immunologist, with uncontrolled AD on topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) (and therefore considered for treatment with dupilumab). This was estimated to be 68%.
- 5.2 In November 2020, the PBAC noted that the proposed estimates changed the assumption regarding patients being inadequately controlled on topical corticosteroids (from 68% to 100%) although the PBAC did not specify that this parameter be changed in the outcome of its March 2020 consideration. The submission has maintained the assumption of 100% of patients with severe AD uncontrolled on TCS in the current estimates, claiming that it is consistent with previous advice from ESC, DUSC and the PBAC.
- 5.3 A summary of the revised eligibility criteria assumptions is presented in Table 9.

Table 9: Revised total estimated number of patients eligible for treatment with dupilumab

Parameter	March 2020/November 2020 PBAC recommendation	July 2023 PBAC resubmission	Source
Australian population aged 12 years and older	22.3M (Year 1)	22.3M (Year 1)	ABS population – 3222.0 Series B
Proportion with atopic dermatitis	9%	9%	7.05 dupilumab DUSC Adv 07-2019, page 3
Proportion of AD patients with severe disease	5%	5%	Market Research (Metis 2019a)
Patients engaged with a specialist	55% (Year 1) – 70% (Year 6)	55% (Year 1) – 70% (Year 6)	Market Research (Metis 2019a)
Engaged patients uncontrolled with TCS	68%	100%	ESC/DUSC advice
Proportion of patients meeting EASI requirement (EASI>20)	95%	95%	Patient data on file
Hand/ Face patients	N/A	Additional 21% initiating patients in each year to account for 17.6% hand/face patients not included in previous estimates.	DUSC utilisation data

Shaded cells show values that are changed compared to the previously accepted estimates.

- 5.4 The sponsor revised the eligible population by applying a 21% increase to the number of whole body patients to derive the total eligible population including patients treated under the hand/face restrictions (17.6% of the total population).
- 5.5 Table 10 outlines the revised eligible patient numbers based on assumptions as outlined in Table 9 above.

Table 10: Revised total estimated number of patients eligible for treatment with dupilumab

	2021	2022	2023	2025	2025	2026
Australian AD Pop. (12+) (#)	22,320,412	22,696,040	23,062,732	23,423,761	23,780,244	24,125,467
Prevalence (%)	9%	9%	9%	9%	9%	9%
Atopic Dermatitis Population (#)	2,008,837	2,042,644	2,075,646	2,108,138	2,140,222	2,171,292
Patients with severe disease (%)	5%	5%	5%	5%	5%	5%
Patients engaged with a specialist (%)	55%	58%	61%	64%	67%	70%
Engaged patients who are uncontrolled on topical therapies (%)	100%	100%	100%	100%	100%	100%
Proportion of patients meeting EASI requirement (EASI≥20) (%)	95%	95%	95%	95%	95%	95%
Eligible patients (#) ^a	1	1	2	2	2	3
Additional patients treated under hands and/or face restriction						
Increase to prevalent population (workbook row 35) to include hands/face patients (17.6% of total)	121.36% ^c					
Overall eligible patients	2	2	3	3	4	4
March 2020 ^b – Eligible Patients	5	5	6	6	6	6

Source: utilisation and cost model workbook sheet 2b. prevalent

^a eligible patient's prior addition of patients treated via hands and/or face restrictions

^b Referred to as Nov 2019 in the submission.

^c The 21.36% increase to the prevalent population was applied to the number of eligible patients, rather than as an addition to patient numbers after accounting for uptake.

The redacted values correspond to the following ranges:

¹ 50,000 to < 60,000

² 60,000 to < 70,000

³ 70,000 to < 80,000

⁴ 80,000 to < 90,000

⁵ 30,000 to < 40,000

⁶ 40,000 to < 50,000

Revised uptake in the eligible population

- 5.6 The submission revised the uptake rates in the eligible population based on the use in the two years of listing of dupilumab on the PBS.
- 5.7 Based on PBS claims data (March 2021-February 2022), the submission noted that a total of 50,000 to < 60,000 packs were dispensed during the first-year listing of dupilumab. Excluding grandfathered patients (approx. 5,000 to < 10,000 packs) and assuming that each initiating patient would use an average of 9.75 packs in the first year of treatment (approx. 36 weeks of treatment), this equates to approximately 500 to < 5,000 patients initiating therapy in Year 1 of listing, which is approximately 7.8% of the eligible population of 60,000 to < 70,000 patients electing to initiate treatment with dupilumab in Year 1.
- 5.8 Based on PBS claims data (1 March 2022 – 31 January 2023), 90,000 to < 100,000 packs of dupilumab were dispensed during the first 11 months of the second year of listing. Extrapolating this to cover the full 12 months of the second year of listing, the submission estimated that a total of 100,000 to < 200,000 packs will be dispensed in

Year 2. Based on the number of packs estimated to be used in Year 2 and the number of packs required to treat patients continuing treatment from Year 1, the resubmission estimated that approximately 5,000 to < 10,000 patients initiated treatment with dupilumab in Year 2 of the deed, equating to an uptake rate from the eligible population of █%.

- 5.9 The resubmission claimed that the uptake of dupilumab has continued to increase month-on-month based on the available data for the first 23 months of listing but noted that the increase in uptake will eventually plateau as most prevalent eligible patients likely to initiate therapy with dupilumab will be treated. The resubmission therefore assumed that the growth in uptake of dupilumab will continue in Year 3, and then reduce and plateau for Years 4 to 6 of estimates (Table 11).
- 5.10 The Pre-PBAC response argued that the proposed uptake rates (█%, █%, █%, █%, █%, █%, █%) are consistent with the pattern of uptake rates (█%, █%, █%, █%, █%, █%) proposed in the November 2020 pricing package accepted by the Department with the assumption of higher uptake in the earlier years of listing with a gradual plateauing in later years.

Table 11: Estimated uptake rate for the adolescent and adult population – dupilumab and whole market

	2021	2022	2023	2024	2025	2026
Eligible patients (#)	█ ¹	█ ¹	█ ²	█ ²	█ ³	█ ³
Patients electing treatment (%) – dupilumab	█	█	█	█	█	█
Patients electing treatment (%) – dupilumab (Nov 2020 PBAC recommendation)	█	█	█	█	█	█
Patients electing treatment (#) - dupilumab	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Patients electing treatment (%) – whole market	█	█	█	█	█	█
Patients electing treatment (#) – whole market	█ ⁴	█ ⁵	█ ⁶	█ ⁶	█ ⁶	█ ⁶

Source: utilisation and cost model workbook sheet 2b. prevalent and Table 5 dupilumab PSD, November 2020 PBAC meeting

The redacted values correspond to the following ranges:

¹ 60,000 to < 70,000

² 70,000 to < 80,000

³ 80,000 to < 90,000

⁴ 500 to < 5,000

⁵ 5,000 to < 10,000

⁶ 10,000 to < 20,000

- 5.11 The resubmission noted that since upadacitinib was PBS-listed for severe AD on 1 February 2022, the PBS data indicated that the share of the overall AD market captured by upadacitinib has steadily increased, with approximately █% of the total market each month for the period of October 2022 to January 2023. The submission therefore assumed that the share of the total AD market captured by upadacitinib will continue to increase to █% in Year 3 of the deed (Year 2 of upadacitinib listing) and will plateau at █% of the market thereafter. Based on these assumptions, the total proportion of the eligible population expected to receive treatment with either

dupilumab or upadacitinib over the 6 years since listing of dupilumab on the PBS is provided in Table 11 above.

5.12 Inputs relating to the response for dupilumab at week 16, week 42 and the persistence of this response from Year 2-6 have not been amended from those previously agreed.

Table 12: Continuation inputs for financial estimates

Input	Value	Source
Initiating – week 16 non-responders	40.4%	Trial data
Initiating – week 42 non-responders	2.6%	Trial data
Initiating – week 52 responders	57.0%	Trial data
Year 2 persistence	83.2%	Time to first rescue regression analysis
Year 3 persistence	79.9%	Time to first rescue regression analysis
Year 4 persistence	77.2%	Time to first rescue regression analysis
Year 5+ persistence	74.8%	Time to first rescue regression analysis
Annual Drop Out	4%	Time to first rescue regression analysis

Source: Table 5.9 of the resubmission

5.13 The increase to the number of initiating patients in the resubmission revised estimates resulted in increased numbers of continuing patients compared with the previously agreed estimates. A summary of the continuing patients in each year for dupilumab and whole market are presented in Table 13 below.

Table 13: Summary of continuing patients – dupilumab and whole market

	2021	2022	2023	2024	2025	2026
Continuing Patients - dupilumab						
Initiating - week 16 non-responders (#)	1	1	1	1	1	1
Initiating - week 42 non-responders (#)	3	3	3	3	3	3
Initiating - week 52 responders (#)	1	1	1	1	1	1
Persistent population (#)		1	2	2	4	4
Continuers (% of total eligible patients)	0.00%	4.17%	8.28%	12.55%	14.32%	15.25%
Grandfathered patients	3	3	3	3	3	3
Continuing Patients – whole market						
Initiating - week 16 non-responders (#)	1	1	1	1	2	2
Initiating - week 42 non-responders (#)	3	3	3	3	3	3
Initiating - week 52 responders (#)	1	1	2	2	2	2
Persistent population (#)		1	2	4	4	4
Continuers (% of total eligible patients)	0.00%	4.17%	9.87%	15.63%	19.83%	22.82%
Grandfathered patients	3	3	3	3	3	3

Source: utilisation and cost model workbook sheet 2b. prevalent

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ < 500

⁴ 10,000 to < 20,000

Revised script numbers and financial estimates

5.14 The resubmission only presented revised financial estimates for 4 future years, noting that the first two years of the revised estimates are for Year 2021 and 2022.

- 5.15 There were no changes to the assumptions or methods of estimating the number of packs per patient in the resubmission’s revised financial estimates. The Sponsor’s estimates and financial implications using the revised assumptions for dupilumab and the whole market are shown in Table 14 below.
- 5.16 As a Category 3 submission the financial estimates have not been independently evaluated. However, the projected prescription volumes appear substantially overestimated compared with the current prescription volumes. For example, each month between November 2022 and February 2023 there were approximately 11,000 packs (Figure 3, the number of packs in March 2023 was approximately 12,000), which is equivalent to approximately 132,000 packs per year. This compares with 200,000 to < 300,000 and 200,000 to < 300,000 packs estimated in 2025 and 2026 respectively for dupilumab. The Pre-PBAC response argued that the comparison of estimates on a four-month period is inappropriate as there is a substantial month-on-month variation in the uptake of dupilumab seen over the first two years of listing. The sponsor claimed that the AD market has not yet stabilised and argued it would be more appropriate to use the actual full year pack numbers as dispensed. The Pre-PBAC response further stated that it is expected that overall utilisation of dupilumab will continue to increase over time as patients who respond to dupilumab will continue treatment as long as response is maintained. The Pre-PBAC response noted that the higher number of packs estimated for years 3 to 5 therefore reflects both utilisation in treatment-naïve patients entering the treatment pool, as well as patients continuing treatment initiated in previous years.

Table 14: Revised packs and costs – dupilumab and whole market

	2021	2022	2023	2024	2025	2026
Commonwealth packs and expenditure – dupilumab						
Aggregate volumes PBS/RPBS	1	2	2	3	3	3
Net cost PBS/RPBS	4	5	6	6	7	7
Commonwealth packs and expenditure – whole market						
Aggregate volumes PBS/RPBS	1	2	3	3	8	8
Net cost PBS / RPBS	4	6	6	7	9	9

Source: utilisation and cost model workbook Sheet 7. MBS

The redacted values correspond to the following ranges:

- ¹ 50,000 to < 60,000
- ² 100,000 to < 200,000
- ³ 200,000 to < 300,000
- ⁴ \$50 million to < \$60 million
- ⁵ \$90 million to < \$100 million
- ⁶ \$100 million to < \$200 million
- ⁷ \$200 million to < \$300 million
- ⁸ 300,000 to < 400,000
- ⁹ \$300 million to < \$400 million

Proposed RSA

5.17 The sponsor proposed revising the current RSA to reflect the higher-than-expected utilisation of dupilumab, in line with the revised financial estimates. The sponsor proposed a two-tier structure for the revised RSA (Table 15):

- Tier 1 (no rebate for use below the tier 1 caps): An increase in the current RSA caps of approximately 11% per year to account for 15% of the patients with severe AD of the hand/face only (1% rebate for use between the tier 1 and tier 2 caps).
- Tier 2: A further increase in the current RSA caps to account for the remaining 85% of patients with severe AD of the face/hands, increasing the proportion of patients being inadequately controlled on topical corticosteroids (from 68% to 100%) and increasing the uptake rates (in year 6 from 1% to 1% of the prevalent pool of patients). Includes additional packs as estimated above (Table 14) with an 1% rebate for use between tiers 1 and 2, and a 1% rebate for use exceeding the tier 2 caps.

5.18 The submission noted the DPMQ per pack of \$[redacted] represents an [redacted]% discount in Commonwealth expenditure for packs in Tier 2 compared with Tier 1 packs. Though not clearly stated in the submission, it is assumed that the sponsor is proposing an 1% rebate for the cost of packs above the Tier 1 caps and up to Tier 2 caps. The submission noted that the final agreed ICER for dupilumab versus standard of care was \$45,000 to < \$55,000/QALY as per the current DPMQ of \$[redacted]. The submission noted that an ICER of \$25,000 to < \$35,000/QALY can be achieved by reducing the DPMQ to \$[redacted] per pack with no changes to the model. The submission noted the reduction in the cost-effectiveness ratio was to address the additional uncertainty associated with the higher-than-expected use of dupilumab on the PBS compared with the currently agreed estimates.

Table 15: Estimated utilisation by patient type and tier – dupilumab (packs)

	Y1 (Mar 2021-Feb 2022)	Y2 (Mar 22-Feb 2023)	Y3 (Mar 2023-Feb 2024)	Y4 (Mar 2024-Feb 2025)	Y5 (Mar 2025-Feb 2026)
Whole body (current caps)	1	2	3	4	4
Tier 1 - Hand and face additional (15% of Hand/face)	6	6	6	7	7
Tier 1 (revised) total	1	2	3	4	5
Tier 2 - Whole body (additional packs)	1	4	11	12	12
Tier 2 - Hand and face (85% of Hand and face, additional packs)	7	8	9	10	10
Total (Tier 1 + Tier 2)	4	12	12	13	13

Source: RSA proposal calculations.xls/Sheet 1

The redacted values correspond to the following ranges:

- ¹ 20,000 to < 30,000
- ² 30,000 to < 40,000
- ³ 40,000 to < 50,000
- ⁴ 50,000 to < 60,000
- ⁵ 60,000 to < 70,000
- ⁶ 500 to < 5,000

- ⁷ 5,000 to < 10,000
- ⁸ 10,000 to < 20,000
- ⁹ 20,000 to < 30,000
- ¹⁰ 30,000 to < 40,000
- ¹¹ 90,000 to < 100,000
- ¹² 100,000 to < 200,000
- ¹³ 200,000 to < 300,000

Impact on Net government expenditure

- 5.19 The resubmission estimated the total cost to the PBS/RPBS for the whole market (dupilumab and upadacitinib) to be \$M in Year 3 (years 1 and 2 of the current deed have already passed). The estimated total cost increased to \$M in Year 5.
- 5.20 The PBAC noted that the calculation of increases to the tier 1 caps to include a proportion of hand/face patients as shown in Table 16 were further increased by the application of higher uptake rates. The PBAC noted that increasing the agreed financial caps by 21% to capture the population with AD of the hands/face only would result in a potential total cost of \$M in year 3, \$M in year 4 and \$M in year 5, with a total cost of \$M over the remaining years of the deed.

Table 16: Impact of proposed Risk Share Arrangement on Government expenditure – whole market

	Y1 (Mar 2021-Feb 2022)	Y2 (Mar 22-Feb 2023)	Y3 (Mar 2023-Feb 2024)	Y4 (Mar 2024-Feb 2025)	Y5 (Mar 2025-Feb 2026)
Amended cap (Feb 2022) ^a (A)					
Tier 1 caps ^a					
% increase from existing caps					
Tier 2 caps					
Tier 2 caps with % rebate					
Total (Tier 1 + 2)					
Total (Tier 1 + 2 with % rebate on Tier 2)					
% increase					
21% increase to account for 17.6% use in hands/face only patients (B)					
Difference between (A) and (B)					

^a Current cap revised to include 15% of hand and face patients
 Source: calculated based on RSA proposal calculations_Dupilumab_March 2023.xls/Whole market

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC advised that it would be reasonable for the current risk sharing arrangement (RSA) financial caps for dupilumab (and upadacitinib), for the treatment of severe atopic dermatitis (AD) in patients aged 12 years and older, to be increased for the

remaining years of the arrangement, to account for patients with severe AD of the hands and/or face. In providing this advice, the PBAC noted that such use was not accounted for in the original RSA caps, however, given the apparent quality life impacts of disease affecting the hands and face appear similar to that for the whole body, considered that use in these patients is likely to be cost-effective. The PBAC considered the submission's other proposed changes to the financial estimates (increasing the proportion of patients inadequately controlled on topical corticosteroids and increasing the uptake rates) to be overestimated and highly uncertain. The PBAC considered that the submission did not provide sufficient justification in relation to changing these assumptions and therefore did not support these amendments.

- 6.2 The PBAC noted that the utilisation of dupilumab over the first 2 years of listing has been substantially higher than the November 2020 estimates that were the basis for the financial caps. The PBAC acknowledged the high clinical need for effective treatments for severe AD and the sponsor's comments regarding the sustainability of ongoing access to PBS subsidised dupilumab. The PBAC also acknowledged correspondence from the sponsor of upadacitinib in support of increasing the RSA caps and regarding the sustainability of the listings for severe AD.
- 6.3 The PBAC noted the script data for dupilumab utilisation (March 2021 to August 2022) indicated that, of patients treated with dupilumab for severe AD, 17.6% were qualifying under the hands/face only criteria. The PBAC noted that in the most recent data available (March 2021 to March 2023) this proportion had increased to 19%. The PBAC acknowledged that utilisation in patients with disease affecting the hands/face only was one of the contributors to the higher-than-expected utilisation of dupilumab (and upadacitinib).
- 6.4 The PBAC recalled that at its March 2020 meeting, it had considered that it would not be appropriate for the financial caps to be increased to account for patients with severe AD exclusively of the hands or face as the cost-effectiveness in these patients is unknown (paragraph 7.21, dupilumab PSD, March 2020). The PBAC considered the cost-effectiveness of dupilumab in the treatment of these patients remained uncertain, but noting the similar baseline mean DLQI scores for patients treated with dupilumab under the whole body PBS criteria and the hand/face criteria (20.5 and 19.2, respectively), and the impact of the disease when the hands or face are affected, accepted the cost-effectiveness is likely to be similar across the two patient cohorts. On this basis, the PBAC advised that it would be reasonable to increase the existing RSA caps to account for the 1% of patients with severe AD exclusively of the hands/face. As outlined below, the PBAC did not accept the other proposed revisions to the financial estimates and therefore the increase should be applied to the existing agreed RSA caps.
- 6.5 The PBAC noted that the caps for the next 3 years (years 3 to 5 of the deed) under the existing RSA is \$1 million and that the submission proposed that this be increased to \$1 million. The PBAC considered the extent of the increase proposed appeared highly

implausible when compared with current PBS utilisation, noting that it incorporated use that is unlikely to be cost-effective, it was based on projections that appeared optimistic, and given the magnitude of the increase (an almost 100% increase) would significantly change the context under which the original recommendation for listing was made, including the price at which dupilumab would be considered cost-effective. The PBAC noted the changes that appeared to be driving this increase were (i) the increase in the proportion of patients uncontrolled with topical corticosteroids (TCS) from 68% to 100%, and (2) the increase in the uptake rates. The PBAC noted the estimate of 68% of patients being uncontrolled on TCS was included in the sponsor's March 2020 submission and considered that there was not a basis to revise this assumption in isolation of the other assumptions informing use. The PBAC noted the increase in the uptake rates was based on current use which included higher continuation rates than assumed in the accepted cost-effectiveness analysis (86% versus 59.6%) and hence included use in patients who were not responders as defined in the trial, which was unlikely to be cost-effective. The PBAC further noted the increased uptake rates rely on the revised estimates of the size of the eligible patient population and assumptions regarding the number of scripts per patient. Overall, the PBAC advised the revised estimates were highly uncertain, appeared to substantially overestimate use (200,000 to < 300,000 packs in 2025 and 200,000 to < 300,000 packs in 2026 compared with current use of approximately 11,000-12,000 packs per month) and did not reflect cost-effective use of dupilumab.

6.6 The PBAC noted that a DUSC review of AD medicines is scheduled to be considered in September 2023, which may help to better understand the current use of these treatments through the PBS. The PBAC recalled that at its July 2022 meeting, the Committee noted that the recommendation for listing had been based on assumptions in the economic model that were favourable to the sponsor, and therefore the price of dupilumab was at the higher end of the range considered cost-effective, in the context of the financial estimates forming the basis for subsidisation caps (para 5.5 dupilumab PSD, July 2022 PBAC meeting). The PBAC considered the cost-effectiveness of dupilumab and upadacitinib when used in a larger patient population would need to be addressed for any further increase in the RSA caps and noted a price reduction for the overall population would be required.

6.7 In summary, the PBAC recommended:

- An increase of 100% to the estimates informing the current caps would be appropriate (approx. \$1.5 mil over 3 years), as shown in the final row of Table 17.
- The structure of the RSA to remain as is, i.e. single-tier with 100% rebate over caps.

Outcome:

Advice provided

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 had no comment.