

**6.03 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.**

1 Purpose of submission

- 1.1 The category 2 submission requested Authority Required listing for dupilumab for the treatment of children aged 6 to 11 years with severe atopic dermatitis (AD) who have had an inadequate response to topical therapies.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus placebo. The key components of the proposed listing are provided below.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Children aged 6 to 11 years with severe AD who have had an inadequate response to topical therapies
Intervention	Tiered (by body weight) dupilumab dosing, whereby: <ul style="list-style-type: none"> - 15 kg to < 30 kg: 600 mg (2 x 300 mg syringes) loading dose, then 300 mg (1 x 300 mg syringe) Q4W - 30 kg to < 60 kg: 400 mg (2 x 200 mg syringes) loading dose, then 200 mg (1 x 200 mg syringe) Q2W - ≥ 60 kg: 600 mg (2 x 300 mg syringes) loading dose, then 300 mg (1 x 300 mg syringe) Q2W
Comparator	Standard of care (SoC; represented by placebo)
Outcomes	Primary outcomes: proportion of patients with EASI-75 at Week 16, proportion of patients with an IGA 0 or 1 at Week 16. Key secondary outcomes: percent change in EASI score from baseline to Week 16, percent change from baseline to Week 16 in weekly average of daily worst itch score. Other relevant secondary outcomes: proportion of patients with EASI-50 at Week 16, change from baseline to Week 16 in CDLQI, proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 or ≥3, proportion of patients with EASI-90, change from baseline in POEM, percent change from baseline in SCORAD.
Clinical claim	In the treatment of children aged 6 to 11 years with severe AD not adequately controlled with topical therapies, dupilumab has superior efficacy to SoC with an increased risk of injection site reactions and conjunctivitis.

Source: Table 1.1, p17 of the submission.

AD = atopic dermatitis; CDLQI = Children's Dermatology Life Quality Index; POEM = patient oriented eczema measure; Q2W = dosing every two weeks; Q4W = dosing every four weeks; SCORAD = scoring atopic dermatitis clinical tool used to assess the extent and severity of eczema, SoC = standard of care.

2 Background

Registration status

2.1 Dupilumab was registered for the treatment of moderate to severe AD in patients aged 6 to 11 years on 17 August 2021. It had previously been registered for the treatment of moderate to severe AD in adults and those aged 12 to 17 years in 2018 and 2019.

Previous PBAC consideration

2.2 Dupilumab has been previously considered by the PBAC for the treatment of severe or moderate to severe AD in adults four times (July 2018, July 2019, March 2020, November 2020), and for the treatment of uncontrolled severe asthma once (November 2020).

3 Requested listing

3.1 An abbreviated version of the proposed restrictions is presented below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
15kg to <30kg 300mg Q4W					
DUPILUMAB Dupilumab 300mg/2mL 2 x 2mL pre-filled syringe	1	2	3 (initial) 2 (continuing, grandfather)	\$3,380.91 (published) \$█ (effective)	Dupixent® Sanofi-Aventis
30kg to <60kg 200mg Q2W					
DUPILUMAB Dupilumab 200mg/1.14mL 2 x 1.14mL pre-filled syringe	1	2	5 (initial, continuing, grandfather)	\$1,754.28 (published) \$█ (effective)	Dupixent® Sanofi-Aventis
≥60kg 300mg Q2W					
DUPILUMAB Dupilumab 300mg/2mL 2 x 2mL pre-filled syringe	1	2	5 (initial, continuing, grandfather)	\$1,754.28 (published) \$█ (effective)	Dupixent® Sanofi-Aventis

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Episodicity:	Chronic
Severity:	Severe
Condition:	Atopic dermatitis
PBS Indication:	Chronic severe atopic dermatitis
Treatment criteria:	Must be treated by a dermatologist, OR clinical immunologist.
Treatment Phase	Initial – treatment of the whole body (15kg to <30kg; 30kg to <60kg; ≥60kg)

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Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
15kg to <30kg 300mg Q4W					
Clinical criteria:	<p>Patient must have a Physicians Global Assessment (PGA) (5-point scale) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days; AND Patient must have an Eczema Area and Severity Index (EASI) baseline score of at least 21 despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days; AND Patient must have a Children’s Dermatology Life Quality Index (CDLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days; AND The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands; AND The treatment must be the sole PBS-subsidised biological medicine for this PBS indication; AND Patient must not have experienced an inadequate response to this biological medicine in this PBS indication.</p>				
Population criteria	<p>Patient must be at least 6 years of age and less than 12 years of age Patient must weigh 15 kg to < 30 kg</p>				
Prescriber instructions:	<p>State each of the qualifying PGA, EASI and CDLQI scores in the authority application. These baseline scores must have been measured within the past 4 weeks. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine is/are to be documented in the patient’s medical records. The EASI and CDLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction.</p>				
Treatment Phase	<p>Continuing or resuming treatment of the whole body</p>				
Clinical criteria:	<p>Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the whole body; AND Patient must have achieved an adequate response within the first 16 weeks of treatment; OR Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; OR Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. vaccination with live vaccines, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application; AND The treatment must be the sole PBS-subsidised biological medicine for this PBS indication.</p>				
Population criteria	<p>Must be treated by a dermatologist, OR clinical immunologist.</p>				

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Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
15kg to <30kg 300mg Q4W					
Prescriber instructions:	<p>For the purposes of this restriction, an adequate response to treatment is defined as:</p> <p>(a) An improvement/maintenance in the Eczema Area and Severity Index (EASI) score of at least 50% compared to baseline; and</p> <p>(b) An improvement/maintenance in Children's Dermatology Life Quality Index (CDLQI) score of at least 4 points compared to baseline.</p> <p>Where an initial baseline (post-topical corticosteroid, pre-biological medicine) CDLQI score was not measured for a patient who had commenced treatment through a clinical trial, early access program or through private, non-PBS-subsidised supply, an absence of worsening in the current CDLQI score compared to that measured at the time of the 'Grandfather listing' authority application will suffice as an adequate response for requirement (b) above.</p> <p>State each of the current EASI and CDLQI scores for this authority application.</p>				

- 3.2 The submission proposed a special pricing arrangement (SPA) for the paediatric population, consistent with the current SPA that applies to use of dupilumab for the treatment of adult and adolescent AD. The sponsor requested an ex-manufacturer price for patients receiving 300 mg Q4W double that for patients receiving 200 mg Q2W, to maintain the same monthly treatment cost.
- 3.3 The submission requested separate listings for each weight dose category specified in the recommended dosing (15kg to <30kg; 30kg to <60kg; ≥60kg), the requested restrictions are otherwise identical. The PBAC considered that there does not appear to be a need for separate listings for each dose/regimen as clinicians can nominate the correct dosing regimen and number of repeats based on the patient's weight.
- 3.4 Although no clinical evidence for patients ≥60kg was presented the Pre-Sub-Committee Response (PSCR) argued there should be allowance for these patients to access dupilumab, either by use of a separate restriction for paediatric patients ≥60kg, or by amendment of the current adult and adolescent restriction criteria for the 300 mg strength to include these patients. The PSCR noted that adolescent patients currently have the same dosing for patients <60kg and ≥60kg. The ESC noted that up to 5% of children aged 11 years may fall into the ≥60kg weight category, based on CDC weight-for-age percentiles¹. The PBAC agreed with the ESC that it would be appropriate to include the 300 mg Q2W dosing for patients <12 year in the listing for dupilumab.
- 3.5 The submission also requested PBS listings for severe AD of the face and/or hands, consistent with the current adult listings. The proposed restrictions for face and/or hands were similar to that for the whole body except for: (i) severity is defined as

¹ <https://www.cdc.gov/growthcharts/data/set2clinical/cj41c071.pdf> and <https://www.cdc.gov/growthcharts/data/set2clinical/cj41c072.pdf>

having 2 of the following EASI symptom sub-scores for erythema, oedema/papulation, excoriation, lichenification rated as 'severe' or the condition must have affected at least 30% of the face/hand surface area instead of EASI ≥ 21 and PGA ≥ 4 ; and (ii) response defined as a reduction in at least 3 of the EASI sub-scores to either mild (1) to none (0) or $\geq 75\%$ reduction in the skin area affected, rather than EASI 75 as for the whole body, as well as improvement in Children's Dermatology Life Quality Index (CDLQI) score of at least 4 points².

- 3.6 The requested listings are the same as the PBS listings for adult and adolescent treatment, with the exception that the baseline Eczema Area and Severity Index (EASI) score has been increased from 20 to 21, and the CDLQI is used instead of the DLQI as was used for adult patients. The submission noted the change in EASI score was intended to reflect the inclusion criteria for the paediatric clinical trial. While the inclusion criteria for Study 1652 included an EASI score ≥ 21 , the current adult and adolescent PBS listing uses an EASI score of at least 20.
- 3.7 The nominated criteria of at least a 4-point improvement on the CDLQI (CDLQI4) was based on PBS listing of dupilumab in adolescents (originally modelled on the adult listing requiring at least a 4 point improvement on the DLQI). Given the minimally clinically important difference (MCID) for the CDLQI is defined as a change of at least 6 points, the submission stated that the PBAC may consider it to be more appropriate to base the response criteria for paediatric patients on the CDLQI MCID. Response rates based on both the EASI 50 and CDLQI4 criteria and the EASI 50 and CDLQI6 criteria were provided in the submission, and a sensitivity analysis of the economic model for response based on EASI 50 and CDLQI6 was also provided. The change in CDLQI criterion had minimal impact on the estimated incremental cost effectiveness ratio (ICER). The ESC noted that difference in this criterion may complicate assessment of those patients on treatment who transition from the CDLQI to DLQI and that, in general, it would be important to ensure that the restrictions allow patients to transition from the paediatric listing to the adult/adolescent listings without needing to cease treatment.
- 3.8 The PBAC considered that restrictions for patients aged less than 12 years should be consistent with restrictions for patients aged 12 or older to reduce complexity for prescribers and to ensure that patients can easily transition to treatment under the adolescent/adult listing. The PBAC considered that the baseline EASI score should be 20 (rather than 21 as proposed) and that the wording in the restrictions for the adolescent/adult population with respect to DLQI was sufficiently inclusive for use of CDLQI in the paediatric listing. The PBAC noted that the listings would need to be

² The requested restriction noted that when an initial baseline CDLQI score was not measured for a patient who commenced treatment through a clinical trial, early access program or private supply, an absence of worsening of CDLQI compared to that measured at the time of 'Grandfather listing' authority application will suffice as an adequate response for improvement in CDLQI score of 4 points. *This corresponds to the adult listing and change in DLQI score.*

constructed in such a way that the Department is able to attribute financial expenditure to the different patient groups and drugs.

- 3.9 The PBAC considered that for the paediatric population it would be appropriate to specify that patients must be less than 12 years of age, without specifying a minimum age for access to treatment. The PBAC noted that dupilumab is currently TGA indicated for patients aged at least 6 years, but considered that use in patients younger than 6 years may be clinically appropriate in some circumstances.
- 3.10 The ESC noted that the submission proposed the inclusion of guidance in the requested restrictions for identification of patients with a sustained response, and in whom an assessment of the need for ongoing treatment is appropriate. The ESC considered that inclusion of guidance may be appropriate given that for many paediatric patients their disease would be expected to resolve over time (see also paragraph 4.2). The PBAC considered that parents and specialists prescribing dupilumab, in line with QUM principles, would discontinue treatment or extend the period between doses where appropriate to manage patients who may no longer require treatment with dupilumab. The PBAC considered that assessment of the need for ongoing treatment would be appropriately managed by specialist clinicians and the restrictions need not include this requirement.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by pruritus (itching), xerosis (dryness) and extensive skin lesions. The clinical manifestations of AD vary depending on the phase (chronic or acute) and severity of disease; ranging from occasional dry and scaly patches in mild cases, to a debilitating disease in more severe cases where more than 50% of the body surface area may be covered by excoriated (scratched and abraded), bleeding and infected lesions. The requested listing is for treatment of severe disease.
- 4.2 AD typically occurs in infancy and early childhood, with onset by two years of age in most patients and is the most common skin disorder in infants and children, with an estimated global prevalence of up to 14% in children aged 6 to 11 years old. The submission noted (p2) the consensus is that the majority of patients with childhood-onset AD will eventually 'outgrow' their disease, approximately 20% of cases of childhood-onset AD persist beyond 8 years after diagnosis, and approximately 5% of cases continue into adulthood (Kim 2016).
- 4.3 The submission indicated (p3) that the itch, discomfort and ongoing sleep disruption experienced by children living with severe AD has a profound impact on many aspects of a child's development, and AD can also have a significantly detrimental effect on a child's mental health, and cited extensive literature supporting this claim.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated placebo, representing standard of care (SoC) as the main comparator. The submission noted (p8) that the PBAC previously accepted this comparator for the use of dupilumab in adult patients with severe AD uncontrolled by topical therapies (paragraph 5.1, July 2019 Public Summary Document (PSD)). The PBAC considered that the nominated comparator was appropriate.
- 5.2 The submission did not include CsA as an additional comparator in the paediatric population, as was done for adults. The submission noted that the Australian product information for ciclosporin stated that use in children was not recommended. It was reasonable to not include CsA as an additional comparator.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (60), health care professionals (9) and consumer groups/organisations (2) and medical organisations (4) via the Consumer Comments facility on the PBS website.
- 6.3 All medical organisations that provided comments noted the significant impacts on quality of life for children with AD, the safety concerns and lack of efficacy for existing treatments and all were supportive of the proposed PBS listing for dupilumab. The National Paediatric Medicines Forum (NPMF) noted a number of paediatric patients are currently accessing treatment via hospital funding or other mechanisms. The Australasian Society of Clinical Immunology and Allergy (ASCIA) reported that the listing of dupilumab in patients aged 12 years or older has made a significant difference to their health-related quality of life, learning outcomes and productivity and is likely to also make a significant difference to younger children. ASCIA also stated that clinical immunology/allergy specialists regularly manage patients of all ages with severe atopic dermatitis, and are experienced in appropriate selection and monitoring of these patients.
- 6.4 Consumer groups (Allergy & Anaphylaxis Australia and Eczema Support Australia) expressed their support for PBS listing dupilumab for children aged <12 years, outlining the urgent need for affordable access to effective treatment for AD. Consumer groups outlined the significant impacts of AD on family life and education and the high cost of managing AD including on workforce participation for carers.

- 6.5 Individuals who had used dupilumab (14) and parents of children who had used dupilumab (3) reported the impact of treatment with dupilumab in terms of clearance of AD, itch reduction, wound healing and improvements in terms of quality of life (ability to function, sleep improvement, confidence, mood and concentration). Parents noted the reduced use of other treatments (antibiotics, steroids, immunosuppressants, bleach baths, wet dressings, creams and moisturisers) some of which have significant and lasting safety implications. A number of individuals who had used dupilumab reported eye irritation and other side effects from dupilumab (headaches, pain, cold sores) but indicated that side effects were tolerable and would not lead to discontinuation because the treatment was effective. Individuals noted that injections can be difficult for children or inconvenient and some would prefer this to be done by a healthcare professional rather than at home.
- 6.6 Parents who had not accessed treatment noted the existing treatments have limited effectiveness and often require a high level of ongoing care which is time-consuming, expensive and can be painful. Parents also noted the significant, debilitating physical and emotional suffering for children with severe AD, and the toll from this suffering that extends to parents and family. Parents noted impacts on children's mental health, sleep, social development and school attendance. Parents noted the prohibitive cost of accessing dupilumab outside the PBS.
- 6.7 Healthcare professionals noted that experience with dupilumab in patients aged ≥ 12 indicated that it is highly effective in treating severe disease and the limited experience in patients < 12 years of age has also shown rapid and sustained effect. Healthcare professionals noted that dupilumab has safety advantages over immunosuppressive therapies and does not require regular blood test monitoring. Healthcare professionals noted that side effects tend to be minor and manageable and few patients are unable to tolerate treatment due to conjunctivitis. Healthcare professionals noted that injections may be difficult for some patients but often these difficulties can be overcome. Healthcare professionals also noted the clinical need in younger children is high and the impacts on quality of life from severe disease are substantial and include sleep, school, sport, and the ability to interact with peers.

Clinical trials

- 6.8 The submission was based on a randomised, double-blind, multicentre trial (Study 1652) comparing the efficacy and safety of dupilumab + topical corticosteroids (TCS) to placebo in paediatric patients aged 6 to 11 years with severe AD inadequately controlled with topical therapies. The trial had a treatment period of 16 weeks, and a follow-up period of 12 weeks, the latter only for those patients who declined or were ineligible to participate in an open-label extension study. There is no relevant longer-term data available from the extension study (Study 1434), as the majority of patients (84%; 33/39) used weight-based dosing (2 mg/kg or 4 mg/kg) and the study CSR noted (p58) that efficacy analyses were confounded because of inclusion of patients who were treated with different dose regimens at different time points.

6.9 Study 1652 had a different dosing structure than the requested restrictions (and Australian product information (PI) recommended dosing). In Study 1652 patients in all weight categories were randomised to receive either:

- 300 mg dupilumab Q4W (following a 600 mg loading dose on Day 0)

or

- 100 mg Q2W (patients weighing <30kg at baseline) or 200 mg Q2W (patients weighing 30 - <60kg at baseline).

6.10 The following table outlines the similarities and differences between the trial and the proposed listing. In addition, a standardised regimen of concomitant TCS was used in Study 1652, while the requested listings do not specify use of concomitant TCS.

Table 2: Dosing regimen in Study 1652 and the requested listing

	Study 1652 (N=367)	PI and requested listing
Weight categories	<30kg: 200mg loading dose then 100mg Q2W + TCS ^a : N=63 (17%)	15kg to <30kg: 600mg loading dose then 300mg Q4W
	≥30kg: 400mg loading dose then 200mg Q2W + TCS; N=59 (16%)	30kg to <60kg: 400mg loading dose then 200mg Q2W
	Any weight: 600mg loading dose then 300mg Q4W + TCS; N=122 (33%)	≥60kg: 600mg loading dose then 300mg Q2W
	Placebo + TCS; N=123 (34%)	-

Source: Section 2.2.3, p59; Table 1.2, p7 of the submission

PI = product information; Q2W = every two weeks; Q4W = every four weeks; TCS = topical corticosteroids

^a Starting on Day 14, all patients were required to initiate TCS treatment using a standardised regimen.

6.11 All results presented by the submission were based on the split between Q2W and Q4W dosing used in Study 1652 which was not consistent with the submission's requested listings. The clinical evidence used in the economic model was based on a post-hoc subgroup analysis of Study 1652 with only patients weighing <30 kg in the Q4W dosing group, and only patients weighing 30 kg to <60 kg in the Q2W dosing group.

6.12 Details of the trials/studies presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
R668-AD-1652 (Study 1652)	A randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical corticosteroids in patients ≥6 years to <12 years of age, with severe atopic dermatitis.	November 2019
	Paller A, Siegfried EC, Thaci D, Wollenberg A et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. Author(s). Title.	J Am Acad Dermatol 2020. 83(5): 1282-1293. Journal Year; Vol(No.): pages

Source: Table 2-1, p56 of the submission.

6.13 The key features of the direct randomised trial are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Dupilumab vs. placebo						
Study 1652	367 (subgroup N=173)	R, DB, MC 16 weeks	Low	6 years to <12 years with severe AD that was not adequately controlled with topical medications	EASI 50, EASI 75, IGA, CDLQI	Post-hoc subgroup for Week 16 EASI 50 and CDLQI

Source: Section 2.2.3, p59 of the submission.

CDLQI – Childhood Dermatology Life Quality Index; DB = double blind; EASI = Eczema Area and Severity Index; IGA = Investigator’s Global Assessment; MC = multi-centre; R = randomised.

6.14 The outcomes are the same as those considered in the adult submissions, with the exception of the CDLQI, which is a child version of the DLQI assessed for adults. The primary outcome in Study 1652 was the proportion of patients with IGA 0 or 1. The proportion of patients with EASI 75 at Week 16 was a key secondary outcome. Other key secondary outcomes included percent change in EASI score from baseline to Week 16, proportion of patients with EASI 50 and change from baseline in CDLQI. While it was not a specified outcome in the trial, for the economic model a combined outcome of the proportion of patients with EASI 50 and CDLQI4 was used.

Comparative effectiveness

6.15 The submission presented efficacy results for the overall trial population and weight-based groups. The clinical efficacy data used in the economic model was based on post-hoc subgroup analysis patients in Study 1652 with severe AD (baseline EASI ≥ 21). This subgroup contained only patients weighing <30 kg in the Q4W dosing group, and only patients weighing 30 kg to <60 kg in the Q2W dosing group. The number of patients was 173, which is almost half of the overall trial population (N=367). The ESC noted that the baseline characteristics of the sub-group used to estimate the Week 16 response rate were not presented.

6.16 The key results relied upon in the model were a combined outcome of EASI 50 and CDLQI4. The post-hoc subgroup results are provided below, followed by the overall trial population results, and results by weight group. Also provided, following Table 6 is a graphical representation of patients achieving EASI 75 in the overall trial population.

Table 5: Results at Week 16 in the post-hoc subgroup of Study 1652

	N	Number (%) meeting criterion at Week 16	Difference vs. placebo % (95% CI)	P-value vs. placebo
EASI 50 <30kg				
Dupilumab 300 mg Q4W	61	58 (95.1)	50.3 (31.36, 69.15)	<0.0001
Placebo	29	13 (44.8)	-	-
EASI 50 30 – 60 kg				
Dupilumab 200 mg Q2W	56	48 (85.7)	41.3 (20.41, 62.13)	0.0001
Placebo	27	12 (44.4)	-	-
CDLQI4 <30 kg				
Dupilumab 300 mg Q4W	61	50 (82.0)	23.3 (2.99, 43.70)	0.0188
Placebo	29	17 (58.6)	-	-
CDLQI4 30 - 60 kg				
Dupilumab 200 mg Q2W	56	46 (82.1)	34.0 (12.64, 55.34)	0.0016
Placebo	27	13 (48.1)	-	-
CDLQI6<30 kg				
Dupilumab 300 mg Q4W	61	45 (73.8)	22.0 (0.77, 43.32)	0.0403
Placebo	29	15 (51.7)	-	-
CDLQI6 30 - 60 kg				
Dupilumab 200 mg Q2W	56	40 (71.4)	38.1 (16.74, 59.45)	0.0011
Placebo	27	9 (33.3)	-	-
EASI 50 and CDLQI4 <30 kg				
Dupilumab 300 mg Q4W	61	50 (82.0)	54.4 (35.47, 73.29)	<0.0001
Placebo	29	8 (27.6)	-	-
EASI 50 and CDLQI4 30 - 60 kg				
Dupilumab 200 mg Q2W	56	40 (71.4)	41.8 (20.90, 62.70)	0.0004
Placebo	27	8 (29.6)	-	-
EASI 50 and CDLQI6 <30 kg				
Dupilumab 300 mg Q4W	61	45 (73.8)	46.2 (26.53, 65.84)	<0.0001
Placebo	29	8 (27.6)	-	-
EASI 50 and CDLQI6 30 - 60 kg				
Dupilumab 200 mg Q2W	56	35 (62.5)	40.3 (20.11, 60.44)	0.0007
Placebo	27	6 (22.2)	-	-

Source: Table 1.2, p8; Table 1.3, p9; Table 1.4, p10, Table 1.5, p11 and Table 1.6, p12 of SAR231893 AD1652 in Attachment 5.
CI = confidence interval; EASI = Eczema Area and Severity Index; Q2W = every two weeks; Q4W = every four weeks

6.17 The submission did not provide any indication of whether any corrections or adjustments were made to the analyses to account for the multiple testing that would have occurred with the post-hoc analyses. Thus, all results should be interpreted with caution. There were statistically significant advantages for dupilumab compared to placebo for EASI 50, CDLQI, and the two outcomes combined. The proportion of responders was marginally lower for CDLQI6 versus CDLQI4 which was then reflected in the composite outcomes given response rates to EASI 50 were generally higher. The submission did not provide any safety outcomes for this post-hoc subgroup.

6.18 The PBAC noted that the clinical evidence from the post-hoc subgroups suggested that response may differ somewhat between patients <30kg on the 300 mg Q4W schedule and those 30-60kg on the 200 mg Q2W schedule, with patients <30kg having numerically greater improvements for the combined outcome of EASI 50 and CDLQI4, compared with those 30-60kg. Overall the PBAC considered that dupilumab appeared to be effective in both groups of patients.

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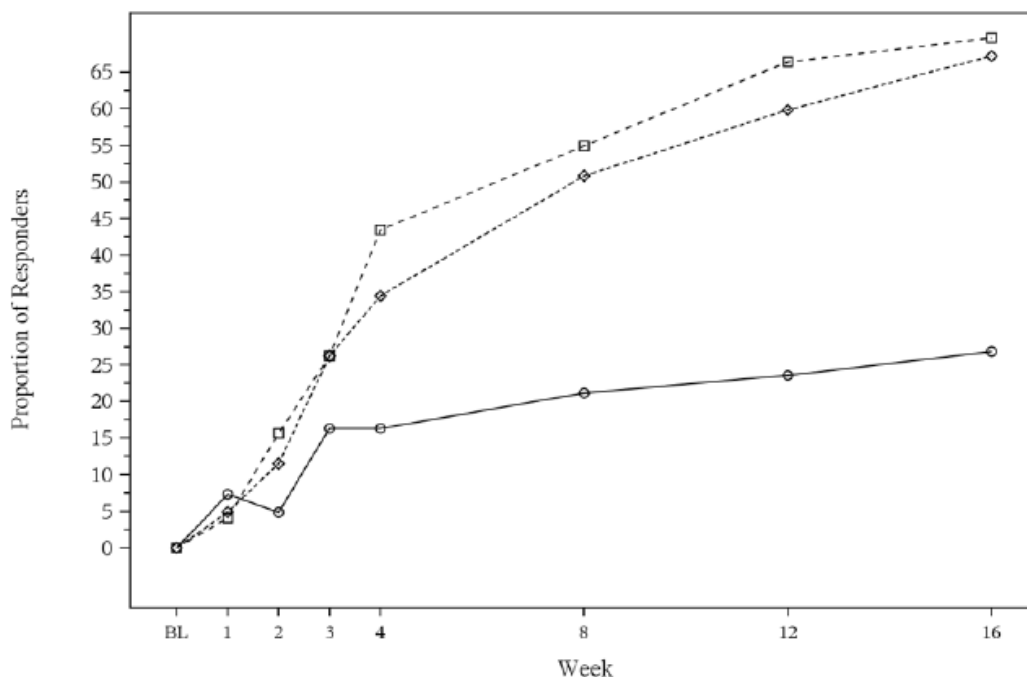
Table 6: The proportion of patients achieving IGA 0 or 1 and EASI-75 at Week 16 in Study 1652 – overall trial and weight groups

	N	Number (%) meeting criterion at Week 16	Difference vs. placebo % (95% CI)	P-value vs. placebo
IGA 0 or 1				
Dupilumab 100 or 200 mg Q2W	122	36 (29.5)	18.1 (8.28, 27.97)	0.0004
Dupilumab 300 mg Q4W	122	40 (32.8)	21.4 (11.36, 31.45)	<0.0001
Placebo	123	14 (11.4)	-	-
IGA 0 or 1 <30kg				
Dupilumab 100 mg Q2W	63	13 (20.6)	NR	0.2663
Dupilumab 300 mg Q4W	61	18 (29.5)	NR	0.0277
Placebo	61	8 (13.1)	-	-
IGA 0 or 1 ≥30kg				
Dupilumab 200 mg Q2W	59	23 (39.0)	NR	0.0002
Dupilumab 300 mg Q4W	61	22 (36.1)	NR	0.005
Placebo	62	6 (9.7)	-	-
EASI-75				
Dupilumab 100 or 200 mg Q2W	122	82 (67.2)	40.4 (28.95, 51.82)	<0.0001
Dupilumab 300 mg Q4W	122	85 (69.7)	42.8 (31.54, 54.14)	<0.0001
Placebo	123	33 (26.8)	-	-
EASI-75 <30kg				
Dupilumab 100 mg Q2W	63	38 (60.3)	NR	0.0003
Dupilumab 300 mg Q4W	61	46 (75.4)	NR	<0.0001
Placebo	61	17 (27.9)	-	-
EASI-75 ≥30kg				
Dupilumab 200 mg Q2W	59	44 (74.6)	NR	<0.0001
Dupilumab 300 mg Q4W	61	39 (63.0)	NR	<0.0001
Placebo	62	16 (25.8)	-	-

Source: Table 2-11, p87; Table 2-12, p89; Table 2-27, p125 of the submission.

CI = confidence interval; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NR = not reported; Q2W = every two weeks; Q4W = every four weeks

Figure 1: Proportion of patients achieving EASI 75 through Week 16 in Study 1652 (overall trial population)



	Treatment		Placebo (N=123)		Q4W (N=122)		Q2W (N=122)	
	0	1	0	1	0	1	0	1
Placebo (N=123)	0	9(7)	6(5)	20(16)	20(16)	26(21)	29(24)	33(27)
Q4W (N=122)	0	5(4)	19(16)	32(26)	53(43)	67(55)	81(66)	85(70)
Q2W (N=122)	0	6(5)	14(11)	32(26)	42(34)	62(51)	73(60)	82(67)

Note: Values after first rescue treatment used were set to missing. Patients with missing score at each visit were considered as a non-responder

Source: Figure 2-6, p90 of the submission.

EASI = Eczema Area and Severity Index; Q2W = every two weeks; Q4W = every four weeks

6.19 All comparisons, with the exception of the comparison of dupilumab 100 mg Q2W and placebo in the <30 kg weight group for the proportion with IGA of 0 or 1, showed a statistically significant advantage for dupilumab compared to placebo. All comparisons were dupilumab versus placebo, and there was no comparison of dupilumab Q2W and Q4W dosing.

6.20 In regard to the weight categories, the submission claimed advantages for dupilumab 300 mg Q4W for patients <30kg, and advantages for dupilumab 200 mg Q2W in patients weighing ≥30kg for EASI and IGA outcomes. These claims were made on the basis of visual comparisons of data, as there were no statistical analyses comparing the different dupilumab dosing regimens in the weight groups.

Comparative harms

6.21 There was no safety data presented for the post-hoc subgroup of Study 1652. Safety data was available for the overall trial and for the weight groups. Overall adverse events and events of special interest, including conjunctivitis and injection site reactions, are provided in the table below.

Table 7: Summary of key adverse events in Study 1652 – overall trial population

Study 1652	Dupilumab 100 or 200 mg Q2W (N=122)	Dupilumab 300 mg Q4W (N=120)	Placebo (N=120)
AE summary			
TEAE	82 (67.2%)	78 (65.0%)	88 (73.3%)
Drug related TEAE	30 (24.6%)	24 (20.0%)	13 (10.8%)
TEAE leading to discontinuation	2 (1.6%)	0	2 (1.7%)
Death	0	0	0
TESAE	0	2 (1.7%)	2 (1.7%)
Drug related TESAE	0	0	0
TESAE leading to discontinuation	0	0	0
Conjunctivitis and injection site reaction			
Number with at least one conjunctivitis event	18 (14.8%)	8 (6.7%)	5 (4.2%)
Conjunctivitis	7 (5.7%)	5 (4.2%)	3 (2.5%)
Conjunctivitis allergic	5 (4.1%)	3 (2.5%)	1 (0.8%)
Conjunctivitis bacterial	5 (4.1%)	0	1 (0.8%)
Conjunctivitis viral	1 (0.8%)	0	0
Number with at least one injection site reaction event	13 (10.7%)	12 (10.0%)	7 (5.8%)

Source: Table 2-19, p107; Table 2-23, p114 of the submission

AE = adverse event; SAE = serious adverse event; TEAE = treatment emergent adverse event; TESAE = treatment emergent serious adverse event

- 6.22 There were no deaths in Study 1652, and no drug-related serious adverse events (SAEs), or SAEs leading to discontinuation. There were two placebo-treated patients (1.7%) and two dupilumab-treated patients (1.6%) who discontinued due to an AE. Conjunctivitis and injections site reactions occurred more frequently in the dupilumab arms of the trial. The cost of conjunctivitis management was included in the economic model.
- 6.23 There was considerable additional literature available on ocular AEs associated with dupilumab, including those in a paediatric population (Siegfried 2019³; McKenzie 2021⁴; Muzumdar 2020⁵; Barbieri 2021⁶; Napolitano 2021⁷; Ferreira 2020⁸; Raffi

³ Siegfried EC, Igelman S, Jaworsk JC, Antaya RJ et al. Use of dupilumab in pediatric atopic dermatitis: Access, dosing and implications for managing severe atopic dermatitis. *Pediatr Dermatol* 2019; 36(1): 172-176.

⁴ McKenzie PL, Rangu S, Treat JR, Castelo-Soccio L. Experience using dupilumab for pediatric atopic dermatitis at a tertiary care center: Inadequate response and adverse events. *Pediatric Dermatol* 2021; 38(5): 1178-1184.

⁵ Muzumdar S, Zubkov M, Waldman R, DeWane ME et al. Characterizing dupilumab facial redness in children and adolescents: A single-institution retrospective chart review. *J Am Acad Dermatol* 2020; 83(5): 1520-1521.

⁶ Barbieri JS, Bunya VY, Massaro-Giordano M, Margolis DJ. Encounters and medication use for ocular surface disorders among patients treated with dupilumab: a cohort study. *J Am Acad Dermatol Int* 2021; 4(3): 1-9.

⁷ Napolitano M, Di Guida A, Fabbrocini G, Patrino C. Ocular adverse events in patients with atopic dermatitis undergoing treatment with dupilumab: An Italian single-center experience. *Dermatol Ther* 2021; 34(5): e15059.

⁸ Ferreira F, Torres T. Conjunctivitis in patients with atopic dermatitis treated with dupilumab. *Drugs in Context* 2020; 9: DOI: [10.7573/dic.2020-2-3](https://doi.org/10.7573/dic.2020-2-3)

2019⁹). There were also reports of facial redness (Kamata 2021¹⁰) and eosinophilia (Francuzik 2021¹¹).

Benefits/harms

6.24 A summary of the comparative benefits and harms for dupilumab versus placebo is presented in the table below.

Table 8: Summary of comparative benefits and harms for dupilumab and placebo – severe paediatric AD

Benefits						
Outcome	Dupilumab	Placebo	RR (95% CI)	Events/100 patients		RD, % (95% CI)
				Dupilumab	Placebo	
EASI 75 response at Week 16 – overall trial population						
Dupilumab 100 or 200 mg Q2W	82/122	33/123	2.5 (1.8, 3.4)	67.2	26.8	40.4 (28.9, 51.8)
Dupilumab 300 mg Q4W	85/122	33/123	2.6 (1.9, 3.6)	69.7	26.8	42.9 (31.6, 54.2)
EASI 50 and CDLQI4 <30 kg						
Dupilumab 300 mg Q4W	50/61	8/29	3.0 (1.6, 5.4)	82.0	27.6	54.4 (35.5, 73.3)
EASI 50 and CDLQI4 30 - 60 kg						
Dupilumab 200 mg Q2W	40/56	8/27	2.4 (1.3, 4.4)	71.4	29.6	41.8 (20.9, 62.7)
Harms – overall trial population						
	Dupilumab	Placebo	RR (95% CI)	Events/100 patients		RD (95% CI)
				Dupilumab	Placebo	
Conjunctivitis	26/242	5/120	2.68 (1.02, 6.6)	10.7	4.2	6.5 (1.2, 11.8)
Injection site reaction	25/242	7/120	1.8 (0.8, 4.0)	10.3	5.8	4.5 (-1.2, 10.2)

Source: compiled during the evaluation

AD = atopic dermatitis; CI = confidence interval; EASI = Eczema Area and Severity Index; Q2W = every two weeks; Q4W = every four weeks; RD = risk difference; RR = risk ratio

6.25 On the basis of direct evidence presented by the submission, for every 100 patients treated with dupilumab in comparison to placebo over 16 weeks of treatment:

- Approximately 40 to 43 additional patients with severe AD would have at least a 75% improvement in EASI score from baseline;
- Approximately 42 to 54 additional patients would have at least a 50% improvement in EASI AND a 4 point improvement in CDLQI score from baseline;
- Approximately 7 additional patients with severe AD will experience conjunctivitis;
- Approximately 5 additional patients with severe AD will experience an injection site reaction.

Clinical claim

6.26 The submission described dupilumab as superior in terms of effectiveness compared with placebo. In regard to safety, the submission described dupilumab as having a

⁹ Raffi J, Suresh R, Fishman H, Botto N et al. Investigating the role of allergic contact dermatitis in residual ocular surface disease on dupilumab (ROSSD). *Int J Women's Dermatol* 2019; 5: 308-313.

¹⁰ Kamata M and Tada Y. A literature review of real-world effectiveness and safety of dupilumab for atopic dermatitis. *JID Innovations* 2021; 1:100042.

¹¹ Francuzik W, Alexiou A, Worm M. Safety of dupilumab in patients with atopic dermatitis: expert opinion. *Expert Opin Drug Saf* 2021; 20(9): 997-1004.

similar safety profile, with the exception of injection site reactions and conjunctivitis, compared with placebo.

- 6.27 The therapeutic conclusion presented in the submission is adequately supported by the evidence presented in the submission. All comparisons of effectiveness, with the exception of one (proportion with IGA 0 or 1 in the <30 kg weight group), showed a statistically significant advantage for dupilumab compared to placebo. The submission presented no evidence specific to the ≥ 60 kg weight group, however the ESC considered that effectiveness in this group is likely to be consistent with evidence in the paediatric population <60kg and the evidence previously considered for the adult/adolescent population.
- 6.28 In its consideration of dupilumab for an adult population in July 2018, the PBAC considered that the efficacy and safety claims were only reasonable for up to 16 weeks of treatment (para 6.36, July 2018 dupilumab PSD). While the submission has applied adult data in the model beyond 16 weeks, there was no longer-term evidence for the use of dupilumab in AD for the paediatric population.
- 6.29 Given recent literature addressing the risk of conjunctivitis with dupilumab and the inclusion of conjunctivitis costs in the economic model, along with publications addressing AEs in a paediatric population being treated for AD (e.g. McKenzie 2021; Muzumdar 2020; Parker 2021) it remains reasonable for the safety claim to be one of inferiority and this was accepted in the PSCR.
- 6.30 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.31 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.32 The submission presented a Markov cohort model that was adapted for a paediatric population from the March 2020 model for adults. As for the March 2020 model for adults, the type of economic evaluation was a cost-utility analysis. The submission listed the following changes from the March 2020 model:
- Patient demographics have been updated to reflect the population in Study 1652. The patient demographics applied in the model do not reflect the Study 1652 post-hoc subgroup that provided the efficacy data.
 - Response rate was based on Study 1652 (change in CDLQI of at least 4 points and proportion of patients with EASI 50 over the first 16 weeks of the model. The model also includes use of adult data from CHRONOS for Week 42 responses and from the SOLO trials for utility values.
 - Results of a new paediatric resource use survey.
 - All costs were updated to October 2021 values.
 - The rates of conjunctivitis were changed to those from Study 1652. The rates of conjunctivitis applied in the model were from the overall trial population.

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- Use of a weighted DPMQ to reflect Q4W dosing for patients weighing 15 to 30 kg. The weighted price accommodates the Q4W dose of dupilumab that cannot be used in the model, however it would have been more informative had the model been designed to use the doses of dupilumab that are being requested for PBS listing, and that were used in the clinical evidence.
- 6.33 The requested cost per patient for dupilumab in paediatric patients was similar to that for adult patients (\$| versus \$| per 2 weeks of treatment) however, the estimated ICER was substantially lower (\$25,000 to < \$35,000/QALY versus \$45,000 to < \$55,000/QALY). This was largely due to differences in non-drug health care resource use (see

- 6.34 Table 9). The Pre-PBAC response argued that this reflects differences in the clinical treatment practices between adult and paediatric patients. Following is a table outlining the values and components used in the paediatric and March 2020 adult model, including the estimated impact on the ICER of the changes.

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Table 9: Impact of changes from the March 2020 adult AD model

	Paediatric model		Adult model		Impact on ICER
Baseline characteristics					
Gender (% male)	49.9%		60%		-0.07%
Age (years)	8.5		38		
Patient weight	31.5 kg		75 kg		
Week 16 response					
Dupilumab	76.9%		59.6%		-1.7%
Placebo	28.6%		19.9%		
Health resource use survey – number of services per year					
	Responder	Non-responder	Responder	Non-responder	-30.97%
Primary care visit	4.5	10.8	3.3	8.1	
Specialist visit	3.0	7.9	3.5	7.6	
Emergency room visit	0.4	3.3	0.1	1.5	
Hospitalisations	0.1	1.9	0.1	1.0	
Phototherapy treatments	3.6	25.3	36.6	93.1	
TCl prescriptions	5.6	11.1	8.7	16.1	
Oral antibiotics	1.2	5.1	1.6	4.5	
Resource use costs	2021 values		2020 values		-0.01%
Conjunctivitis – annual events					
	Responder	Non-responder	Responder	Non-responder	-0.34%
Dupilumab	0.11	0.11	0.44	0.0	
Placebo	0.04	0.04	0.0	0.0	
Utility values					
Baseline (both arms)	0.637		0.60		0.88%
Week 0-16 (before response assessed)	Dupi = 0.845 ^a Placebo = 0.678		Dupi = 0.847 Placebo = 0.686		
Week 16 responders (both arms)	0.929 ^a		0.910		
Week 44 responders (both arms)	0.827 ^a		0.790		
Drug cost					
Requested DPMQ	Q2W: \$ ¹ ; Q4W: \$ ¹		Q2W: \$ ¹		-
DPMQ, per 2 weeks of treatment	\$ ¹		\$ ¹		-3.31%
ICER/QALY					
Base case	\$ ¹		\$ ²		-

Source: Table 3-1, p174 of the submission

DPMQ = dispensed price maximum quantity; Dupi = dupilumab; Q2W = every two weeks; Q4W = every four weeks; TCl = topical calcineurin inhibitors;

^a Table 3-1 of the submission had the Week 0-16 utility for dupilumab as 0.847, and for placebo 0.680, however the model used the values 0.845 and 0.678, respectively. The latter values were also reported in Table 3-7 of the submission. Similarly, for Week 16 responder utility Table 3-1 reported 0.931, however the model used 0.929, and 0.929 is also reported in Table 3-7 of the submission. Finally, for Week 44 responders Table 3-1 had the value 0.829, but the model and Table 3-7 have the value 0.827.

^b The proposed ex-manufacturer price is the same per patient per year but Q4W dosing reduces supply chain costs for some patients.

^c Base case ICER for the March 2020 model corrected for an error in applying non-conditional probabilities to derive Week 42 response.

The redacted values correspond to the following ranges:

¹\$25,000 to < \$35,000

²\$45,000 to < \$55,000

6.35 The table below provides a summary of the key components of the current paediatric model, along with a summary of the March 2020 adult model that the current paediatric model was based on.

Table 10: Summary of model structure, key inputs and rationale

Component	March 2020 adult model	Current paediatric model
Type of analysis	Cost-utility analysis	Cost-utility analysis
Comparator	Placebo for SoC	Placebo
Outcomes	% of patients with DLQI4 and EASI 50, life years, quality adjusted life years, resource utilisation	% of patients with CDLQI4 or DLQI and EASI 50, quality adjusted life years, resource utilisation
Clinical evidence	PGA=4 and EASI ≥20 sub-group of CHRONOS, SOLO 1, SOLO 2 & Study 1021 for Week 16 response rates and CHRONOS (Week 44 data) for Week 42 response rates.	Post-hoc subgroup of Study 1652 including only patients weighing ≤60 kg; maintenance response data from the adult CHRONOS trial, and utility values from the adult SOLO trials.
Time horizon	5 years	5 years
Method(s) used to generate results	Markov cohort model (with a prior decision tree for initial treatment and the first cycle of maintenance treatment)	As per March 2020
Health states	Four possible health states: <ul style="list-style-type: none"> • Induction treatment (16 weeks) • Responder (CDLQI4 and EASI 50) • Non-responder (change in CDLQI < 4 points from baseline and/or change in EASI score <50% from baseline) • All-cause death 	As per March 2020
Cycle length ^a	6 months	As per March 2020
Transition probabilities	% of patients with response (DLQI4 and EASI 50), maintenance of response (DLQI4 and EASI 50), All-cause death: Age and sex specific Australian mortality rates (Australian life tables)	As per March 2020, with the exception that Week 16 response used CDLQI instead of DLQI

Source: Table 3-2, p175-176 of the submission; Table 12, p21 of the March 2020 dupilumab PSD.

CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; SoC = standard of care

^a For the Markov component of the model.

6.36 The data sources applied in the economic model included both paediatric and adult sources, with adult response data used beyond Week 16 and for all utility values. The pre-PBAC response (p1) argued that in the absence of paediatric-specific values the use of adult values was appropriate and adequately captures the benefits of dupilumab therapy in paediatric patients. While the baseline disease characteristics were sourced from the overall trial population of Study 1652, response data was sourced from a post-hoc subgroup. The following table outlines the clinical evidence applied in the model.

Table 11: Evidence sources used in the model

Variable	Source	Paediatric or adult
Patient characteristics	Demographic data from the Study 1652 overall trial population (N=367)	Paediatric
Week 16 response rate	EASI 50 and CDLQI post-hoc subgroup with weight groups lumped together (N=173)	Paediatric
Week 42 response rate and ongoing maintenance	CHRONOS	Adult
Discontinuation	SOLO trials (rate cannot be confirmed)	Adult
Utility values for baseline, responders; non-responders	Adult data sourced from post-hoc analysis of SOLO1 and SOLO2 for 18 to 25 year olds; CHRONOS	Adult
Background mortality	Australian life table data, age and gender-adjusted	Paediatric
Conjunctivitis	Number of events used to calculate treatment cost – Study 1652 Treatment episodes – clinician survey	Paediatric Adult
Other resource use	Clinician survey	Paediatric

Source: Section 3.3 – Section 3.6, p181-194 of the submission.

CDLQI = Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index

- 6.37 The submission stated that as the Week 16 responses were similar between Study 1652 and CHRONOS, there was no clinical rationale to suggest maintenance of response will differ between adults and children. There was no evidence presented to demonstrate that maintenance of response will not differ between adults and children. The PSCR noted that if maintenance of response was lowered or raised by 10% in sensitivity analysis, the impact on the ICER was minor (ICER only changed by approximately \$1,000).
- 6.38 The PSCR acknowledged (p3) that baseline utility values may differ between adult and paediatric patients and argued that, as quality of life impacts on the ICER are driven by the change in utility following initiation of treatment, it is reasonable to assume that any change in utility would be similar for patients responding to therapy regardless of age or baseline utility value. No evidence was presented to support the assumption that the change in utility will be the same for adults and paediatric patients.
- 6.39 The submission pooled together results for the two weight groups from Study 1652. There was no evidence used in the model for the ≥ 60 kg weight group. There were no between-trial-arm comparisons provided for Study 1652, and it may not be reasonable to assume the results are statistically the same across weight groups. The results for the proportion with EASI 50 and CDLQI4 in the < 30 kg and 30–60 kg weight groups in Study 1652 were numerically different for the dupilumab group. Those results are provided in the table below.

Table 12: Probability of Week 16 response for each weight group in Study 1652

Response	Dupilumab <30 kg	Dupilumab 30 – 60 kg
EASI 50 and CDLQI4 response at Week 16	50/61 (82.0%)	40/56 (71.4%)
	Weight groups combined	
EASI 50 and CDLQI4 response at Week 16	90/117 (76.9%)	

Source: Table 1.5, p11 of AD162_Australia_request26APR2021_30APR21 in Attachment 5 of the submission.

CDLQI = Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index

6.40 The response rates used across the model duration are provided in the table below. For Years 2 to 5 the submission applied values from the adult CHRONOS trial, which were based on a regression approach using time to first rescue treatment or withdrawal in the CHRONOS trial. The data were applied as an annual proportion of patients that had not required rescue or withdrawn from the trial, which the submission considered to be an appropriate proxy for the maintenance of effect. Maintenance of response applied in the paediatric model was based on the same probability of response as was applied in the adult and adolescent model in years two to five.

Table 13: Probability of response applied in the model

Response	Dupilumab	Placebo	Source
EASI 50 and CDLQI response at Week 16	76.9%	28.6%	Study 1652 subgroup
EASI 50 and DLQI response at Week 42, conditional on response at Week 16	73.6%	19.1%	CHRONOS Week 44 data
Year 2	83.2%	52.0%	CHRONOS (proportion of patients that had not required rescue or withdrawn from trial)
Year 3	79.9%	10.3%	
Year 4	77.2%	6.2%	
Year 5	74.8%	3.9%	

Source: Table 3-5, p184; Table 3-6, p187 of the submission.

CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index

6.41 In its consideration of the adult model in March 2020, the ESC had noted that in the regression analysis used to estimate continued response, the full data set from CHRONOS from baseline was applied for the SOC (i.e. placebo) arm, whereas only data for patients who met the efficacy endpoint at 16 weeks was used for the dupilumab arm. The ESC previously considered the maintenance of response rates from these different approaches was not comparable and this approach favoured dupilumab. The ESC noted that the same concern would apply to the response rates applied in the current model. The ESC noted that the proportion of patients responding in the model dropped sharply in the placebo arm in the first 2 years. Further, the ESC considered that the baseline level of sustained response for paediatric patients is likely to be higher than that in the adult/adolescent population based on the natural history of AD in this population.

6.42 The absolute reduction in response and proportions of responders at each time point as applied in the paediatric model are shown in

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- 6.43 Table 14. Figure 2 compares the proportion of responders in each population in the paediatric submission and adult populations from the March 2020 pre-PBAC response.

Table 14: Absolute reduction in response to both arms at Year 2 – paediatric model

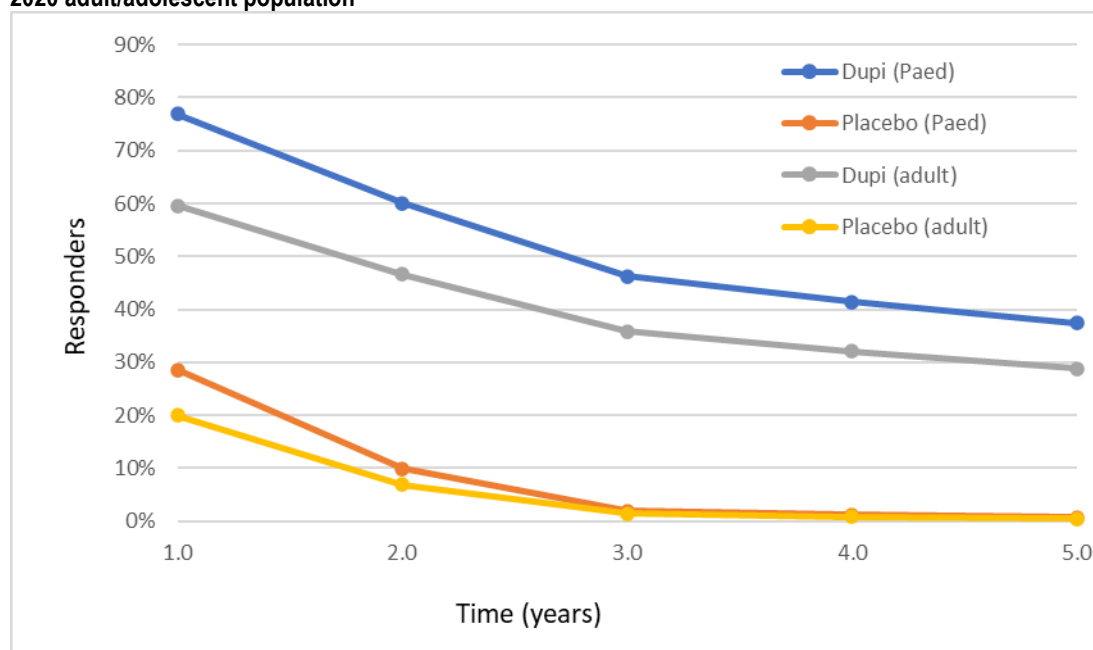
Percent responding - start of cycle	Dupilumab	Placebo	Difference	% change dupilumab (absolute)	% change placebo (absolute)
Year 1	73.58% ^a	19.05% ^b	54.53%		
Year 2 ^c	60.10%	9.90%	50.20%	-13.48%	-9.15%
Year 3 ^c	46.29%	1.96%	44.33%	-13.81%	-7.94%
Year 4 ^c	41.41%	1.18%	40.23%	-4.88%	-0.78%
Year 5 ^c	37.37%	0.74%	36.63%	-4.04%	-0.44%

^a Week 16 proportion of 76.9% multiplied by Week 44 proportion of 95.7%.

^b Week 16 proportion of 28.6% multiplied by Week 44 proportion of 66.7%.

^c The Year 2 to 5 proportion responding is the proportion who maintained treatment at the end of the previous year. This was calculated as the proportion responding in the previous year multiplied by probability of death multiplied by probability of response multiplied by probability of discontinuation minus sustained remission. As an example, the values used to calculate 60.10% are provided here: $60.10 = 73.58 \times (1 - \text{probability death life table}) \times 83.2\% \times (1 - 1.81\%) - 0.00$.

Figure 2. Trace of proportion of modelled cohort in responder health state for paediatric population and November 2020 adult/adolescent population



Source: constructed based on data from March 2020 dupilumab pre-PBAC response and Dupilumab paediatric model “traces” worksheet.

6.44 The ESC noted that the proportion of patients responding in the model dropped sharply in the placebo arm in the first 2 years of the model. The ESC noted that natural resolution of AD (sustained response) for paediatric patients is likely to be higher than that in the adult/adolescent population based on the natural history of AD in this population. The ESC considered that a 20-30% natural resolution rate might be reasonable, compared to the model in which almost all SoC patients were classed as non-responders by 5 years. The submission presented a sensitivity analysis, where 63.6% of patients have sustained response and cease dupilumab after 52 weeks of therapy, and 52.4% of these patients experienced a relapse and recommenced dupilumab treatment after a mean of approximately 24 weeks (overall 30.3% or patients have sustained response and do not continue treatment). The ESC noted that

the limitation of this sensitivity analysis was that it assumed that all patients with sustained response ceased dupilumab treatment after 52 weeks, whereas in clinical practice this would be unlikely to occur. The proportions for this sensitivity analysis were sourced from the open-label Study 1434, which included 33 patients from Study 1412, a weight-based (2mg/kg or 4mg/kg dose) phase 2a pharmacokinetic study, and 6 patients from Study 1652. The proportion with sustained response was based on the 33 patients from Study 1412. The ESC noted this increased the ICER to \$35,000 to < \$45,000/QALY.

- 6.45 The ESC noted that other non-treatment health state costs were based on mean values from a clinician survey that included unrealistic outlier values (for example up to 70 primary care consultations, 50 specialist consultations, 30 emergency room visits and 20 hospitalisations per year for uncontrolled patients). In addition, the ESC considered that costs for hospitalisations (\$3,497 per hospitalisation) appeared high and may have represented more complex or extended duration than would be expected for AD-related hospitalisations. The ESC noted that the non-treatment health state costs generated significant cost offsets in the model and appeared to be substantially overestimated. Reducing the non-treatment health state medical treatment costs (subcutaneous injection training, doctor visits, ER and hospitalisation costs) by 50% increased the ICER to \$55,000 to < \$75,000 /QALY.
- 6.46 The ESC noted that the estimates for phototherapy costs from the clinician survey also included outliers (up to 36 courses per year along with duration of up to 30 weeks per course) which suggested double counting of phototherapy costs. Further, the ESC considered that the inclusion of phototherapy costs for paediatric patients was not appropriate as patients of this age are unlikely to be treated with phototherapy. In the sponsor's clinician survey, 43% of clinicians reported they would treat 0% of children with phototherapy, and 19% would treat 5% or fewer of their patients with phototherapy. Removing phototherapy costs resulted in an ICER of \$35,000 to < \$45,000/QALY. The PBAC considered that inclusion of some costs for phototherapy may be reasonable as a small number of clinicians may use phototherapy in patients considered to be suitable, however the mean value of 25.3 services per year for non-responders appeared to be substantially overestimated. In addition, the PBAC noted that other health resource costs based on mean values from the clinician survey generated significant cost offsets, and appeared to be overestimated, particularly hospitalisations and emergency room visits.
- 6.47 In the July 2020 adult model the key drivers were considered to be time horizon, maintenance of response from Year 2 onward, and health state costs including phototherapy. Similar key drivers are associated with the paediatric model. A summary of the key drivers of the economic model is provided in the table below.

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Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: \$/QALY
Time horizon	5 years, as per the adult model.	High, favours dupilumab. ICER increases to \$ ² when time horizon is shortened to one year.
Clinical evidence	Only Week 16 response was sourced from a paediatric population. Maintenance of response and utility values are sourced from adult data.	Cannot be tested as there is no paediatric data available
Utilities	Utility values sourced from an adult population (SOLO trials) with no consideration of possible differences in utility for children and adults.	Cannot be tested
Cost of phototherapy	Based on number of course of treatment, number of treatments per week and weeks of phototherapy sourced from the clinician survey.	Moderate, favours dupilumab. ICER increases to \$ ³ when phototherapy costs are removed.
Other healthcare costs	Based on mean values from clinician survey for paediatric patients.	High, favours dupilumab. ICER increases to \$ ² when other healthcare costs are decreased by 50%.

Source: Section 3.4 to Section 3.6, p184-194 of the submission.

The redacted values correspond to the following ranges:

¹\$25,000 to < \$35,000

²\$55,000 to < \$75,000

³\$35,000 to < \$45,000

6.48 Results of the stepped economic evaluation are provided below.

Table 16: Results of the stepped economic evaluation

Step and component	Dupilumab	Placebo	Increment
Step 1: trial-based analysis			
Costs (\$)			
% with response	76.92%	28.57%	48.35%
Incremental cost/responder (\$)			
Step 2: time horizon extended to 42 weeks			
Costs (\$)			
% with response	73.58%	19.05%	54.53%
Incremental cost/responder (\$)			
Step 3: extrapolated to 5 years (base case)			
Costs (\$)			
% with response	33.82%	0.74%	33.08%
Incremental cost/responder (\$)			
QALYs	3.88	3.49	0.3926
Incremental cost/extra QALY gained (base case) (\$)			

Source: Table 3-13, p195-196 of the submission.

6.49 Results of sensitivity analyses are provided in the table below.

Table 17: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)
Base case		0.3926	1
Probability EASI 50 and CDLQI response at 16 weeks (base case: dupilumab 76.9%; placebo 28.6%)			
Dupilumab lower 95% CI 69.3%		0.35	1
Dupilumab upper 95% CI 84.6%		0.43	1
EASI 50 and CDLQI6 at 16 weeks		0.35	1
Health care resource use survey (base case: paediatric)			
Adult survey		0.39	2
Removal of phototherapy costs		0.39	2
Health state (medical treatment) costs (subcutaneous injection training, doctor visits, ER and hospitalisation costs)			
Decreased by 50% per year		0.39	3
Increased by 50% per year		0.39	4
Time horizon (base case: 5 years)			
1 year		0.10	5
10 years		0.55	6
Discount rate (base case: 5%)			
0%		0.43	1
3.5%		0.40	1
Sustained response (base case: not included) in both arms			
63.6% have sustained response at Week 52 and stop treatment; 52.4% relapse and recommence treatment ^a		0.25	2
63.6% have sustained response at Week 52 and stop treatment; 80% relapse and recommence treatment ^b		0.33	6
50.0% have sustained response at Week 52 and stop treatment; 52.4% relapse and recommence treatment ^c		0.28	6

Source: Table 3-16, p199-200 of the submission.

CDLQI = Child Dermatology Life Quality Index; CI = confidence interval; DLQI = Dermatology Life Quality Index; EASI = Eczema area and severity index; ER = emergency room

^a Proportions result in 30.3% in both arms having sustained response and not resuming treatment.

^b Proportions result in 12.7% in both arms having sustained response and not resuming treatment.

^c Proportions result in 23.8% in both arms having sustained response and not resuming treatment.

The redacted values correspond to the following ranges:

¹\$25,000 to < \$35,000

²\$35,000 to < \$45,000

³\$55,000 to < \$65,000

⁴\$0 to < \$5,000

⁵\$65,000 to < \$75,000

⁶\$25,000 to < \$35,000

6.50 The model result was not sensitive to changes in the probability of response at Week 16 (such as using the alternate EASI 50 and CDLQI6 outcome), rate of discontinuation, discount rate, the proportion >30 kgs, and utility gain for EASI 50 and CDLQI response. The model result was sensitive to the time horizon and health care resource use. Using inputs from the adult health care resource use survey instead of the paediatric survey increased the ICER to \$35,000 to <\$45,000/QALY. This increase was likely due to the different responder and non-responder values used across the paediatric and adult surveys, with differences being greater in the paediatric survey for all items except phototherapy treatment and TCS/TCI prescriptions. The pre-PBAC response (p1) argued that it was not appropriate to use adult health resource use estimates when paediatric-specific data were available.

6.51 Noting that the base case health state costs appeared substantially overestimated, and included significant offsets for phototherapy treatment, the ESC considered that the base case ICER appeared underestimated. The ESC noted that the ICER increased to \$65,000 to <\$75,000/QALY when the model assumed 30.3% in both arms had a sustained response and did not resume treatment, no phototherapy costs and health state costs decreased by 50%. Multivariate sensitivity analyses are shown in Table 18.

Table 18: Results of multivariate sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)
Base case		0.3926	1
Removal of phototherapy costs and sustained response			
No phototherapy costs included plus 63.6% have sustained response at Week 52 and stop treatment; 52.4% relapse and recommence treatment		0.25	2
Removal of phototherapy costs and change in health state (medical treatment) costs			
No phototherapy costs included and medical treatment cost decreased by 50%		0.39	3
No phototherapy costs included and medical treatment cost increased by 50%		0.39	4
Sustained response in both arms, no phototherapy costs and health state (medical treatment) costs decreased by 50%			
63.6% have sustained response at Week 52 and stop treatment; 52.4% relapse and recommence treatment ^a , no phototherapy costs and health state costs decreased by 50%		0.25	5

Source: Table 3-16, p199-200 of the submission; Excel workbook 'Dupilumab (Dupixent) Paediatric AD Economic Model'.

^a Presented in the submission and in Table 3.9.1, 6.03.COM.92; proportions result in 30.3% in both arms having sustained response and not resuming treatment.

The redacted values correspond to the following ranges:

¹\$25,000 to < \$35,000

²\$35,000 to < \$45,000

³\$55,000 to < \$65,000

⁴\$5,000 to < \$15,000

⁵\$65,000 to < \$75,000

Drug cost/patient/year

Table 19: Drug cost per patient for dupilumab

	Trial dose and duration	Model	Financial estimates
Dupilumab			
Dose	100 or 200 mg Q2W 300 mg Q4W; 16 weeks	200 mg Q2W (with 200 mg Q2W and 300 mg Q4W weighted by body weight)	200 mg Q2W 300 mg Q4W
Cost/patient/month ^a (\$)	100 or 200 mg Q2W: █ 300 mg Q4W: █	█ (4 weeks)	200 mg Q2W: █ 300 mg Q4W: █
Cost/patient/year ^a (\$)	100 or 200 mg Q2W: █ 300 mg Q4W: █		200 mg Q2W: █ 300 mg Q4W: █

Source: Table 3-9, p190 of the submission; worksheet '3a. Scripts proposed' of the Excel workbook 'Dupilumab (Dupixent) Paediatric AD Utilisation Workbook'.

Q2W = every two weeks; Q4W = every four weeks

^a Costing for the trial and financial estimates assumed 100% compliance. Cost included loading dose of 400 mg for Q2W dosing (2 injections) and 600 mg for Q4W dosing (2 injections).

6.52 The cost per patient was consistent across the trial, model and financial estimates.

Estimated PBS usage & financial implications

6.53 This submission was not considered by DUSC. The submission applied an epidemiological approach to the financial estimates. The table below summarises the inputs used for the financial estimates.

Table 20: Key inputs for financial estimates

Component	Data source
Epidemiology	
Prevalence data	<u>Paediatric population</u> : ABS 3222.0 Series B individuals aged 6 to 11 years inclusive 2022 to 2027. <u>Prevalence of AD</u> : 9%, sourced from Metis 2019a market research. This was a sample of N = 103 moderate to severe AD patients, and the 9% value was for patients diagnosed with either dermatitis, eczema or AD not caused by food allergy.
Eligible patients	<u>Severe AD</u> : 5%, sourced from Metis 2019a market research. <u>Specialist engagement</u> : 100% - sponsor assumption based on July 2019 DUSC advice, (7.05.DUSC ADV.4). <u>Uncontrolled with existing therapy</u> : 100% - sponsor assumption based on Table 19 of the March 2020 PSD. <u>EASI score ≥21</u> : 95% - consistent with adult and adolescent PBS listing and trial eligibility criteria for Study 1652, with the 95% sourced from the sponsor's adult early access programs. <u>Proportion receiving Q2W or Q4W dosing</u> : Based on the proportion in Study 1652 weighing 15 kg to 30 kg (52%; 300 mg Q4W), 30 kg to 60 kg (48%; 200 mg Q2W) and >60kg (0%), the submission estimated the number receiving treatment with 200 mg Q2W and 300 mg Q4W.
Utilisation	
Uptake and treatment	<u>Uptake</u> : Year 1: 7%; Year 2: 6%; Year 3: 5.5%; Year 4: 5%; Year 5: 4%; Year 6: 4%; sponsor assumption. <u>Grandfathered patients</u> : The submission assumed there would be approximately 50 grandfathered patients that will be sourced from patients receiving dupilumab privately, or as part of the sponsor's early access programs. <u>Response rates</u> : The Week 16 response rate was 76.9%, which was sourced from the post-hoc subgroup of Study 1652. The Week 42 response rate was 73.6% (i.e. 95.7% of those who respond at Week 16 (76.9% × 95.7% = 73.6%)). The 95.7% rate was sourced from the CHRONOS adult trial. <u>Persistence</u> : Responders at Week 42 become continuing patients in the following year. The probability of sustained response after Week 42 was sourced from the CHRONOS trial, using a regression approach.
Number of scripts	Script numbers were calculated by weight category, i.e., 15 to <30 kg and 30 to <60 kg. <u>First year of treatment</u> : Consisted of an initiation script and the first maintenance script. There are three potential outcomes for patients in the first year of therapy (all rates are sourced from the adult CHRONOS trial: 1) Fail to respond to initiation script: 23% are expected to fail to respond (1-Week 16 responders 77%). 2) Fail to respond to maintenance script: 3.3% 3) Maintain response: 73.6% <u>Subsequent years of treatment</u> : Q2W patients: 13.04 packs per year; Q4W patients: 6.5 packs per year. Compliance was assumed to be 100%, based on 94.3% compliance for the Q2W group and 98.3% compliance for the Q4W group in Study 1652.
Cost of medicines	
Dupilumab	Requested price: Q2W: \$ [REDACTED]; Q4W: \$ [REDACTED]
Patient co-payment	Co-payment calculated as \$29.01, based on PBS item 1964J (etanercept for severe chronic plaque psoriasis).
Impact on other medicines	
Other agents	It is expected that 10.7% of dupilumab-treated patients will require PBS treatment for conjunctivitis

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Component	Data source
	as well concomitant disease flares during episodes of conjunctivitis which require treatment with pimecrolimus. Of the possible treatments, only pimecrolimus (\$31.35) is priced above the weighted co-payment. Based on the published price for dupilumab, the submission has estimated cost savings of \$█ in Year 1, decreasing to \$█ in Year 6. The submission assumed no cost offsets using the requested effective price.
MBS usage and costs	
MBS items	The submission assumed increased MBS costs for training for subcutaneous injections and ophthalmologist referrals for conjunctivitis, and cost offsets for fewer primary care and specialist consultations, and fewer phototherapy sessions. The number of services was sourced from the clinician survey.

Source: Table 4.2, p205; Table 4.3, p207-208; Table 4.4, p208; Table 4.7, p210; Table 4.9, p212; Table 4.10, p213; Table 4.11, p215-216; Table 4.13, p218; Table 4.14, p218; Table 4.15, p219; Table 4.22, p24; Table 4.24, p226; Table 4.29, p231; Table 4.30, p231-232; Table 4.31, p232 of the submission; Table 5, 3.02 November 2020 PBAC Minutes.

AD = atopic dermatitis; EASI = Eczema area and severity index; PSD = public summary document; Q2W = every two weeks; Q4W = every four weeks

6.54 The estimated patient numbers, prescription numbers and costs for the PBS listing of dupilumab for the treatment of severe AD in paediatric patients are provided below. The submission assumed uptake of 7% in Year 1, decreasing to 4% in Years 5 and 6.

6.55 For reference, estimates for the adult and adolescent population in November 2020 are provided in the table, although the adult and adolescent population (aged ≥12 is much larger than the paediatric population (aged 6-11 years).

Table 21: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients initiated	█ ²	█ ²	█ ³	█ ³	█ ³	█ ³
Nov 2020 initiators for adults and adolescents	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number continuing treatment	█ ^{a3}	█ ³	█ ²	█ ²	█ ²	█ ²
Number of scripts dispensed ^b	█ ⁴	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Nov 2020 scripts for adult and adolescents	█ ⁶	█	█ ⁸	█ ⁹	█ ¹⁰	█ ¹¹
Estimated financial implications of dupilumab for paediatric severe AD						
Cost to PBS/RPBS less copayments	█ ¹²	█ ¹⁴	█ ¹⁴	█ ¹⁴	█ ¹⁴	█ ¹⁴
Nov 2020 net cost for adults and adolescents	█ ¹³	█ ¹⁵	█ ¹⁶	█ ¹⁷	█ ¹⁸	█ ¹⁹
Net financial implications						
Net cost to PBS/RPBS	█ ¹²	█ ¹⁴	█ ¹⁴	█ ¹⁴	█ ¹⁴	█ ¹⁴
Net cost to MBS	█ ¹²	█ ¹²	█ ¹²	█ ¹²	█ ¹²	█ ¹²
Net cost to Government	█ ¹²	█ ¹⁴	█ ¹⁴	█ ¹⁴	█ ¹⁴	█ ¹⁴

Source: Table 4.10, p213; Table 4.11, p215-216; Table 4.15, p219; Table 4.22, p224; Table 4.30, p231-232; Table 4.31, p232 of the submission; Table 5, 3.02 November 2020 PBAC Minutes.

AD = atopic dermatitis

^a Grandfathered patients.

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^b First year of treatment: initiation script and first maintenance script. Patients can fail to respond (23%), fail to respond to maintenance script (3.3%); or maintain response (73.6%). In subsequent years of treatment, Q2W patients use 13.04 packs per year and Q4W patients use 6.5 packs per year. Compliance was assumed to be 100%, based on Study 1652. Blue shading indicates data presented in the November 2020 submission.

The redacted values correspond to the following ranges:

¹⁵15,000 to < 10,000

²500 to < 5,000

³< 500

⁴5,000 to < 10,000

⁵10,000 to < 20,000

⁶30,000 to < 40,000

⁷40,000 to < 50,000

⁸50,000 to < 60,000

⁹60,000 to < 70,000

¹⁰70,000 to < 80,000

¹¹80,000 to < 90,000

¹²\$0 to < \$10 million

¹³\$30 million to < \$40 million

¹⁴\$10 million to < \$20 million

¹⁵\$40 million to < \$50 million

¹⁶\$50 million to < \$60 million

¹⁷\$60 million to < \$70 million

¹⁸\$70 million to < \$80 million

¹⁹\$80 million to < \$90 million

- 6.56 The total cost to the PBS/RPBS of listing dupilumab for the treatment of severe AD in paediatric patients was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$70 million to < \$80 million in the first 6 years of listing. The submission's estimates assumed there will be no patients who weigh ≥ 60 kg. The PBAC considered that there are likely to be a small number of patients aged <12 years who weigh ≥ 60 kg, but noted that this did not impact on the financial estimates as the cost per month is equivalent for the three different dosing regimens.
- 6.57 The estimated net cost to the PBS relied upon data from adult trials of dupilumab. The net costs were also influenced by the low uptake rates (7% in Year 1 decreasing to 4% in Year 6). While the submission indicated these rates were based on uptake of dupilumab for the adult and adolescent population, the uptake in children <12 years may differ. The PBAC considered that uptake in the adult population may give an indication of the uptake in children <12 years but rates remain uncertain and the financial estimates were moderately sensitive to uptake rates.
- 6.58 The PBAC noted that the submission's estimates were based on the population aged 6-11 years whereas it had recommended use in patients aged <12 years. The PBAC considered that usage in patients less than 6 years of age would be limited noting a dose/regimen for patients weighting <15 kg has not been established. The PBAC considered that a small increase in the patient numbers to account for such use may be reasonable.
- 6.59 The estimated MBS costs rely on estimates of the use of phototherapy from the clinician survey. Based on the clinician survey, it was assumed that responders would have 3.63 phototherapy sessions per year, and non-responders would have 25.33. It should be noted that the clinicians reported that on average they would treat only

15.5% of paediatric patients with phototherapy, and the median proportion treated was 2%. In addition, 43% of clinicians reported they would not treat children with phototherapy, and 19% reported they would treat 5% or fewer of their patients with phototherapy. This suggests that the proportions applied for phototherapy use in the submission's financial estimates represent usage by a small proportion of clinicians. The ESC considered that, as for the economic model, the financial estimates should not include phototherapy costs as it is unlikely to be used in this patient population. The PBAC considered that the offsets for reduced use of phototherapy, primary care and specialist visits on the MBS appear overestimated and are unlikely to be realised. The PBAC considered the financial estimates should be revised to reduce the estimated offsets from reduced MBS costs.

- 6.60 The sensitivity analyses that had the greatest impact on the estimates were changes in prevalence of AD and prevalence of severe AD, as well as inclusion of the sustained response filter. Most changes to the parameters resulted in corresponding changes in total costs, e.g. increasing uptake rates by 10% increased estimated total cost by 10%.
- 6.61 The PBAC noted the rate of natural resolution of AD (sustained response) is expected to be higher for the paediatric population and the financial estimates were sensitive to assumptions around discontinuation for patients with sustained response. The submission's base case assumed that no patients would stop dupilumab therapy due to sustained response, and therefore the results provide an estimation of the maximum potential cost of listing dupilumab (assuming all other variables used in the estimates were accurate). The submission presented a sensitivity analysis, where 63.6% of patients have sustained response and cease dupilumab after 52 weeks of therapy, and 52.4% of these patients experienced a relapse and recommenced dupilumab treatment after a mean of approximately 24 weeks (overall 30.3% of patients have sustained response and do not continue treatment), as in the economic model sensitivity analyses (see also paragraph 6.44). This change decreased the estimated net cost by 25%, to \$60 million to <\$70 million for the first 6 years of listing. The PBAC agreed with the ESC that it would be reasonable for the financial estimates to assume that a proportion of patients experience sustained response and discontinue dupilumab without relapse requiring retreatment, and that the sensitivity analysis presented in the submission was a reasonable estimate of the extent of discontinuations.
- 6.62 The ESC also noted that it was unclear whether the financial estimates accounted for discontinuation of patients who would transition to the existing adult listings for dupilumab at 12 years of age. The Pre-PBAC response indicated that due to difficulties in estimating the age distribution of paediatric patients expected to initiate therapy with dupilumab on the PBS, it is not possible to estimate the rate at which these patients would reach the age at which they would transition to the adult/adolescent listing. The PBAC considered that this would overestimate the number of continuing patients who would be treated under the paediatric listing in the forward estimates.

Quality Use of Medicines

- 6.63 The submission stated (p236) that the sponsor committed to undertaking a program to support healthcare professionals to correctly identify eligible patients, to provide professional healthcare education for to identifying the appropriate patients for continuation, or cessation, of dupilumab therapy, as well as information on dosing and administration of dupilumab.
- 6.64 The ESC noted that there is a reasonable proportion of patients in this age group whose disease would resolve based on the known natural history of atopic dermatitis (see also paragraph 4.2). Additional safeguards to prevent ongoing use when no longer required would minimise inappropriate exposure to a biological agent in children, also noting inferior safety to SoC.

Financial Management – Risk Sharing Arrangements

- 6.65 The submission indicated that the sponsor is willing to work with the Department to develop a risk-sharing arrangement (RSA). The Pre-PBAC response noted that the existing caps are shared with upadacitinib, which is not listed for patients aged <12 years. The pre-PBAC response indicated that the sponsor considered it would not be appropriate for the existing caps to be expanded to include paediatric patients. The PBAC noted that a separate cap for the paediatric population would require separate PBS listings for the paediatric and adolescent/adult populations.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of dupilumab for patients aged less than 12 years with severe atopic dermatitis. The PBAC noted the substantial clinical need for effective treatments for these patients and was satisfied that dupilumab provides, for some patients, a significant improvement in efficacy over standard care. The PBAC considered that the clinical evidence suggests 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 as for the adult/adolescent population.
- 7.2 The PBAC noted the substantial number of comments from patients, carers, health professionals and organisations in support of PBS listing of dupilumab in paediatric patients. The PBAC noted that many of these comments identified the benefits from treatment with dupilumab for children in terms of sleep, education, self-esteem and confidence and also acknowledged the considerable burden of AD and current treatments on carers. The PBAC considered that there is a high clinical need for effective treatments in the paediatric population.
- 7.3 The PBAC considered that restrictions for patients aged <12 years should be consistent

with restrictions for patients aged 12 or older to reduce complexity for prescribers and to ensure that patients can easily transition to treatment under the adolescent/adult listing. The PBAC considered that the baseline EASI score should be 20 (rather than 21 as proposed) and that the wording in the restrictions for the adolescent/adult population with respect to DLQI was sufficiently inclusive for use of CDLQI in the paediatric listing. The current maximum number of repeats available for the 300 mg presentation (5) currently caters for dosing in adults Q2W. In children under 30 kg, 300 mg is administered Q4W, resulting in an extended duration of treatment at the maximum number of repeats. The PBAC considered it would be reasonable for the existing 300 mg presentation listings to be retained, but a prescribing instruction to direct the prescriber to seek no more than 3 repeat prescriptions for the initial treatment restriction and no more than 2 repeat prescriptions for the continuing treatment restriction under the Q4W regimen.

- 7.4 The PBAC considered that for the paediatric population a minimum age for access to treatment was not required. The PBAC noted that dupilumab is currently TGA indicated for patients aged at least 6 years, but considered that use in patients younger than 6 years may be clinically appropriate in some circumstances. The PBAC considered that this may be particularly important for patients who have started school, but are not yet 6 years of age, noting the consumer comments regarding the importance of education for paediatric patients.
- 7.5 The PBAC noted that the natural history for the paediatric population differed from that in the adolescent/adult population in that many more paediatric patients would be expected to experience disease resolution with time, compared with the adolescent/adult population. The PBAC noted that the submission suggested the inclusion of guidance in the restrictions for assessment of the need for ongoing treatment in patients whose disease may have resolved. The PBAC considered that parents and specialists prescribing dupilumab, in line with QUM principles, would discontinue treatment or extend the period between doses where appropriate to manage patients who may no longer require treatment with dupilumab. The PBAC considered that assessment of the need for ongoing treatment would be appropriately managed by specialist clinicians and the restrictions need not include this requirement.
- 7.6 The PBAC considered that the nominated comparator of placebo, representing SoC, was appropriate.
- 7.7 The PBAC noted that the submission was based on a randomised, double-blind, multicentre trial (Study 1652) comparing the efficacy and safety of dupilumab + TCS to placebo + TCS in paediatric patients aged ≥ 6 to < 11 years with severe AD inadequately controlled with topical therapies. Although Study 1652 had a different dosing structure than the requested restrictions the PBAC considered it was sufficiently representative of expected use in Australian clinical practice. The PBAC noted that the clinical evidence from the post-hoc subgroups suggested that response may differ somewhat between patients < 30 kg on the 300 mg Q4W schedule and those

30-60kg on the 200 mg Q2W schedule, with patients <30kg having numerically greater improvements for the combined outcome of EASI 50 and CDLQI4 compared with those 30-60kg. The PBAC noted that this may be due to the higher initial loading dose for the <30kg subgroup. However, overall the PBAC considered that dupilumab appeared to be effective in both groups of patients and the clinical claim of superior efficacy over SoC was reasonable.

- 7.8 The PBAC noted that no evidence was presented for patients ≥ 60 kg but considered that efficacy is likely to be consistent with the <60 kg paediatric population and with the adolescent/adult population who are treated with the same dosing regimen. The PBAC noted that no directly relevant long term evidence was available for the paediatric population.
- 7.9 The PBAC noted that conjunctivitis and injection site reactions occurred more frequently in the dupilumab arms of study 1652 and considered that the claim of inferior safety was reasonable.
- 7.10 The PBAC noted that the economic model presented was essentially the same as that presented for the adult population, with some inputs adjusted using data for the paediatric population (patient demographics, week 16 response and health resource use). The PBAC considered that the model structure and time horizon were reasonable, noting they were previously accepted for the adult population.
- 7.11 The PBAC noted that maintenance of response applied in the model was based on adult trial data as no applicable long term data was available for the paediatric population. The PBAC considered that maintenance of response may differ somewhat in paediatric patients due to differences in the natural history of AD between adults and children. The PBAC noted that the sensitivity analysis assuming a sustained response for around 30% of patients, where patients in the dupilumab arm don't resume treatment, resulted in an increase in the ICER from \$20 million to <\$30 million/QALY to \$30 million to <\$40 million/QALY. The PBAC considered that this likely better reflected use in the paediatric population where patients are more likely to experience AD resolution over time. The PBAC noted that response rates for the <30kg and 30-60kg weight groups were combined in the economic model and considered that it may not be reasonable to assume response rates are the same for the two groups. However, the PBAC noted that this is unlikely to impact the ICER if the proportion of patients in each weight group is representative of the population treated.
- 7.12 The PBAC noted that the economic model was sensitive to the healthcare costs for responders and non-responders. The PBAC noted that these costs were based on a clinician survey specific to paediatric patients but considered that there was a high level of uncertainty in the mean values from the survey. The PBAC noted that the ESC considered the inclusion of phototherapy costs was inappropriate as phototherapy is not generally used in children. The PBAC considered that inclusion of some costs for phototherapy may be reasonable as a small number of clinicians may use

phototherapy in patients considered to be suitable, however the mean value of 25.3 services per year for non-responders appeared to be substantially overestimated. In addition, the PBAC noted that other health resource costs based on mean values from the clinician survey generated significant cost offsets, and appeared to be overestimated, particularly hospitalisations and emergency room visits. The PBAC considered that inclusion of overestimated healthcare costs for non-responders appeared to underestimate the ICER for the paediatric population, however, overall the PBAC considered that the ICER remained within an acceptable cost-effectiveness range even when phototherapy and other healthcare costs were reduced.

- 7.13 The PBAC noted that utilisation estimates were based on an epidemiological approach including patients aged 6-11 years, whereas it had recommended use in patients aged <12 years. The PBAC considered that usage in patients less than 6 years of age would be limited as the dose/regimen for patients weighing <15 kg has not been established. The PBAC considered that in children 4 or 5 years of age, who weigh at least 15 kg, uptake would be expected to be up to half the uptake in children 6-11 years of age. The PBAC considered that a small increase in the patient numbers to account for such use may be reasonable.
- 7.14 The PBAC noted that in the financial estimates no patients were assumed to weigh ≥ 60 kg and therefore expected to use the 300 mg Q2W regimen. The PBAC considered that this was not reasonable as some patients included in the cohort would be expected to weigh ≥ 60 kg, however this assumption did not impact the net financial impact as the cost per month is equivalent for each dosage regimen.
- 7.15 The PBAC noted that uptake rates were based on uptake in the adult population and considered that this was a reasonable approach in the absence of alternative data, though uptake rates remain uncertain and the financial estimates were sensitive to the assumed rates. The PBAC also noted the rate of natural resolution of AD (sustained response) is expected to be higher for the paediatric population than for adolescents/adults. The submission presented a sensitivity analysis where 30.3% of patients have sustained response and discontinue treatment, based on the open label extension Study 1434. The PBAC considered the financial estimates should be revised to include 30.3% sustained response (as in the sensitivity analysis) to better reflect likely use of dupilumab in practice.
- 7.16 The PBAC noted it is difficult to estimate the rate at which paediatric patients would transition to the adult/adolescent listing. The PBAC considered that the utilisation of dupilumab under the proposed continuing paediatric listing may have been overestimated because older paediatric patients would access dupilumab under the existing adult/adolescent listing once they reach 12 years of age.
- 7.17 The PBAC considered that use of phototherapy was overestimated and offsets from its use were therefore overestimated in the financial estimates. The PBAC considered that the offsets for reduced primary care and specialist visits also appear overestimated and are unlikely to be realised. The PBAC considered the financial

estimates should be revised to remove MBS cost offsets from reduced specialist visits and reduce MBS offsets from primary care and phototherapy by at least 50%.

- 7.18 The PBAC noted that the sponsor indicated a willingness to enter a risk sharing agreement (RSA). The PBAC considered that a 100% rebate would be required for expenditure exceeding the estimated financial cost for dupilumab 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 or where patients' disease has resolved and no longer requires treatment. The PBAC noted that a separate cap for the paediatric population would require separate PBS listings for the paediatric and adolescent/adult populations. The PBAC considered that RSA caps should be based on revised financial estimates which have been adjusted to include:
- A small increase in the size of the patient population to account for the minimum age not being specified in the restriction as described in paragraph 7.13.
 - Allowance for sustained response as described in paragraph 7.11.
- 7.19 The PBAC recommended that the grandfather listing be in operation for 12 months to transition patients commenced on non-PBS subsidised treatment to PBS subsidised supply, where these patients would otherwise have met the initial treatment criteria based on EASI score.
- 7.20 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for dupilumab:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over SoC;
 - b) The treatment is expected to address a high and urgent unmet clinical need, however alternative treatments are available and therefore this criterion is not met; and
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.21 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Amend existing dupilumab ‘Chronic severe atopic dermatitis’ listings as follows to:

- (i) include patients under the age of 12 years – applicable to both strengths; and
- (ii) provide prescriber directions to seek a lower number of repeat prescriptions in a patient no higher than 30 kg in weight – applicable to the 300 mg strength only; and
- (iii) amend the ‘grandfather’ listings to remove the current patient population, but to replace it with those who have initiated dupilumab treatment as a child (less than 12 years) prior to the implementation date of this recommendation

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DUPILUMAB						
dupilumab 300 mg/2 mL injection, 2 x 2 mL syringes		12292Y	1	2	5	Dupixent
Restriction Summary 12498 / Treatment of Concept: 12497						
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Prescribing rule level	Administrative Advice: Instructions on the use of the Eczema Area and Severity Index and copyright details can be found here: https://www.dupixent.co.uk/-/media/EMS/Conditions/Dermatology/Brands/Dupixent-UK/global/1051-EASI-Leaflet-v6-webready.pdf					
	Administrative Advice: Instructions on the use of the Dermatology Life Quality Index and copyright details can be found here: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index					
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.						

Indication: Chronic severe atopic dermatitis	
Treatment Phase: Initial treatment of the whole body	
Clinical criteria:	
Patient must have a Physicians Global Assessment (PGA) (5-point scale) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 day	
AND	
Clinical criteria:	
Patient must have an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days	
AND	
Clinical criteria:	

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	Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days
	AND
	Clinical criteria:
	The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Clinical criteria:
	Patient must not have experienced an inadequate response to this biological medicine in this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	<i>Patient must be less than 12 years of age</i>
	Prescribing Instructions: State each of the qualifying (i) PGA, (ii) EASI and (iii) DLQI scores in the authority application. Acceptable scores can be: (a) current scores; or (b) past scores, including those previously quoted in a PBS authority application for another drug listed for this indication. The EASI and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction. In addition to stating them in this authority application, document them in the patient's medical records. Document the details of the medium to high potency topical corticosteroids (or calcineurin inhibitors) initially trialled in the patient's medical records.
	Prescribing Instructions: In a patient weighing no greater than 30 kg, prescribe up to 3 repeat prescriptions only – do not default to prescribing the listing's specified number of repeats.
	Administrative Advice: Instructions on the use of the Physician's Global Assessment (5-point scale) can be obtained from Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
Restriction Summary 11374 / Treatment of Concept: 11374	
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Continuing or resuming treatment of the whole body
	Clinical criteria:
	Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the whole body
	AND
	Clinical criteria:
	Patient must have achieved an adequate response within the first 16 weeks of treatment; or
	Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; or
	Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. family planning, vaccination with live vaccines, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application

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	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	Patient must be less than 12 years of age
	Prescribing Instructions:
	For the purposes of this restriction, an adequate response to treatment is defined as:
	(a) An improvement/maintenance in the Eczema Area and Severity Index (EASI) score of at least 50% compared to baseline; and
	(b) An improvement/maintenance in Dermatology Life Quality Index (DLQI) score of at least 4 points compared to baseline
	Where an initial baseline (post-topical corticosteroid, pre-biological medicine) DLQI score was not measured for a patient who had commenced treatment through a clinical trial, early access program or through private, non-PBS-subsidised supply, an absence of worsening in the current DLQI score compared to that measured at the time of the 'Grandfather listing' authority application will suffice as an adequate response for requirement (b) above.
	State each of the current EASI and DLQI scores for this authority application.
	Prescribing Instructions:
	In a patient weighing no greater than 30 kg, prescribe up to 2 repeat prescriptions only – do not default to prescribing the listing's specified number of repeats.
Restriction Summary 12506 / ToC: 12507	
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Initial treatment of the face and/or hands
	Clinical criteria:
	The condition must have at least 2 of the following Eczema Area and Severity Index (EASI) symptom sub-scores for erythema, oedema/papulation, excoriation, lichenification rated as severe despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days; or
	The condition must have affected at least 30% of the face/hands surface area despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days
	AND
	Clinical criteria:
	Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days
	AND
	Clinical criteria:
	The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Clinical criteria:
	Patient must not have experienced an inadequate response to this biological medicine in this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:

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	Patient must be 12 years of age or older; or
	<i>Patient must be less than 12 years of age</i>
	<p>Prescribing Instructions: State each of the 4 Eczema Area and Severity Index (EASI) symptom sub-score ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe) for: (i) erythema, (ii) oedema/papulation, (iii) excoriation, (iv) lichenification Acceptable scores can be: (a) current scores; or (b) past scores, including those previously quoted in a PBS authority application for another drug listed for this indication. State the percentage face/hand surface area affected by the condition (must be at least 30%) where EASI symptom sub-scores are not provided. This percentage surface area can also be stated in addition to the EASI symptom sub-scores. The EASI/percentage surface area and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction. In addition to stating them in this authority application, document them in the patient's medical records. Document the details of the medium to high potency topical corticosteroids (or calcineurin inhibitors) initially trialled are in the patient's medical records.</p>
	<p>Prescribing Instructions: In a patient weighing no greater than 30 kg, prescribe up to 3 repeat prescriptions only – do not default to prescribing the listing's specified number of repeats.</p>
	Restriction Summary 11377 / ToC: 11377
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Continuing or resuming treatment of the face and/or hands
	Clinical criteria:
	Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the face/hands
	AND
	Clinical criteria:
	Patient must have achieved an adequate response within the first 16 weeks of treatment; or
	Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; or
	Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. family planning, vaccination with live vaccines, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	<i>Patient must be less than 12 years of age</i>
	<p>Prescribing Instructions: For the purposes of this restriction, an adequate response to treatment of the face/hands is defined as: (a) (i) A rating of either mild (1) to none (0) on at least 3 of the assessments of erythema, oedema/papulation, excoriation and lichenification mentioned in the Eczema Area and Severity Index (EASI); or</p>

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	(ii) At least a 75% reduction in the skin area affected by this condition compared to baseline; and (b) An improvement in Dermatology Life Quality Index (DLQI) score of at least 4 points compared to baseline Where an initial baseline (post-topical corticosteroid, pre-biological medicine) DLQI score was not measured for a patient who had commenced treatment through a clinical trial, early access program or through private, non-PBS-subsidised supply, an absence of worsening in the current DLQI score compared to that measured at the time of the 'Grandfather listing' authority application will suffice as an adequate response for requirement (b) above. Document each qualifying response measure in the patient's medical records for PBS compliance auditing purposes
	Prescribing Instructions: In a patient weighing no greater than 30 kg, prescribe up to 3 repeat prescriptions only – do not default to prescribing the listing's specified number of repeats.
Restriction Summary 11504 / ToC: 11425	
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - treatment of the whole body (Grandfather listing)
	Clinical criteria: Patient must have been receiving treatment with this biological medicine for this PBS indication prior to 1 March 2024
	<i>Patient must be continuing treatment with this biological medicine that has been initiated as non-PBS supply for this PBS indication in a patient aged less than 12 years, prior to [insert listing date here 1 Month 202X]</i>
	AND
	Clinical criteria: Patient must have had a Physicians Global Assessment (PGA) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria: Patient must have had an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria: Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; or Patient must have, where the above baseline DLQI was not recorded in the patient's medical records, a current age-appropriate DLQI score (of any value) measured
	AND
	Clinical criteria: The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria: Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria: The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Clinical criteria: Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Treatment criteria: Must be treated by a dermatologist; or Must be treated by a clinical immunologist
	AND

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	Population criteria:
	Patient must be 12 years of age or older; or
	Prescribing Instructions: State each of the qualifying PGA, EASI and DLQI scores in the authority application. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine must be documented in the patient's medical records. The EASI and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction.
	Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only.
	Prescribing Instructions: For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Prescribing Instructions: In a patient weighing no greater than 30 kg, prescribe up to 2 repeat prescriptions only – do not default to prescribing the listing's specified number of repeats.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Instructions on the use of the Physician's Global Assessment (5-point scale) can be obtained from Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
Restriction Summary 11491 / ToC: 11479	
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - treatment of the face and/or hands (Grandfather listing)
	Clinical criteria: Patient must have been receiving treatment with this biological medicine for this PBS indication prior to 1 March 2021
	<i>Patient must be continuing treatment with this biological medicine that has been initiated as non-PBS supply for this PBS indication in a patient aged less than 12 years, prior to [insert listing date here 1 Month 202X]</i>
	AND
	Clinical criteria:
	The condition must have had at least 2 of the following Eczema Area and Severity Index (EASI) symptom sub-scores for erythema, oedema/papulation, excoriation, lichenification rated as severe despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to commencing non-PBS-subsidised therapy with this biological medicine; or
	The condition must have affected at least 30% of the face/hands surface area despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; or
	Patient must have, where the above baseline DLQI was not recorded in the patient's medical records, a current age-appropriate DLQI score (of any value) measured
	AND
	Clinical criteria:
	The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological medicine
	AND

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	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this condition
	AND
	Clinical criteria:
	Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	Patient must be less than 12 years of age
	Prescribing Instructions:
	State each of the 4 Eczema Area and Severity Index (EASI) symptom sub-score ratings for erythema, oedema/papulation, excoriation, lichenification that were present prior to having commenced non-PBS-subsidised therapy, in the authority application. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine is/are to be documented in the patient's medical records.
	Prescribing Instructions:
	A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only.
	Prescribing Instructions:
	For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Prescribing Instructions:
	In a patient weighing no greater than 30 kg, prescribe up to 2 repeat prescriptions only – do not default to prescribing the listing's specified number of repeats.
	Administrative Advice:
	This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
medicinal product pack					
DUPILUMAB					
dupilumab 200 mg/1.14 mL injection, 2 x 1.14 mL syringes	12291X	1	2	5	Dupixent
Restriction Summary 12498 / Treatment of Concept: 12497					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)				
Prescribing rule level	Administrative Advice: Instructions on the use of the Eczema Area and Severity Index and copyright details can be found here: https://www.dupixent.co.uk/-/media/EMS/Conditions/Dermatology/Brands/Dupixent-UK/global/1051-EASI-Leaflet-v6-webready.pdf				
	Administrative Advice: Instructions on the use of the Dermatology Life Quality Index and copyright details can be found here: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
Administrative Advice: Special Pricing Arrangements apply.					

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	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Initial treatment of the whole body
	Clinical criteria:
	Patient must have a Physicians Global Assessment (PGA) (5-point scale) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 day
	AND
	Clinical criteria:
	Patient must have an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days
	AND
	Clinical criteria:
	Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days
	AND
	Clinical criteria:
	The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Clinical criteria:
	Patient must not have experienced an inadequate response to this biological medicine in this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	<i>Patient must be less than 12 years of age</i>
	Prescribing Instructions:
	State each of the qualifying (i) PGA, (ii) EASI and (iii) DLQI scores in the authority application. Acceptable scores can be: (a) current scores; or (b) past scores, including those previously quoted in a PBS authority application for another drug listed for this indication.
	The EASI and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction. In addition to stating them in this authority application, document them in the patient's medical records.
	Document the details of the medium to high potency topical corticosteroids (or calcineurin inhibitors) initially trialled in the patient's medical records.
	Administrative Advice:
	Instructions on the use of the Physician's Global Assessment (5-point scale) can be obtained from Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
Restriction Summary 11374 / Treatment of Concept: 11374	
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Continuing or resuming treatment of the whole body

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	Clinical criteria:
	Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the whole body
	AND
	Clinical criteria:
	Patient must have achieved an adequate response within the first 16 weeks of treatment; or
	Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; or
	Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. family planning, vaccination with live vaccines, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	<i>Patient must be less than 12 years of age</i>
	Prescribing Instructions:
	For the purposes of this restriction, an adequate response to treatment is defined as: (a) An improvement/maintenance in the Eczema Area and Severity Index (EASI) score of at least 50% compared to baseline; and (b) An improvement/maintenance in Dermatology Life Quality Index (DLQI) score of at least 4 points compared to baseline Where an initial baseline (post-topical corticosteroid, pre-biological medicine) DLQI score was not measured for a patient who had commenced treatment through a clinical trial, early access program or through private, non-PBS-subsidised supply, an absence of worsening in the current DLQI score compared to that measured at the time of the 'Grandfather listing' authority application will suffice as an adequate response for requirement (b) above. State each of the current EASI and DLQI scores for this authority application.
	Restriction Summary 12506 / ToC: 12507
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Initial treatment of the face and/or hands
	Clinical criteria:
	The condition must have at least 2 of the following Eczema Area and Severity Index (EASI) symptom sub-scores for erythema, oedema/papulation, excoriation, lichenification rated as severe despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days; or
	The condition must have affected at least 30% of the face/hands surface area despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days
	AND
	Clinical criteria:
	Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days
	AND
	Clinical criteria:
	The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands
	AND

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	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Clinical criteria:
	Patient must not have experienced an inadequate response to this biological medicine in this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	<i>Patient must be less than 12 years of age</i>
	Prescribing Instructions:
	State each of the 4 Eczema Area and Severity Index (EASI) symptom sub-score ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe) for:
	(i) erythema,
	(ii) oedema/papulation,
	(iii) excoriation,
	(iv) lichenification
	Acceptable scores can be:
	(a) current scores; or
	(b) past scores, including those previously quoted in a PBS authority application for another drug listed for this indication.
	State the percentage face/hand surface area affected by the condition (must be at least 30%) where EASI symptom sub-scores are not provided. This percentage surface area can also be stated in addition to the EASI symptom sub-scores.
	The EASI/percentage surface area and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction. In addition to stating them in this authority application, document them in the patient's medical records.
	Document the details of the medium to high potency topical corticosteroids (or calcineurin inhibitors) initially trialled are in the patient's medical records.
	Restriction Summary 11377 / ToC: 11377
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Continuing or resuming treatment of the face and/or hands
	Clinical criteria:
	Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the face/hands
	AND
	Clinical criteria:
	Patient must have achieved an adequate response within the first 16 weeks of treatment; or
	Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; or
	Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. family planning, vaccination with live vaccines, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:

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	Patient must be 12 years of age or older; or
	<i>Patient must be less than 12 years of age</i>
	<p>Prescribing Instructions: For the purposes of this restriction, an adequate response to treatment of the face/hands is defined as: (a) (i) A rating of either mild (1) to none (0) on at least 3 of the assessments of erythema, oedema/papulation, excoriation and lichenification mentioned in the Eczema Area and Severity Index (EASI); or (ii) At least a 75% reduction in the skin area affected by this condition compared to baseline; and (b) An improvement in Dermatology Life Quality Index (DLQI) score of at least 4 points compared to baseline Where an initial baseline (post-topical corticosteroid, pre-biological medicine) DLQI score was not measured for a patient who had commenced treatment through a clinical trial, early access program or through private, non-PBS-subsidised supply, an absence of worsening in the current DLQI score compared to that measured at the time of the 'Grandfather listing' authority application will suffice as an adequate response for requirement (b) above. Document each qualifying response measure in the patient's medical records for PBS compliance auditing purposes</p>
Restriction Summary 11504 / ToC: 11425	
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - treatment of the whole body (Grandfather listing)
	Clinical criteria:
	Patient must have been receiving treatment with this biological medicine for this PBS indication prior to 1 March 2021
	<i>Patient must be continuing treatment with this biological medicine that has been initiated as non-PBS supply for this PBS indication in a patient aged less than 12 years, prior to [insert listing date here 1 Month 202X]</i>
	AND
	Clinical criteria:
	Patient must have had a Physicians Global Assessment (PGA) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	Patient must have had an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; or
	Patient must have, where the above baseline DLQI was not recorded in the patient's medical records, a current age-appropriate DLQI score (of any value) measured
	AND
	Clinical criteria:
	The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
	AND
	Clinical criteria:
	Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine

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	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	Prescribing Instructions: State each of the qualifying PGA, EASI and DLQI scores in the authority application. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine must be documented in the patient's medical records. The EASI and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction.
	Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only.
	Prescribing Instructions: For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Instructions on the use of the Physician's Global Assessment (5-point scale) can be obtained from Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
Restriction Summary 11491 / ToC: 11479	
	Indication: Chronic severe atopic dermatitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - treatment of the face and/or hands (Grandfather listing)
	Clinical criteria:
	Patient must have been receiving treatment with this biological medicine for this PBS indication prior to 1 March 2021
	<i>Patient must be continuing treatment with this biological medicine that has been initiated as non-PBS supply for this PBS indication in a patient aged less than 12 years, prior to [insert listing date here 1 Month 202X]</i>
	AND
	Clinical criteria:
	The condition must have had at least 2 of the following Eczema Area and Severity Index (EASI) symptom sub-scores for erythema, oedema/papulation, excoriation, lichenification rated as severe despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to commencing non-PBS-subsidised therapy with this biological medicine; or
	The condition must have affected at least 30% of the face/hands surface area despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; or
	Patient must have, where the above baseline DLQI was not recorded in the patient's medical records, a current age-appropriate DLQI score (of any value) measured
	AND
	Clinical criteria:
	The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Clinical criteria:
	Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological

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	medicine
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised biological medicine for this condition
	AND
	Clinical criteria:
	Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine
	AND
	Treatment criteria:
	Must be treated by a dermatologist; or
	Must be treated by a clinical immunologist
	AND
	Population criteria:
	Patient must be 12 years of age or older; or
	Prescribing Instructions: State each of the 4 Eczema Area and Severity Index (EASI) symptom sub-score ratings for erythema, oedema/papulation, excoriation, lichenification that were present prior to having commenced non-PBS-subsidised therapy, in the authority application. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine is/are to be documented in the patient's medical records.
	Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only.
	Prescribing Instructions: For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

9 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.

10 Sponsor's Comment

The sponsor had no comment.