

**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 submission requested an increase in the financial caps for the current risk share arrangement (RSA) to reflect the higher than estimated use of dupilumab for severe chronic atopic dermatitis (AD) since listing on 1 March 2021.
- 1.2 The sponsor requested the PBAC to reconsider previously estimated utilisation of dupilumab in patients aged 12 years or older, with severe AD. The sponsor presented revised financial estimates to inform revised RSA caps with changes to assumptions regarding:
 - the proportion of patients uncontrolled on topical corticosteroids (TCS) (from 68% to 100%)
 - the proportion of patients engaged with a specialist (from 55-70% to 100%)

2 Requested listing

- 2.1 The submission 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 revised pricing proposal which included a revised economic model and revised financial estimates following the March 2020 recommendation.
- 3.2 In March 2022, the PBAC recommended extending the listing of dupilumab to include patients aged less than 12 years with severe AD.
- 3.3 A summary of the March 2020, November 2020 PBAC consideration and current proposal is provided in the table below.

Public Summary Document – July 2022 PBAC Meeting

Table 1: Summary of the March 2020, November 2020 PBAC consideration and current proposal

	March 2020 PBAC consideration	November 2020 consideration	Current proposal
Requested effective DPMQ	\$████	\$████ proposed Revised to \$████ following PBAC's recommendation.	\$████ (small increase due to mark-ups) \$████ used in the financial estimates.
Key assumptions input for calculating the estimated net cost to PBS/RPBS			
Addition of adolescent population	The PBAC noted the financial estimates would need to be revised to include patients aged 12-17 years. The PBAC noted that the population size increases by approximately 9%. The PBAC noted that a reduced dose (200 mg every other week) is recommended in patients aged 12-17 years with a body weight of <60 kg and considered the reduced dose should be accounted for in the financial estimates (paragraph 7.18, Dupilumab PSD, March 2020 PBAC Meeting).	The PBAC noted that the financial estimates were updated to include the adolescent (12 to 17 years) population and to remove offsets for phototherapy use. These amendments were considered consistent with the committee's March 2020 advice (para 5.5, dupilumab PSD, November 2020 PBAC meeting).	Remains unchanged.
Proportion of topical corticosteroid (TCS) therapy patients who have uncontrolled AD	Estimated 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 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). However, the PBAC did not recommend revisions to this input.	The PBAC noted that the proposed estimates changed the assumption regarding patients being adequately 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 PBAC maintained that this parameter should remain unchanged (para 5.7, dupilumab PSD, November 2020 PBAC meeting).	Assumes 100% of patients on TCS therapy would have uncontrolled AD.
Proportion of patients engaged with specialist	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% (pg 4, DUSC advice, July 2019). The ESC noted that it was unclear how many patients would re-	Remained unchanged from March 2020.	Assumes 100% patients would be engaged with a specialist.

Public Summary Document – July 2022 PBAC Meeting

	March 2020 PBAC consideration	November 2020 consideration	Current proposal
	engage with specialist care if dupilumab is listed (paragraph 6.6, dupilumab PSD, March 2020 PBAC meeting). Yr 1-6 assumptions: 55%, 58%, 61%, 64%, 67%, 70%		
Uptake rates applied to prevalent patient pool	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 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). 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)	Revised uptake rates based on PBS uptake of biologic therapies for ankylosing spondylitis, psoriasis and Crohn disease. Pricing proposal (as per sponsor's clarification in pre-PBAC response): 5%, 4.50%, 4.0%, 3.5%, 3.5%, 3.5% (total PBS population). 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).	Agreed uptake rates based on PBAC's Nov 2020 recommendation remain unchanged.
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).	Request to vary current RSA to reflect additional utilisation of dupilumab in the first year of listing.

Source: DUSC advice, July 2019, Dupilumab 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).

Public Summary Document – July 2022 PBAC Meeting

Under the current RSA, the sponsor is required to rebate $\frac{1}{2}$ % of Commonwealth expenditure above the agreed caps.

- 3.5 The submission presented the agreed annual caps on government expenditure from 1 March 2021 to 28 February 2026 as shown in Table . 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). The revised annual caps for the severe AD market following listing of UPA on the PBS are also provided in Table

Table 2: Dupilumab and upadacitinib severe AD subsidisation caps

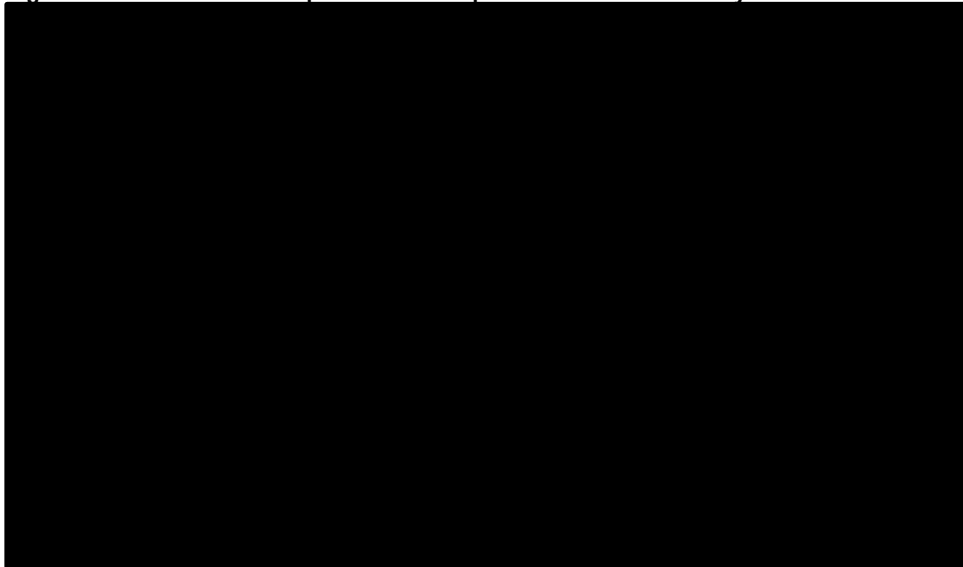
	Year 1 Mar 2021 to Feb 2022	Year 2 Mar 2022 to Feb 2023	Year 3 Mar 2023 to Feb 2024	Year 4 Mar 2024 to Feb 2025	Year 5 Mar 2025 to Feb 2026
Original cap (March 2021) (\$)	\$█	\$█	\$█	\$█	\$█
Amended cap (Feb 2022)* (\$)	\$█	\$█	\$█	\$█	\$█
Growth (\$)	\$█ (1.1%)	\$█ (9.6%)	\$█ (7.1%)	\$█ (5.5%)	\$█ (4.9%)

*Amended to account for the inclusion of UPA

Source: Attachment 1 – █ █ █ █ █ █ █ █ █ █ Main submission body (pg 3)

- 3.6 The submission noted that in the first 11 months of listing the total Commonwealth expenditure for dupilumab for the treatment of severe AD for patients aged 12 years or older (█) was more than the subsidisation cap for Year 1 of the RSA (\$█ between March 2021 and January 2022 vs \$█). Figure 1 shows the Year 1 subsidisation cap was exceeded in █ months after the initial listing. The Pre-PBAC response noted that for the first year of listing (1st March 2021 to 28th February 2021) the total cumulative Commonwealth expenditure for Year 1 of the RSA was \$█. The Pre-PBAC response further noted over the first three months of Year 2 of the RSA (March 2022 to May 2022), █% of the Year 2 cap has already been consumed (\$█ between March 2022 to May 2022 vs \$█) and therefore it is very likely that the total year 2 utilisation will be significantly higher than the agreed cap.

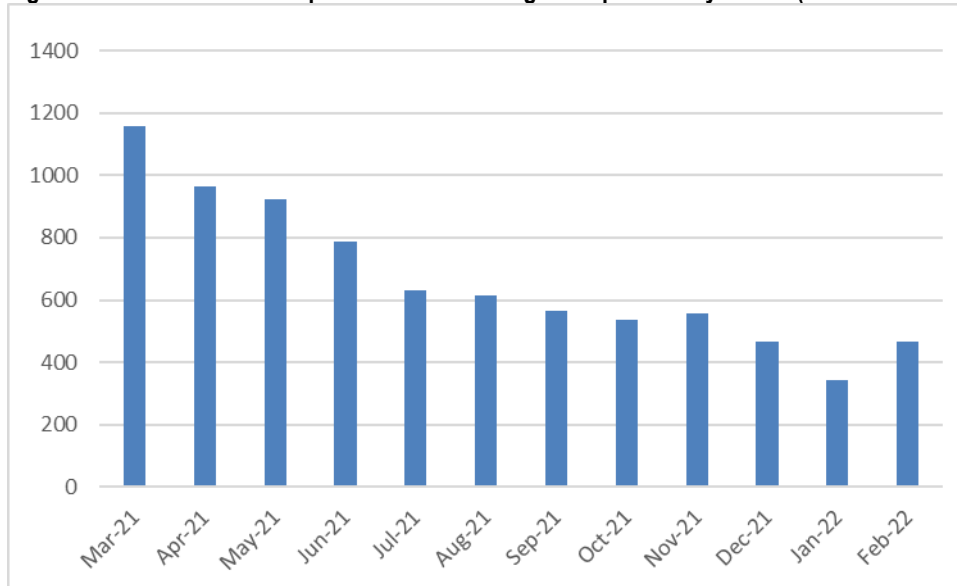
Figure 1 Total cumulative expenditure vs. cap – March 2021 to January 2022



Source: Figure 1.1 main submission body.

3.7 PBS data from the first year of listing indicates that in the first 12 months of listing (1 March 2021 to 28 February 2022) there were 8,016 patients initiated on dupilumab. The number of incident patients per month is shown in Figure 2. The number of prevalent (all treated) patients per month is shown in Figure 3.

Figure 2 Number of incident patients first initiating on dupilumab by month (PBS items 12291X and 12292Y)

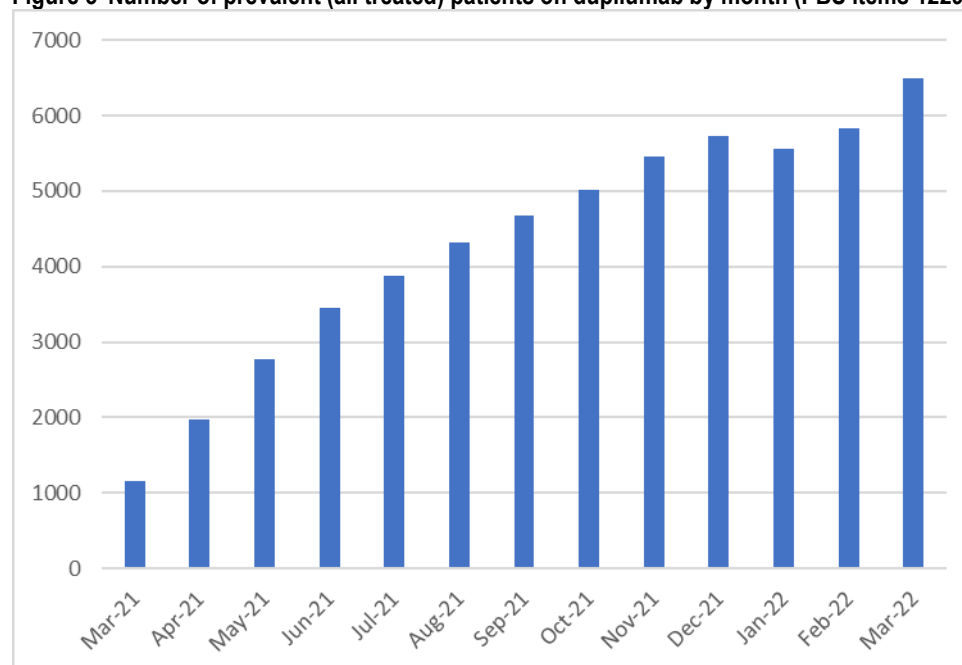


Source: Data extracted from the PBS data maintained by Department of Health and Aged Care, processed by Services Australia. All claims records for PBS items 12291X and 12292Y were extracted based on the date of supply from 1 March 2021, date of their first listing, to 31 March 2022, the most complete month.

3.8 The pre-PBAC response noted that the claims data provided to Sanofi by the Department of Health and Aged Care indicated that 640 packs of dupilumab were supplied in March 2021, whereas the data from Figure 2 showed that 1,158 patients

initiated on dupilumab for AD. Note data from Figure 2 was determined by the date of the service was processed by Services Australia and not the date of prescribing or the date of supply by the pharmacy.

Figure 3 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 and Aged Care, 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 2022, the most complete month.

3.9 The sponsor noted that the rebate paid under the terms of the RSA results in an average selling of \$1 per pack supplied, 1% below the agreed cost-effective price. The Sponsor also stated that the amount required to rebated represents a significant cost to the sponsor and threatens the viability of dupilumab in Australia.

3.10 The PBAC noted that in response to the submission regarding the revision of RSA caps appearing on the agenda for the July 2022 PBAC meeting, the sponsor of upadacitinib, AbbVie Pty Ltd, provided a letter to the PBAC raising the same concerns as the current minor submission. The PBAC noted that the sponsor for upadacitinib also supported a re-assessment of the current utilisation caps.

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 an individual and 2 consumer

organisations, Allergy & Anaphylaxis Australia (AAA) and Eczema Support Australia (ESA) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dupilumab including the effectiveness of treatment and the major improvement in quality of life for patients with severe AD when treated with dupilumab. ESA and AAA noted they no longer receive calls from desperate members who were not responding well to treatment for severe AD because of access of dupilumab on the PBS.

Estimated PBS utilisation and financial implications

- 4.3 The submission noted that estimating the size of the patient population in a disease with minimal local epidemiological data and uptake by patients in a market where there have been no new treatments for over 20 years presented a significant challenge. The pre-PBAC response stated that the current utilisation estimates included in the RSA underestimate both the size of the eligible patient cohort and uptake within that cohort.

External factors affecting uptake

- 4.4 The submission argued that the supply of dupilumab has been greater than anticipated due to 1) implementation of an Authority Required listing with telephone/online approval and 2) the move during the pandemic to telehealth consultations, enabling greater access to specialists for prescribing than estimated.
- 4.5 In March 2020, the PBAC noted that an Authority Required (Written only) restriction level was requested. The PBAC considered that the authority approval method may need further refinement between the Department and Services Australia. The expected number of applications requiring processing, logistics and nature of any collected clinical evidence as stated in the restriction are to be considered in determining the authority approval method (paragraph 7.25, dupilumab PSD, PBAC March 2020 meeting). Following the positive recommendation, the implementation of an Authority Required listing with telephone/online approval was agreed during the final listing negotiations between the Department and the Sponsor. The submission stated that ‘feedback from clinicians currently prescribing dupilumab to their severe AD patients is that this method of gaining approval significantly reduces the time required to initiate a patient on dupilumab compared with treatments requiring a written authority and that, as a result of this, they have been able to initiate more patients on therapy in a shorter period of time than would otherwise have been the case’. It is unclear whether the telephone/online authority approval method is likely to have resulted in a more rapid uptake of dupilumab compared with a written Authority as claimed in the submission, and to what extent the authority approval method may have impacted overall uptake.
- 4.6 The submission stated that the majority of dermatologists operate via private practice and therefore the impact of the pandemic on access has been less than that for other specialities such as respiratory physicians. The submission also stated that the transition to telehealth consultations removed predicted workforce constraints

limiting access to prescribers. No further evidence in support of this claim was provided. It is unclear whether the availability of telehealth consultations increased the uptake of dupilumab or whether the overall impacts of the pandemic have resulted in reduced consultations with dermatologists and clinical immunologists. The extent of any such impacts is also unknown. The Pre-PBAC response provided an analysis of the use of telehealth during the COVID-19 pandemic (Guzman et al 2021) which indicated that following the expansion of access to telehealth in March 2020, overall specialist consultations returned to pre-pandemic levels in the second half of 2020. 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.

Use outside PBS restrictions

- 4.7 The PBAC previously considered there is potential for substantial use beyond the requested restriction to those with less severe AD, those with comorbid conditions such as asthma, and those with reduced QoL due to overly complex topical regimens. As noted by the submission, given the intent of the RSA it is necessary to determine whether the higher than predicted utilisation is the result of an underestimation of the size and/or uptake within the eligible population or due to use beyond the requested restriction.
- 4.8 The submission claimed there is no compelling evidence there has been substantive use outside the restriction. As noted in the submission, dupilumab was listed for uncontrolled severe asthma in April 2021 and it seems unlikely there would be leakage to this population from the AD listing. The submission also noted that patients are required to satisfy multiple measures of disease activity to qualify for initial and continuing treatment with dupilumab as per the Authority required listing and the submission argued that the risk of use outside the reimbursed restriction is therefore low.
- 4.9 To further support this claim the submission presented a survey of clinicians currently caring for patients treated with dupilumab (METIS 2022) with results for patients initiating and continuing therapy. A total of 47 clinicians responded to the survey, providing data on 212 patients currently receiving dupilumab. However, the number of participating dermatologists (n=46) was small relative to invited participants (n=506) and data on only a small number of patients 211 relative to PBS supplied patients (>5,000) was shown, therefore the representativeness of the survey sample and potential reporting bias is unclear.
- 4.10 The survey reported that 193 patients (92%) fulfilled the PBS initiation criteria of having a baseline Physician's Global Assessment (PGA) score of 4 and a baseline Eczema Area and Severity Index (EASI) score of 20 or greater (8% of the 211 patients initiated dupilumab did not fulfill the PBS criteria). The submission argued that the results of this survey indicate that use outside the eligible cohort does not explain the

substantially higher than expected utilisation observed. It is not clear whether the results of the survey are strongly supportive of the claim that use outside the PBS initiation criteria is low, however, if representative, they may suggest that the extent of use outside restrictions does not fully account for the higher than anticipated uptake of dupilumab.

- 4.11 Prescribing data for dupilumab extracted from the PBS data maintained by the Department indicates that few patients (8 of the 8,016 incident patients) in the first year of listing were aged less than 12 years and the majority of scripts supplied (93%) adhered to the treatment criteria requiring the prescriber to be a dermatologist or clinical immunologist. No data regarding the baseline PGA or EASI score were available from this analysis.
- 4.12 The PBAC also previously considered there remains a high risk of leakage to patients who do not have sufficient response according to the continuing criteria (paragraph 7.2, dupilumab PSD, March 2020 PBAC meeting). The submission also compared the assumptions used in the utilisation estimates for the proportion of patients continuing therapy after the initial 16 week treatment period with an analysis of the 10% PBS sample. This analysis included 313 patients who initiated dupilumab on the PBS for the treatment of severe AD from March 2021 to November 2021. Results indicated that 217 patients in the dataset (69.3%) received more than 6 packs of dupilumab and were assumed therefore to have demonstrated adequate response at the week 16 assessment and qualified for continuing treatment. This is somewhat higher than the estimated 59.6% of patients assumed to respond to therapy and continue treatment for the March 2020 PBAC submission's economic model and financial estimates (which were based on the clinical trial data). The submission argued that this indicates that, in part, the higher than expected utilisation of dupilumab on the PBS is due to more patients responding to therapy and continuing treatment beyond the initial treatment course than anticipated. The higher proportion of patients continuing treatment on the PBS compared with the estimated proportion continuing treatment based on the trial data, may also be an indication that patients who do not have sufficient response to treatment are continuing to receive treatment on the PBS. However, PBS data for dupilumab is too immature to give reliable estimates of continuation rates. The Pre-PBAC response argued that there was no information suggesting that the higher than assumed continuation rate was driven by patients inappropriately continuing treatment.
- 4.13 The utilisation estimates did not account for patients with severe face and/or hand AD who would not otherwise meet the criteria for severe AD. Both the pre-PBAC response and communication from the sponsor for upadacitinib argued that exclusion of patients qualifying for treatment with advanced AD therapies due to severe AD of the hands and face is likely to be a significant contributor to the higher than expected observed utilisation of these treatments. The sponsor for upadacitinib estimated that up to one third of total services in AD would be for patients with severe AD of the face and hands who would not otherwise qualify for treatment. Both sponsors argued

inclusion of these patients in any revised utilisation estimates would be appropriate on the basis of the quality of life impact experienced by patients in this subgroup and the meaningful improvements to their AD.

- 4.14 At the 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). 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). The PBAC also recalled that in post-hoc analyses presented in the dupilumab submission similar improvements in EASI score were observed in all of the body areas assessed, however the PBAC previously considered that this would not necessarily translate to the equivalent incremental effectiveness or quality of life improvements and therefore equivalent cost-effectiveness to the whole body listing is uncertain (para 7.9 dupilumab PSD, March 2020).

Utilisation estimates

- 4.15 The PBAC previously considered that the financial estimates for dupilumab were uncertain with respect to the patient population for initiation, uptake and continuation (paragraph 7.18 dupilumab PSD, July 2019). A number of key assumptions underpinning the utilisation estimates for dupilumab for severe atopic dermatitis were acknowledged by the DUSC, the ESC and the PBAC as being uncertain. These inputs, sources and the PBAC's comments are summarised in the table below.

Public Summary Document – July 2022 PBAC Meeting

Table 2: Key assumptions for estimation of eligible population

Parameter	Assumption, source	Previous evaluation, ESC, DUSC, PBAC comments
Australian population aged 12 years and older	22.3M (Year 1) – 24.1M (Year 6) ABS	PBAC considered appropriate to expand to population aged 12+.
Proportion with atopic dermatitis	9% Increased from 6.9% from July 2019 submission based on DUSC advice.	July 2019 – DUSC disagreed with the Pre-Sub-Committee Response that 6.9% prevalence was consistent with global estimates; expecting AD prevalence of at least 8% in Australia based on global trends (p3).
Proportion of AD patients with severe disease	5% Market Research (Metis 2019a)	-
Patients engaged with a specialist	Yr 1-6 assumptions: 55%, 58%, 61%, 64%, 67%, 70% (3% growth per annum) Market Research (Metis 2019a)	The evaluation considered this assumption could be 100% for moderate-to-severe population. However, DUSC disagreed noting that there would be workforce constraints and would not reach 100% (pg 4, DUSC advice, July 2019). ESC noted that it was unclear how many patients would re-engage with specialist care if dupilumab is listed (para 6.6, dupilumab PSD, March 2020 PBAC meeting).
Engaged patients uncontrolled with TCS	68% Market Research (Metis 2019b)	Identified in the evaluation as a major source of uncertainty in the financial estimates (Table 19, dupilumab PSD, March 2020 PBAC meeting). PBAC maintained that this parameter should remain unchanged (para 5.7, dupilumab PSD, November 2020 PBAC meeting).
Proportion of patients meeting EASI requirement (EASI \geq 20)	95% Patient data on file	PBAC noted that this was consistent with its previous advice (para 7.4, dupilumab PSD, July 2019 PBAC meeting) and considered this was appropriate.
Responders at Week 16	59.6% (pooled results from trials for those meeting EASI-50/DLQI 4 response criteria)	Consistent with the economic evaluation.
Responders at Week 42	95.7% (as per economic evaluation)	Changed during the evaluation to be consistent with the economic evaluation (Table 19, dupilumab PSD, March 2020 PBAC meeting).
Continuing patients treatment persistence	Year 2 = 83.2% Year 3 = 79.87% Year 4 = 77.16% Year 5+ = 74.76% from time to first rescue treatment or treatment discontinuation analysis	The evaluation considered this reasonable (Table 19, dupilumab PSD, March 2020 PBAC meeting).

Source: DUSC advice, July 2019, Dupilumab PSD, March 2020 PBAC meeting; Dupilumab PSD, November 2020 PBAC meeting; Main submission body.

- 4.16 The submission proposed two revisions to key inputs to the financial estimates from the previous submission that were the basis for calculation of the caps for the RSA. The Sponsor requested that the financial estimates for calculation of RSA caps be revised by increasing the proportion of:

Public Summary Document – July 2022 PBAC Meeting

- Patients uncontrolled on TCS from 68% to 100%
 - Patients engaged with a specialist from 55-70% to 100%
- 4.17 In July 2019, DUSC reviewed the assumptions used to estimate the population eligible for treatment with dupilumab. The statements made by DUSC in July 2019 were in the context of a moderate-to-severe AD population. The July 2019 resubmission requested listing for the moderate-to-severe population based on advice from the July 2018 meeting where the PBAC considered that “there was limited evidence that supported the contention that either severity of AD [moderate versus severe] or experience with CsA [yes versus no] are treatment effect modifiers” (Dupilumab PSD, July 2018, paragraph 6.21). At that time the PBAC acknowledged there is significant disease burden from AD and a high clinical need for effective treatments for moderate to severe AD. However, the PBAC considered that dupilumab was not cost-effective at the price proposed in the resubmission and the estimated financial implications were very high and uncertain. In the March 2020 resubmission, the sponsor requested listing for severe AD patients only for which the PBAC made a positive recommendation.
- 4.18 The DUSC advice noted that the evaluator considered the assumption of patients engaged with a specialist could be 100%, but DUSC disagreed noting that there would be workforce constraints, and this would not reach 100%: “DUSC considered that a majority of moderate-to-severe AD patients were likely to be referred to dermatologists/immunologists, but noted this was likely to be limited due to workforce constraints of specialists” (DUSC advice July 2019).
- 4.19 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%. During the evaluation of the March 2020 resubmission, it was stated that it was inappropriate to have assumed some severe AD patients would be ‘adequately controlled’ on treatment. It was further noted in the evaluation that this is a major source of uncertainty in the financial estimates and may have underestimated the eligible patients (Table 19, Dupilumab PSD, March 2020 PBAC meeting). However, the PBAC did not recommend revision of this input (paragraph 4.16, Dupilumab PSD, November 2020 PBAC meeting).
- 4.20 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. In November 2020 the PBAC noted that this revision to the financial estimates (in addition to the proposed adjusted uptake rates) was the main driver of the substantial (over 50%) increase to the total cost of dupilumab over the forward estimates compared to that based on assumptions from the March 2020 recommendation. At that time the PBAC

recommended the financial estimates should be amended with the submission's revised uptake estimates and the reduced effective price but did not recommend a change to the proportion of patients assumed to be inadequately controlled on topical corticosteroids (paragraph 5.7, dupilumab PSD, November 2020 PBAC meeting).

- 4.21 In addition to the proportion of patients engaged with a specialist and the proportion of patients inadequately controlled on TCS, the Pre-PBAC response maintained that the uptake rates proposed by the PBAC for Year 2-6 were significantly lower than was expected, though these rates were not changed in the revised financial estimates presented in the Category 3 submission. At its March 2020 meeting the PBAC considered "it is not reasonable to assume the uptake rate of new patients from the prevalent pool would increase each year", but rather that the rates proposed in the submission should be considered to include both treatment-naïve patients initiating therapy with dupilumab, along with patients continuing therapy from previous years (para 6.56, dupilumab PSD, March 2020 PBAC meeting). The Sponsor argued that the agreed pattern of uptake was not consistent with the observed uptake for novel therapies in areas of high clinical need on the PBS.

Revised financial estimates

- 4.22 The sponsor presented a summary of the revised assumptions applied to reach the total population eligible to receive treatment with dupilumab as presented in the table below.

Public Summary Document – July 2022 PBAC Meeting

Table 4: Revised Total estimated number of patients eligible for treatment with dupilumab

	2021	2022	2023	2024	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
Severe Disease (%)	5%	5%	5%	5%	5%	5%
Severe Disease (#)	100,442	102,132	103,782	105,407	107,011	108,565
Engaged with a specialist (%)	100%	100%	100%	100%	100%	100%
Engaged with a specialist (#)	100,442	102,132	103,782	105,407	107,011	108,565
Uncontrolled on TCS (%)	100%	100%	100%	100%	100%	100%
Uncontrolled on TCS (#)	100,442	102,132	103,782	105,407	107,011	108,565
EASI≥20 (%)	95%	95%	95%	95%	95%	95%
EASI≥20 (#)	95,420	97,026	98,593	100,137	101,661	103,136
Revised – Eligible Patients	■ ¹	■ ¹	■ ¹	■ ⁶	■ ⁶	■ ⁶
March 2020 ^a – Eligible Patients	■ ²	■ ²	■ ⁵	■ ⁵	■ ⁵	■ ⁵
Increase	167%	154%	141%	130%	119%	110%
Agreed uptake in ≥18 years	5%	4.24%	3.63%	3.07%	3.00%	2.93%
Agreed uptake in 12-17 years	5%	4.29%	3.67%	3.11%	3.03%	2.96%
Revised total initiating patients	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Revised total continuing patients	■ ⁴	■ ³	■ ³	■ ⁷	■ ⁷	■ ⁷
March 2020 ^a uptake – total initiating patients	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
March 2020 ^a uptake – total continuing patients	■ ⁴	■ ³	■ ³	■ ³	■ ³	■ ³

Source: Utilisation and cost model workbook Dupixent '2b. Patients – prevalent' (Attachment 4)

Abbreviations: pop. = population; AD = atopic dermatitis; TCS = topical corticosteroids; EASI = eczema area and severity index

^a Referred to as Nov 2019 in the submission.

The redacted values correspond to the following ranges:

¹ 90,000 to < 100,000

² 30,000 to < 40,000

³ 500 to < 5,000

⁴ < 500

⁵ 40,000 to < 50,000

⁶ 100,000 to < 200,000

⁷ 5,000 to < 10,000

- 4.23 The submission only presented revised financial estimates for 5 years, noting that the first year of the revised estimates is for Year 2021.
- 4.24 The proposed changes to the proportion engaged with a specialist and uncontrolled on TCS increased the eligible patient numbers compared with the March 2020 estimates by 167% in year 1, with the percentage increase reducing in each year of listing, although in all years the revised patient numbers are more than double the agreed numbers.
- 4.25 The Sponsor's estimates and financial implications using the revised assumptions are presented below. The revised total cost to the PBS/RPBS of listing dupilumab was estimated to be \$100 million to < \$200 million in Year 6, and a total of \$400 million to < \$500 million in the remaining 5 years of listing included in the estimates provided (years 2-6). This represents a 113% overall increase to the previously estimated cost over years 2-6 of listing.

Public Summary Document – July 2022 PBAC Meeting

4.26 In the revised estimates the number of patients initiating treatment in Year 1 (500 to < 5,000) remains below the actual number of patients who initiated treatment based on PBS scripts for the first year of listing (8,016). However, the actual number of initiating patients in each month decreased throughout the first year of listing (see Figure 2). In February 2022 there were 465 patients initiated on dupilumab.

4.27 No changes were made to the continuation rate applied in the financial estimates.

Table 3: Revised estimated use and financial implications

Year	2021	2022	2023	2024	2025	2026
Estimated extent of use						
Patient (initiation)	1	1	1	1	1	1
Patients (continuing)	2	1	1	10	10	10
Number of scripts dispensed ^a	3	6	8	11	13	13
Estimated financial implications of dupilumab at the effective price						
Cost to PBS/RPBS less co-payment	4	7	9	12	14	14
Net financial implications						
Net cost to PBS/RPBS for dupilumab	4	7	9	12	14	14
Net saving to affected medicines	5	5	5	5	5	5
Net cost to MBS	5	5	5	5	5	5
Net cost to PBS/RPBS	4	7	9	12	14	14

^a Assuming 13.04 per year as estimated by the submission (pg 22)

Abbreviations: MBS = Medical Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: Main body submission. Cells in grey represent past years as dupilumab was listed 1 March 2021.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ 50,000 to < 60,000

⁴ \$40 million to < \$50 million

⁵ \$0 to < \$10 million

⁶ 70,000 to < 80,000

⁷ \$60 million to < \$70 million

⁸ 80,000 to < 90,000

⁹ \$80 million to < \$90 million

¹⁰ 5,000 to < 10,000

¹¹ 90,000 to < 100,000

¹² \$90 million to < \$100 million

¹³ 100,000 to < 200,000

¹⁴ \$100 million to < \$200 million

Financial Management – RSA

4.28 In relation to the November 2020 pricing proposal the PBAC considered that overall, “the modifications the sponsor made to the economic model were still potentially based on optimistic assumptions that favoured dupilumab, however the PBAC considered them to be acceptable in the context of high clinical need in this therapeutic area, along with a corresponding price reduction to achieve the same base case ICERs reviewed in March 2020” (para 5.4, dupilumab PSD, November 2020 PBAC meeting). This recommendation was also in the context of the financial estimates accepted by the PBAC in November 2020 as the basis for subsidisation caps.

4.29 The Sponsor proposed that the current RSA be revised to reflect their updated utilisation estimates. The Sponsor also proposed that the same percentage increase be applied to their revised RSA to account for sequential use due to the recent listing of UPA. The original and proposed subsidisation caps are presented in the table below. The proposed caps represent an overall 1% increase for years 2-5 of the existing subsidisation caps. The proposed increase to subsidisation caps includes an additional \$1.2 million in each year in “cap uplift” to account for additional/subsequent use for upadacitinib.

Table 6: Original and proposed subsidisation caps

Year	2021	2022	2023	2024	2025
Original subsidisation caps (\$)					
Estimates with revised assumptions (\$)					
Amended cap (Feb 2022)* (\$)					
Original seq. treat. cap uplift† (\$)					
Sequential treat. cap uplift	1.2%	9.6%	7.1%	5.5%	4.9%
Revised seq. treat. cap uplift† (\$)					
Proposed new subsidisation cap (\$)					
Percentage increase to existing caps	1%	1%	1%	1%	1%

†Seq. treat. uplift refers to the increase in the severe AD subsidisation cap due to the introduction of upadacitinib as of 1 February 2022
Source: Main submission body (pg 28)

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

5 PBAC Outcome

5.1 The PBAC did not advise that its previous recommendation regarding the risk sharing arrangement (RSA) subsidisation caps for dupilumab for the treatment of severe atopic dermatitis (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, 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 double those previously recommended and agreed by the sponsor for listing on the 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.

5.2 The PBAC noted that for the first year of listing, the total cumulative Commonwealth payment was \$50 million to < \$60 million, which was more than 1/3 the Year 1 cap (\$180 million) and the submission requested that the RSA be revised to more accurately reflect the drivers of utilisation in the eligible patient cohort. The PBAC recalled that the RSA with

financial caps was established to address the potential for use outside the intended population and the potential continuing use in patients who do not have adequate response, where use of dupilumab was likely to be less cost-effective (para 7.21, dupilumab PSD, March 2020).

- 5.3 The PBAC noted that the submission argued that utilisation above the financial estimates was due to underestimation of the size of the patient population and uptake. The submission proposed two revisions to key inputs to the financial estimates from the previous submission that were the basis for calculation of the caps for the RSA: 1) increasing the proportion of patients uncontrolled on TCS from 68% to 100%; and 2) increasing the proportion of patients engaged with a specialist from 55-70% to 100%. The PBAC noted that no data was provided in the submission to support the increase in the proportion of patients uncontrolled on TCS. 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.
- 5.4 The PBAC noted that the submission argued that there is no evidence to suggest that use of dupilumab outside of the current PBS restrictions is driving the higher than expected observed utilisation. The submission presented data from a survey of clinicians which indicated that for the 47 clinicians who responded (out of 506 invited clinicians), 92% of patients fulfilled the PBS initiation criteria of having a baseline PGA score of 4 and EASI of 20 or greater. The PBAC considered that the sample size for the survey was relatively small in terms of both patients and clinicians and the representativeness of the survey sample and potential reporting bias is unclear.
- 5.5 The PBAC also noted that the submission presented a comparison of the assumptions used in the utilisation estimates for the proportion of patients continuing therapy after the initial 16-week treatment period with an analysis of the 10% PBS sample. This indicated that the proportion of patients who received continuing treatment (69.3%) was somewhat higher than estimated based on the trial data (59.6%). The PBAC considered that there was no evidence to confirm that these additional continuing patients had sufficient response to treatment and it was unclear why response in clinical practice would be superior to the clinical trial setting. The PBAC considered that higher rates of continuation in clinical practice may be indicative of ongoing use in patients who do not achieve the level of response assumed in the economic model and therefore continuing use in this population would be less cost-effective. However, the PBAC noted that the available data for dupilumab are currently insufficient to provide a reliable estimate of PBS continuation rates.

Public Summary Document – July 2022 PBAC Meeting

- 5.6 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.
- 5.7 The PBAC noted that the proposed changes to the proportion of patients engaged with a specialist and the proportion uncontrolled on TCS increased the eligible patient numbers compared with the March 2020 estimates by 167% in year 1, with the percentage increase reducing in each year of listing. Overall, the proposed revisions to the estimates increased the total cost to the PBS/RPBS from \$200 million to < \$300 million to \$400 million to < \$500 million in the remaining 5 years of listing included in the estimates provided (years 2-6). The PBAC noted that PBS script data indicates that the number of initiating and prevalent patients appears to be plateauing after a high initial uptake in the first year after listing. The PBAC considered that the proposed revisions to the key inputs to the financial estimates were not well-justified (see paragraph 5.3) and revised estimates were likely overestimated.
- 5.8 The PBAC recalled that in its November 2020 consideration of the dupilumab listing proposal for severe atopic dermatitis, it considered that overall, “the modifications the sponsor made to the economic model were still potentially based on optimistic assumptions that favoured dupilumab, however the PBAC considered them to be acceptable in the context of high clinical need in this therapeutic area, along with a corresponding price reduction to achieve the same base case ICERs reviewed in March 2020” (para 5.4, dupilumab PSD, November 2020 PBAC meeting). The PBAC 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. The PBAC considered that it would not be appropriate to revise assumptions for the financial estimates in isolation, without also reassessing the cost-effectiveness in the broader population.
- 5.9 The PBAC considered that a submission requesting listing in a broader population, including a less severe population and/or patients with severe AD exclusively of the hand and/or face would be welcomed.
- 5.10 The PBAC noted that this submission is not eligible for an Independent Review as it was not seeking a change to the listing that includes a new indication, objectively different subtype of disease or new population.

Outcome:

Not recommended

6 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.

7 Sponsor's Comment

The Sponsor is disappointed with this outcome and considers that, in light of the recognised challenges with estimating utilisation for the first new treatment in over 20 years in a patient population with high unmet clinical need, a revision of the current utilisation estimates is both timely and appropriate. Sanofi will continue to work with the PBAC and the Department of Health and Aged Care in good faith to resolve this matter