4.02 Review of cost-effectiveness of drugs for atopic dermatitis

DUPILUMAB
Injection 300 mg in 2 mL single dose pre-filled syringe,
Injection 200 mg in 1.14 mL single dose pre-filled syringe
Dupixent
Sanofi-Aventis Australia Pty Ltd.

UPADACITINIB
Tablet 15 mg,
Tablet 30 mg,
Rinvoq®,
AbbVie Pty Ltd.

1 Purpose of submission

1.1 The purpose of this item was consideration of the cost-effectiveness of PBS-listed drugs (dupilumab and upadacitinib) for treatment of severe atopic dermatitis (AD). This was in the context of the request to increase the financial caps in place for the agreed Risk Sharing Arrangement (RSA). Sponsors of both drugs provided input into this consideration.

2 Background

Previous PBAC consideration

2.1 Dupilumab was recommended for use in severe AD at the PBAC's March 2020 meeting. In November 2020, the PBAC provided further advice regarding the sponsor's listing proposal which included a revised economic model and increased financial estimates. Upadacitinib was recommended on the basis of cost-minimisation to dupilumab between the July 2021 and November 2021 PBAC meetings.

2.2 In July 2022 and July 2023, the sponsor for dupilumab submitted Category 3 submissions requesting an increase in the financial caps for the current RSA to reflect the higher than estimated use of dupilumab for severe chronic AD. At its July 2022

meeting the PBAC considered the proposed revisions to the previously agreed assumptions informing the financial estimates were not adequately supported. In July 2023 the PBAC advised that it would be reasonable for the current RSA financial caps for dupilumab (and upadacitinib), for the treatment of severe AD in patients aged 12 years and older, to be increased by % for the remaining years of the arrangement, to account for patients with severe AD of the hands and/or face. However, 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.

2.3 The sponsor for upadacitinib also provided input regarding the July 2022 and July 2023 requests for variation of the RSA caps initiated by the sponsor of dupilumab.

2.4 At its March 2022 meeting the PBAC recommended extending the listing of dupilumab to patients aged less than 12 years with severe AD. The PBAC considered that the clinical evidence suggested the magnitude of benefit in patients aged 6-11 years is similar to that in the adult/adolescent population and the cost-effectiveness was acceptable at the same price per month (paragraph 7.1 dupilumab PSD, March 2022 PBAC meeting). The sponsor advised that it is not proceeding with a PBS listing for this population at this time, and the process for this listing has ceased[1].

2.5 The Drug Utilisation Sub-Committee (DUSC) of the PBAC considered the utilisation of dupilumab at its September 2023 meeting.

3 Consideration of the evidence

Consumer comments

3.1 The PBAC noted and welcomed the input from individuals (1), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the unmet need for individuals with severe AD and the lack of effectiveness of other available treatments for those with severe AD. Input also described the potential effects of the current RSA on the availability of new therapies. The comments noted the need for access to dupilumab treatment for children six months and older.

3.2 The PBAC noted the advice received from the Australasian College of Dermatologists noting that the use of targeted treatments has significantly improved patients' quality of life. The advice also noted that the higher-than-expected utilisation appears to be reflective of an increased number of patients presenting for therapy rather than

[1] *Note: The sponsor has since advised the Department of Health and Aged Care that it intends to proceed with the listing of dupilumab for the treatment of severe AD in patients aged 6 to 11.*

inappropriate use. The comments noted concern regarding the potential for treatments becoming unavailable to patients and the impact of financial caps on availability of other AD treatments.

Economic analysis

3.3 The Economic Sub-Committee (ESC) of the PBAC noted the proposals submitted by the sponsors of dupilumab and upadacitinib in addressing the PBAC's concerns regarding the cost-effectiveness of these medicines. The ESC considered that a reduction in the price of dupilumab and upadacitinib would be appropriate to account for:

- use in patients with less severe AD;
- increased continuation rate (78%) compared with the modelled rate (59.6% at week 16, 95.7% at week 42) (Table 2, dupilumab PSD, July 2022 PBAC meeting);
- any substantial increase in the RSA caps, which would change the context under which the original recommendation for listing was made.

3.4 The PBAC noted that upadacitinib was recommended on a cost-minimisation basis with dupilumab and the prices considered cost-effective would need to be aligned.

3.5 In addition, the ESC considered that the PBAC may wish to consider restriction changes that would encourage patients with response to try a "drug holiday" (pause treatment) to assess disease activity, with allowance for patients to easily restart therapy if required. The ESC considered this may be appropriate given AD is a disease which fluctuates and may resolve over time. Consideration of the impact on financial estimates/RSA caps from changes to the restriction would be required. The PBAC noted that clinical advice suggested that adolescent/adult patients were currently able to pause treatment to assess disease activity and considered that changes to the restrictions were not justified at this time.

Estimated PBS usage & financial implications

3.6 The DUSC also reviewed of utilisation of dupilumab. Refer to the DUSC report for further advice regarding utilisation.

3.7 The PBAC noted that analysis of utilisation data indicates that the number of initiating patients per quarter has been fairly stable since the fourth quarter of 2021. As a high proportion of patients are remaining on treatment, the total number of treated patients has continued to increase. The DUSC analysis noted that the rate of growth does not appear to be decreasing (DUSC Analysis September 2023, page 17).

3.8 The DUSC report noted the number of treated patients was within the estimate of total eligible patients with severe AD, however it is unknown whether the greater than predicted utilisation is due to higher uptake than predicted within the total eligible population, or use outside the restriction in patients with mild to moderate disease.

3.9 The utilisation of dupilumab and upadacitinib is substantially higher than the RSA caps. The PBAC noted that expenditure for Year 2 of the Deed was $ (% of the agreed caps) and for the first 8 months of Year 3 expenditure was $ (% of the agreed caps).

3.10 The ESC and DUSC considered that it remains unclear whether the higher than expected utilisation is due to underestimated eligible patients, underestimated uptake, underestimated continuation rates, or leakage into patients with less severe AD or a combination of several factors. In addition, the PBAC noted that clinician advice that additional patients with severe AD were re-engaging with specialists because of the availability of new effective treatments.

3.11 The PBAC considered that there was no clear basis for forecasting estimated utilisation for the remaining 2 years of the Deed (and beyond) as the number of initiating patients would be expected to decline in the future, but it is not known over what time period this would occur and hence when the overall market would stabilise.

4 Dupilumab

Proposal

4.1 Following advice received from the PBAC in relation to the July 2023 proposal, the sponsor proposed a renegotiation of the current RSA with a reduction in price (AEMP) of % applied to all pack sizes. The sponsor proposed that revised RSA caps be based on the reduced price and the same utilisation estimates as presented in the July 2023 submission.

4.2 The sponsor stated that the requested amendments to the RSA would "return the PBS listing to a sustainable footing, ensuring the continued viability of supply of dupilumab to the Australian AD patient community, the sustainability and attractiveness of the severe AD market for potential new entrants and our ability to provide this highly effective treatment to additional age cohorts for AD and launch future indications in other areas of high unmet clinical need in Australia".

Table 1: Proposed RSA caps

	Y1 (Mar 2021-Feb 2022)	Y2 (Mar 2022-Feb 2023)	Y3 (Mar 2023-Feb 2024)	Y4 (Mar 2024-Feb 2025)	Y5 (Mar 2025-Feb 2026)
A. Current caps (with Feb 2022 increase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. Caps (as above + 21% increase for hand/face only population per July 2023 PBAC advice)	-	-	[redacted]	[redacted]	[redacted]
C. Caps incl hand/face – patient numbers	-	-	[redacted]	[redacted]	[redacted]
Proposed revised patient numbers - initiating	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- continuing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D. Proposed revised caps	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% increase from existing caps (**A**)	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
% increase from caps including hand/face only patients (**B**)	-	-	[redacted]%	[redacted]%	[redacted]%

Source: September 2023 submission Table 6.6, 6.8

Sponsor hearing

4.3 The sponsor requested a hearing for this item. The sponsor discussed the impact of rebates for use above the financial caps on the viability of dupilumab on the PBS. The clinician noted that for children, severe AD often resolves over time, whereas for adults the condition is likely to be lifelong and require ongoing treatment. The clinician noted that there was no evidence that a "drug holiday" was an effective part of therapeutic management of patients and there is a risk of significant flare which would then take time to resolve after resuming treatment. The clinician noted a number of new severe AD patients are presenting for treatment after having been disengaged with specialist treatment for a number of years due to the lack of effective treatments. The clinician noted the high response rate in clinical practice, where topical treatments can be used concomitantly with dupilumab or upadacitinib.

Economic analysis

4.4 The proposal from the sponsor of dupilumab noted PBAC advice that the extent of the proposed increases to the RSA caps and the commensurate financial impact, would significantly change the context under which the original recommendation for listing was made. Specifically, the recommendation for listing had been based on assumptions in the economic model that were considered favourable, and therefore the price of dupilumab was at the higher end of the range considered cost-effective. As such, the cost-effectiveness of dupilumab, when used in a larger patient population would need to be addressed by a reduction in cost (i.e. price) to Government for any further increase in the RSA caps (paragraph 6.6, dupilumab ratified Public Summary Document (PSD), July 2023 PBAC meeting).

4.5 The sponsor proposed a reduced AEMP for dupilumab from $[redacted] per pack to $[redacted], a reduction of [redacted]%, which, when applied in the economic model presented in the November 2019 submission reduced the ICER from $45,000 to < $55,000/QALY to $25,000 to < $35,000/QALY.

4.6 The corresponding DPMQ per pack would be $[redacted]. Application of this DPMQ (which includes increased dispensing fees compared with the November 2019 submission) resulted in an ICER of $25,000 to < $35,000/QALY.

4.7 The ESC noted that the reduced ICER of $25,000 to < $35,000/QALY did not account for the substantially higher proportion of patients remaining on treatment than was assumed in the economic model. The ESC noted sensitivity analyses that showed that increasing dupilumab costs by increasing the 16 week continuation rate from 59.6% to 78% (as per DUSC analysis), without increasing the proportion of responders, increased the ICER from $25,000 to < $35,000/QALY to $45,000 to < $55,000/QALY. The Pre-PBAC response noted that changing the week 16 response rate from 59.6% to 78% (for both cost and response) decreased the ICER from $25,000 to < $35,000/QALY to $25,000 to < $35,000/QALY. The Pre-PBAC response also noted that Services Australia data covering the period 1 March 2021 to August 2022 indicated a Week 16 continuation rate of approximately 86%, whilst the DUSC review, using more recent data (up to June 2023) indicated a response rate of 78%, suggesting that this data may not yet be mature enough to provide an accurate estimation of the true continuation rate.

4.8 The ESC also noted the reduced ICER of $25,000 to < $35,000/QALY did not account for potential use in patients with less severe or fluctuating disease. The ESC noted that the ICER would be underestimated if the treatment benefit is reduced when baseline disease severity is lower.

Estimated PBS usage & financial implications

4.9 The sponsor's proposal stated that the estimated pack numbers were unchanged from the those in the July 2023 submission. In calculating the prescription numbers the following adjustments were made so that the July 2023 estimates remained unchanged after accounting for the [redacted]% increase in the caps recommended at the July 2023 meeting to include patients with severe AD of the hands and/or face:

- Revised the proportion of patients on TCS engaged with a specialist from 100% to 68%.
- Revised the number of hand/face AD only patients to align with the July 2023 PBAC advice.
- Revised the uptake rates from a maximum of 15.5% from year 3 onwards to [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% for years 1-6.
- Adjustment to allow for switching between dupilumab and upadacitinib of 1.43%, 11.53%, 8.07%, 6.05%, 5.31% and 8.63% for years 1-6 (refer to the Section 4

utilisation estimates model, sheet '2b. Patients – prevalent', row 75). The sponsor noted that in its recommendation for upadacitinib in July 2021, the PBAC considered patients could re-initiate with a second biologic and would trial dupilumab then upadacitinib, or vice versa and that a small increase in the subsidisation caps would be reasonable. The sponsor stated the additional use for switching was estimated by back-calculating the number of treated patients from the subsidisation caps documented in the Deed of Variation (see Table 6.4 page 12 of the proposal). The workings for the back-calculated figures were not provided and could not be verified.

- Inclusion of an additional cohort of 'unaccounted for patients' (the Prevalent 4 population). The additional uptake assumptions for this cohort were %, %, %, %, % and % for years 1-6 (refer to the Section 4 utilisation estimates model, sheet '2b. Patients – prevalent', rows 136 to 164).

4.10 In relation to the utilisation estimates in the July 2023 submission, the PBAC considered they were highly implausible when compared with current PBS utilisation and optimistic (paragraph 6.5, ratified dupilumab PSD, July 2023 PBAC meting). The estimates assume a relatively high rate of overall growth for years 4 and 5. The ESC noted that the financial estimates presented did not address the PBAC's previous concerns. Further, the adjustments made to the uptake rates and additional cohorts could not be verified and added further complexity to the calculations.

Table 2: Utilisation estimates (patients)

	Year 1	Year 2	Year 3	Year 4	Year 5
A. Patients – Mar 21	[1]	[1]	[1]	[1]	[1]
B. Patients – incl UPA	[1]	[1]	[1]	[1]	[1]
C. Patients – incl face/hand	[1]	[1]	[1]	[1]	[2]
D. Patients – Sep 23 proposal (incl grandfather)	[2]	[3]	[3]	[4]	[4]
% increase from current RSA caps (from **B to D**)	%	%	%	%	%
Annual growth for estimates (**D**)	-	%	%	%	%

Source: ratified PSD July 2023

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 to < 10,000*

[3] *10,000 to < 20,000*

[4] *20,000 to < 30,000*

Table 3: Utilisation and financial estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
A. Packs – Mar 21* estimates	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][4]
B. Packs – incl UPA estimates	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][4]
C. Packs – incl face/hand estimates	[redacted][1]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]
D. Packs – July 2023/Sep 2023 submission/proposal estimates	[redacted][4]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][8]
% increase from current RSA caps (from **B to D**)	-	-	[redacted]%	[redacted]%	[redacted]%
% annual growth for estimates (**D**)	-	[redacted]%	[redacted]%	[redacted]%	[redacted]%
B. Current caps (with Feb 2022 increase) $	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D. Net cost to PBS/RPBS (eff)	[redacted][9]	[redacted][10]	[redacted][11]	[redacted][12]	[redacted][12]

Source: September submission Table 6.3, 6.4, 6.5, 6.6, 6.8, DUSC analysis
***** minor amendments due to use of workbook version 10.81
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] *100,000 to < 200,000*
[7] *200,000 to < 300,000*
[8] *300,000 to < 400,000*
[9] *$40 million to < $50 million*
[10] *$90 million to < $100 million*
[11] *$100 million to < $200 million*
[12] *$200 million to < $300 million*

Financial Management – Risk Sharing Arrangements

4.11 The Sponsor proposed increases to the RSA caps as shown in Table 4.

Table 4: Proposed RSA caps

	Y1 (Mar 2021-Feb 2022)	Y2 (Mar 2022-Feb 2023)	Y3 (Mar 2023-Feb 2024)	Y4 (Mar 2024-Feb 2025)	Y5 (Mar 2025-Feb 2026)
Current caps (with Feb 2022 increase)					
Caps (as above + % increase for hand/face only population per July 2023 PBAC advice)	-	-			
Caps incl hand/face – estimated patient numbers	-	-			
Proposed revised patient numbers - initiating					
- continuing					
Proposed revised caps					
July 2023 proposed revised caps					
% increase from existing RSA caps	%	%	%	%	%
% increase from caps including hand/face only patients	-	-	%	%	%
Pre-PBAC proposed revised caps					

Source: September 2023 proposal Table 6.6, 6.8, July 2023 PSD, Table 17.

* for years 3-5 this is the increase from caps as advised by PBAC at its July 2023 meeting to include hand/face AD only patients.

4.12 The Sponsor requested that the PBAC consider retroactively applying changes to the RSA (i.e. years 1-3) to: "1) reflect the understanding that the higher than predicted utilisation remains within the eligible patient cohort; 2) ensure that sustainable listing conditions are in place for the full term of the agreement; 3) recognise that this issue was first raised in 2021". The Secretariat noted reimbursements for the period elapsed have already been accrued and reflect the contractual arrangements under the current Deed of Agreement between the Commonwealth and the sponsor.

4.13 The ESC noted that even with the reduction in price for dupilumab, the requested increase to the financial caps remained very high (>$ for years 4 and 5) and was only marginally reduced from the July 2023 submission. The Pre-PBAC response proposed an % reduction to the proposed caps, as shown in Table 4.

Paediatric listing

4.14 As noted above, the sponsor has advised that it is not proceeding with a PBS listing for the paediatric population[2].

4.15 The total cost to the PBS/RPBS of listing dupilumab for the treatment of severe AD in paediatric patients was estimated in the March 2022 submission to be $10 million to < $20 million in Year 6, and a total of $70 million to < $80 million in the

[2] *Note: The sponsor has since advised the Department of Health and Aged Care that it intends to proceed with the listing of dupilumab for the treatment of severe AD in patients aged 6 to 11.*

first 6 years of listing. The PBAC also considered that a small increase in the patient numbers to account for use in patients <6 years may be reasonable. Uptake rates for the estimates for paediatric patients were based on the agreed estimated uptake in the adult population. The PBAC considered that the financial estimates should also incorporate a 30.3% sustained response as paediatric patients would be expected to have a higher rate of natural resolution (paragraph 7.15, dupilumab PSD, March 2022 PBAC meeting).

4.16 The PBAC recalled its March 2022 consideration of dupilumab for the paediatric population allowed for separate RSA caps for the new population. As such, the PBAC considered there was no basis for not proceeding with the listing of dupilumab for paediatric patients, and noted that this listing was of high priority for consumers[3].

5 Upadacitinib

Proposal

5.1 The sponsor for upadacitinib provided input regarding the PBAC's consideration of the cost-effectiveness and utilisation of dupilumab and upadacitinib for severe AD. The sponsor proposed revised RSA financial caps based on:

1. A % reduction in the AEMP of upadacitinib.
2. Revised caps based on actual utilisation and ongoing growth (although an estimate of the future growth rate was not provided; this was subsequently provided in the pre-PBAC response, see Table 6).
3. A % rebate for use above the RSA caps (this was revised in the pre-PBAC response, see Table 6).

Sponsor hearing

5.2 The sponsor requested a hearing for this item. The sponsor noted concern regarding the sustainability of upadacitinib on the Australian market, as well as other indications for upadacitinib where there is a % rebate level applied to caps. The sponsor noted the current circumstances with regards to the caps were also impacting on the sponsor's ability to provide clinician and patient education and support for ongoing research into treatments for AD.

Comparative effectiveness

5.3 The sponsor noted that some AD patients experience fluctuations in severity and during stable and non-flaring periods may have less severe disease more aligned with moderate-severe AD. The sponsor presented an analysis of the utility data from the clinical trials to assess the relative impact on the cost-effectiveness of treatments for

[3] *Note: The sponsor has since advised the Department of Health and Aged Care that it intends to proceed with the listing of dupilumab for the treatment of severe AD in patients aged 6 to 11.*

AD for moderate versus severe disease. As shown in Table 5 the utility gain was 30% less for patients with moderate AD compared with severe AD. This was proposed as a basis for considering the cost-effectiveness in a population with low-range severe AD.

Table 5: EQ-5D utility data from pooled analysis of upadacitinib trials in patients with moderate/severe AD

	Moderate AD (EASI 16 to <20 or IGA=3)		Severe AD (EASI ≥20 and IGA=4	
	Mean (95% CI)	N	Mean	Mean (95% CI)
Baseline	0.78 (0.76, 0.79)*	1366	0.67 (0.63, 0.70)*	1218
Week 16 responder	0.94 (0.92, 0.95)*	701	0.90 (0.88, 0.92)*	623
Week 52 responder (conditional on wk16 response)	0.94 (0.92, 0.95)*	491	0.90 (0.88, 0.93)*	431
Utility difference (responder vs baseline)	0.16*		0.23*	

Source: Table 1 upadacitinib proposal September 2023

** Note that the results presented in Table 5 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the relevant upadacitinib trials (M16-045, M18-891, M16-047). Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

Economic analysis

5.4 The sponsor noted that as upadacitinib was listed on a cost minimisation basis to dupilumab it does not have access to the cost-effectiveness model that has previously been considered by PBAC. The sponsor considered that the relative change in utility gain for the moderate population could be used to assess the cost-effectiveness in the low-range severe population without an economic model as it could be assumed that a % reduction in the price of upadacitinib would account for the 30% reduction in the utility gain while maintaining the ICER at approximately the same level. The sponsor considered this approach provided a reliable level of internal and external validity with the original PBAC decision. The sponsor noted that a similar approach was taken by the PBAC in assessing the relative cost-effectiveness of treatments for severe AD of the hand/face and also for the Post Market Review of psoriasis medicines.

5.5 The sponsor proposed an overall % price reduction to the current AEMP for upadacitinib (from $ to $) based on a % price reduction in an assumed % of patients with low-range severe AD.

5.6 The sponsor considered that the difference in utility gain of 30% should be viewed as a conservative estimate of the potential utility difference between the low-range severe and severe AD populations.

Estimated PBS usage & financial implications

5.7 The sponsor maintained that the utilisation being significantly above the RSA caps is driven by a substantial underestimate of uptake of treatment within the eligible patient pool.

5.8 The sponsor considered that the rate of continuation for dupilumab, as estimated in the DUSC analysis, falls within the probable range for real world use based on the trial data. However, the sponsor incorrectly reported the continuation rate in the DUSC analysis as 70% whereas the analysis indicated that 78% of patients received a second

prescription of dupilumab. In the financial estimates for dupilumab which formed the basis of the RSA caps, a continuation rate of 59.6% at week 16 was used based on that observed in the clinical trials and assumed in the economic model (paragraph 4.12, Table 2, dupilumab PSD, July 2022 PBAC meeting).

5.9 Overall, the sponsor considered there was little evidence from the DUSC analysis to suggest that the considerable extent of use above the utilisation estimates could be attributed to use outside the PBS restriction criteria. The sponsor considered it is highly likely that an underestimation of the size of the eligible population and/or higher than anticipated uptake rates are key factors driving the higher than predicted number of patients initiating treatments for severe AD.

Financial Management – Risk Sharing Arrangements

5.10 The Sponsor proposed the following re-specification of the RSA subsidisation caps.

1. A [redacted]% price reduction to the current AEMP for upadacitinib (from $[redacted] to $[redacted]) based on a [redacted]% price reduction in an assumed [redacted]% of patients with low-range severe AD.
2. Current levels of actual utilisation for dupilumab and upadacitinib to form the basis of the first year of a revised five-year RSA (with appropriate, evidence-based predictions of utilisation growth thereafter).
3. Expenditure over annual subsidisation caps should be reimbursed at [redacted]% (reduced from [redacted]%).

5.11 The sponsor considered that a [redacted]% rebate level would be justified because the [redacted]% price reduction is likely to be a conservative estimate of the cost-effective price and would address the uncertainty in the initial recommended listing, expenditure with the [redacted]% rebate would remain cost-effective, and the current levels of utilisation are still below the estimated total eligible severe AD population (approximately 40,000 to < 50,000 patients as per Table 1 Dupilumab PSD, November 2020 PBAC meeting).

5.12 The pre-PBAC response proposed revised RSA subsidisation caps as shown in Table 6 for a new 5-year RSA starting from March 2024. The sponsor proposed 2 tiers with different rebate levels. Tier 1 was based on the current level of utilisation (with 2.2% annual population growth) and tier 2 was projected based on a polynomial trend function plateauing by year 5 of the new RSA.

Table 6: Abbvie proposed subsidisation caps

	Mar 24 - Feb 25 DY1	Mar 25 - Feb 26 DY2	Mar 26 - Feb 27 DY3	Mar 27 - Feb 28 DY4	Mar 28 - Feb 29 DY5	Rebate level
Subsidisation caps - tier 1	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	[redacted]%
Subsidisation caps - tier 2	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	[redacted]%

Source: Abbvie Pre-PBAC response

6 PBAC Outcome

6.1 The PBAC noted that the current agreed subsidisation caps are being exceeded by [redacted]. These subsidisation caps were agreed on the basis of estimated utilisation upon first entry into the existing market. The PBAC considered that, at the current level of utilisation, without the current RSA arrangements, dupilumab and upadacitinib would not be considered cost-effective at their current prices. The PBAC noted that the current Risk Sharing Arrangements (RSAs) are formalised under Deeds of Agreement between the Commonwealth and the sponsors of dupilumab and upadacitinib. The Deeds encompass subsidisation caps that cover the period up to February 2026. The PBAC considered that one of the main purposes of RSAs are to manage uncertainties, including those associated with budget impact and appropriate cost-effective use, as is the case with the current arrangements in place for these medicines. The PBAC considered that renegotiation of any Deed arrangements was ultimately a matter for the Commonwealth, however provided the following advice for consideration at time of negotiation of any future RSA.

6.2 The PBAC noted that utilisation of dupilumab over the first 2.7 years of listing has been substantially higher than the November 2020 forecasted estimates that were the basis for the current RSA financial caps. Specifically, the expenditure for Year 2 of the Deed was [redacted]% of the agreed cap and for the first 8 months of Year 3 expenditure was [redacted]% of the agreed cap for the full year. The PBAC noted that DUSC concluded that the number of treated patients was within the estimate of total eligible patients with severe AD, however it is unknown whether the greater than predicted utilisation is due to higher uptake than predicted, within the estimate of total eligible population, or use outside the restriction in patients with mild to moderate disease. The PBAC noted the input from clinicians and clinical advisory groups that suggested there was not a substantial amount of utilisation outside the severe AD population, and that a substantial number of additional patients with severe AD have re-engaged with specialists due to the availability of effective treatments. The PBAC considered that, based on the available utilisation data, the reasons for the actual use exceeding that estimated in 2020 remain unclear but may be due to the estimated number of eligible patients, uptake and/or continuation rates being underestimated, as well as use in patients with less severe AD.

6.3 The PBAC noted that the severity of AD can fluctuate over time and hence patients with predominately moderate disease may access treatment during a period where their disease is classified as severe, and then remain on treatment. The PBAC noted the utility values are a driver for the dupilumab economic model and dupilumab (and upadacitinib) would be less cost-effective in patients with less severe disease. The PBAC recalled this was raised during its consideration of the July 2019 resubmission for a listing for dupilumab for moderate-to-severe AD where the submission was not recommended as dupilumab was not considered cost-effective at the price proposed in the resubmission (paragraphs 7.12, 7.17 dupilumab PSD, July 2019 PBAC meeting).

6.4 The PBAC noted that the actual treatment continuation rate has exceeded that assumed in the original utilisation estimates for dupilumab. The DUSC analysis indicated that 78% of patients received a second prescription of dupilumab whereas the estimates were based on the 59.6% continuation rate observed in the clinical trial. The PBAC acknowledged that the utilisation data may not yet be mature enough to provide an accurate estimate of the continuation rate long-term, however noted that the higher proportion of patients remaining on treatment has contributed to the higher than expected use.

6.5 The PBAC considered that a price reduction would be required for dupilumab and upadacitinib to be cost-effective noting ESC's advice that a reduced price would be needed to account for the potential use in patients with less severe AD, the higher continuation rate observed versus estimated based on the dupilumab clinical trial and the current expenditure being [redacted] higher than forecasted at the time the listing was recommended.

6.6 The PBAC acknowledged the tension between cost-effectiveness per se, and total budget impact. The PBAC maintained that the cost-effectiveness of a medicine can be summarised by the ICER. However, the PBAC reiterated that the ICER considered acceptable is influenced by a range of contextual factors, including total budget impact. The PBAC noted that budget impact is further considered by Government, with Cabinet consideration required for any items with a predicted budget impact >$20 million per annum, reflecting the substantial opportunity cost associated with these public investment decisions. The PBAC recalled precedents where total budget impact is small (such as in orphan indications) and a relatively high ICER has been considered cost-effective. Conversely, the PBAC recalled that relatively low ICERs have been required for medicines and vaccines with population level or high-volume utilisation predicted.

6.7 The PBAC recalled its advice that 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 (paragraph 6.6 dupilumab PSD, July 2023). The PBAC noted that the ICER for dupilumab was accepted in November 2020 in the context of financial caps of < $[redacted] in year 1 increasing to <$[redacted] in year 6. The PBAC noted the forecasted versus actual expenditure in year 2 was $[redacted] versus $[redacted] and for year 3 was $[redacted] versus $[redacted] (pro-rated based on $[redacted] in the first 8 months). The PBAC further noted both sponsors expected the expenditure to continue to increase over the remaining Deed period. However, the PBAC considered that there was no clear basis for forecasting estimated utilisation for the remaining 2 years of the Deed (and beyond) as the number of initiating patients would be expected to decline in the future as the market becomes saturated, but it is not known over what time period this would occur and hence when the overall market would stabilise.

6.8 The PBAC also recalled the dupilumab economic model included assumptions that were favourable to the sponsor (para 5.8 dupilumab PSD, July 2022 PBAC meeting) and thus the estimated ICER was potentially optimistic.

6.9 Overall, the PBAC considered an ICER of $15,000/QALY would be more reasonable in the context of the actual and predicted use for dupilumab and upadacitinib.

6.10 The PBAC recalled in March 2022 it recommended the listing of dupilumab for the paediatric population. The PBAC noted the recommendation allowed for separate RSA caps for the new population and as such considered there was no basis for not proceeding with this listing, especially given that this listing was of high priority for consumers. The PBAC advised that the sponsor should engage with the Department to progress the listing of dupilumab for paediatric patients as a matter of priority[4].

Dupilumab proposal

6.11 The PBAC noted an [redacted]% price reduction was proposed for dupilumab (AEMP reduced from $[redacted] to $[redacted]), and when applied in the economic model presented in the November 2019 submission reduced the ICER from $45,000 to < $55,000/QALY to $25,000 to < $35,000/QALY. The PBAC considered dupilumab was not cost-effective at the price proposed because the potential use in less severe disease and higher continuation rates were not accounted for, and the ICER remained too high.

6.12 The PBAC noted the ESC analysis in which the dupilumab costs (but not the proportion of responders) were increased in the economic model to account for a 16 week continuation rate of 78%, increased the ICER from $25,000 to < $35,000/QALY to $45,000 to < $55,000/QALY (paragraph 4.7). The PBAC also noted that the pre-PBAC response presented an analysis in which both the costs and proportion of responders were increased to 78% and that this resulted in an ICER of $25,000 to < $35,000/QALY. The PBAC considered the ESC analysis to be potentially conservative, however noted the benefit may be less in the additional 18.4% of patients continuing therapy versus that expected based on the clinical trial (59.6%) and that this would be expected to reduce the cost-effectiveness of dupilumab treatment.

6.13 The PBAC considered the ICER of $25,000 to < $35,000/QALY presented in the dupilumab proposal was underestimated given the potential for use in less severe patients and lower benefit in the additional patients continuing treatment. The PBAC also recalled the economic model included assumptions that were favourable to the sponsor (para 5.8 dupilumab PSD, July 2022 PBAC meeting).

6.14 The PBAC considered the ICER of $25,000 to < $35,000/QALY was unacceptably high. As noted in paragraph 6.9 the PBAC considered an ICER of $15,000/QALY would be cost effective in the current, much larger than predicted, population. The PBAC noted a DPMQ of $[redacted] (35% reduction from the current DPMQ) would be required to achieve

[4] *Note: The sponsor has since advised the Department of Health and Aged Care that it intends to proceed with the listing of dupilumab for the treatment of severe AD in patients aged 6 to 11.*

an ICER of $15,000/QALY. However as outlined in paragraph 6.13, the PBAC considered the ICER to be underestimated. For example, based on the ESC analysis incorporating the cost of dupilumab associated with the increased continuation rate, without additional responders, would require a price reduction of 48%. Overall, the PBAC considered dupilumab would likely be cost-effective with a price reduction in the order of 50%.

6.15 The PBAC noted that the dupilumab sponsor proposed the RSA caps be revised based on the financial estimates included in the July 2023 submission. The PBAC noted adjustments were made to the uptake rates assumed in the July 2023 submission, and an additional cohort of 'unaccounted for patients' was added, so that July 2023 estimates remained unchanged after accounting for the % increase in the caps recommended at the July 2023 meeting to account for patients with severe AD of the hands and/or face.

6.16 The dupilumab sponsor estimated that in year 4 of the Deed (March 2024 – February 2025) there would be approximately patients treated compared with estimated at the time of the listing. The corresponding numbers for year 5 were approximately versus . The PBAC noted the sponsor proposed to account for the increase in use by increasing the RSA caps in year 4 from $ to $ (including the proposed % price reduction; reduced by % in the pre-PBAC response to $) and in year 5 from $ to $ (including the proposed % price reduction; reduced by % in the pre-PBAC response to $). The PBAC recalled in July 2023 that it considered the estimates were highly implausible when compared with current PBS utilisation and optimistic (paragraph 6.5, ratified dupilumab PSD, July 2023 PBAC meting). The PBAC noted the adjustments made to the uptake rates and additional cohorts could not be verified and added further complexity to the calculations. Overall, the PBAC considered the estimates were not a reliable basis for revised RSA caps.

6.17 The PBAC noted the sponsor did not propose revising the current rebate (%) for use exceeding the financial caps.

6.18 The PBAC's original recommendation was based on accepting a relatively high ICER, for a condition of this type and commonness, coupled with a total cost that was reasonable at the predicted uptake numbers, which, in agreeing to the Deed, the sponsor accepted. The PBAC considered that any renegotiation of the Deed arrangements increasing the cap would also need to consider a substantially lower price to be consistent with the basis of the Committee's original recommendation.

Upadacitinib proposal

6.19 The PBAC noted as upadacitinib was listed on a cost-minimisation basis to dupilumab, the sponsor did not have access to the accepted cost-effectiveness evaluation. The PBAC noted a % price reduction was proposed for upadacitinib (AEMP reduced from $ to $), and this was based on a % price reduction in an assumed % of patients with low-range severe AD. The PBAC noted the potential impact on the cost-effectiveness of higher continuation rates was not considered. The PBAC considered that the

treatment benefit may be less in the additional 18.4% of patients continuing therapy versus that expected based on the clinical trial (59.6%) and that this would reduce the cost-effectiveness of treatment.

6.20 The PBAC considered the ICER at the proposed price remained unacceptably high. As noted in paragraph 6.9 the PBAC considered an ICER of $15,000/QALY would be cost effective in the current, much larger than predicted, population.

6.21 The PBAC noted that a new five year, two tier RSA was proposed in the pre-PBAC response. Tier 1 was based on the current level of utilisation (with 2.2% population growth) and tier 2 was projected based on a polynomial trend function plateauing by year 5 of the new RSA. The rebate level proposed for use between tiers 1 and 2 was %, and for above tier 2 was %. For the first year of the new Deed (March 2024 – February 2025) the sponsor proposed a tier 1 RSA cap of $ and a tier 2 cap of $, which compared with the existing RSA cap of $. The corresponding financial caps for the second year of the Deed were $ and $, respectively versus $ for the existing RSA cap. The proposed caps for the fifth year of the Deed were $ and $, respectively. The PBAC noted the substantial increase in the proposed versus existing caps and the reduced rebate levels. The PBAC noted the simpler approach for forecasting utilisation which was based on utilisation to date, and that the growth was expected to plateau, but not until year 5. The PBAC noted there was no clear basis for determining when the overall market would stabilise.

6.22 The PBAC's original recommendation was based on accepting a relatively high ICER, for a condition of this type and commonness, coupled with a total cost that was reasonable at the predicted uptake numbers, which, in agreeing to the Deed, the sponsor accepted. The PBAC considered that any renegotiation of the Deed arrangements increasing the cap would also need to consider a substantially lower price to be consistent with the basis of the Committee's original recommendation.

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

Sponsor for Dupilumab (Dupixent) - Sanofi-Aventis Australia Pty Ltd

When Dupixent was PBS listed for severe atopic dermatitis in adolescents and adults in Australia, it was the first new systemic treatment in over 20 years for a patient population with high unmet clinical need. This presented challenges in estimating the utilisation of Dupixent, which has exceeded expectations, despite a high level of due diligence on the part of both parties.

The conditions of the current RSA for advanced therapies listed on the PBS for patients with severe AD aged 12 years and over have put these listings on an unsustainable footing. For the last two years and in multiple submissions to the PBAC, Sanofi has been working with the Department and the PBAC to address the challenges of the current situation. Sanofi is continuing to work, in good faith, with the Department of Health and Aged Care to resolve this matter.

Sponsor for Upadacitinib (Rinvoq) – AbbVie Pty Ltd

AbbVie welcomes the PBAC's acknowledgement that clinicians and clinical advisory groups suggest that there is not a substantial amount of utilisation outside the severe AD population. Given this, AbbVie reiterates that any future RSA should include all current utilisation, reasonable assumptions about future growth, and an over-the-cap reimbursement percentage reflecting a sharing of risk.