

**5.12 LEBRIKIZUMAB,
Injection 250 mg in 2 mL single use autoinjector,
Ebglyss[®],
ELI LILLY AUSTRALIA PTY LTD.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (Telephone/Online) listing for lebrikizumab (LEB) for the treatment of severe atopic dermatitis (AD).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus dupilumab (DUPI).

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

Component	Description
Population	<p>Patients aged 12 years or older with severe atopic dermatitis, affecting the whole body or the face and/or hands, who are inadequately controlled on topical therapies.</p> <p>Key baseline characteristics defining patients eligible for treatment:</p> <p>Whole body:</p> <ul style="list-style-type: none"> • EASI \geq 20, AND PGA = 4 <p>Face and/or hands:</p> <ul style="list-style-type: none"> • 2 x EASI symptom subscores rated as 'severe' (3), OR • \geq 30% Surface area of face and/or hands affected
Intervention	<p>In adults and adolescents weighing \geq40 kg:</p> <p>Initiation: LEB 500 mg SC injection as loading doses at Week 0 & 2, followed by LEB 250 mg SC injection Q2W until week 16.</p> <p>Maintenance: LEB 250 mg SC injection Q4W</p>
Comparator	<p>Main comparator:</p> <ul style="list-style-type: none"> - In adult patients: DUPI 600 mg SC injection as a loading dose followed by 300 mg SC injection Q2W - In adolescents \geq 60 kg: DUPI 600 mg SC injection as a loading dose followed by 300 mg SC injection Q2W - In adolescents 30 kg to < 60 kg: DUPI 400 mg SC injection as a loading dose, followed by 200 mg SC injection Q2W <p>Secondary comparator:</p> <ul style="list-style-type: none"> - In adult patients: UPA 15 or 30 mg tablet, once daily - In adolescent patients: UPA 15 mg tablet, once daily
Outcomes	<p>Primary outcomes: Proportion of patients with a 75% improvement in EASI score at Week 16 (EASI 75); proportion of patients achieving IGA score of 0 or 1 with a \geq 2-point improvement at Week 16.</p> <p>Secondary outcomes: Proportion of patients achieving a 50% improvement in EASI score (EASI 50); proportion of patients achieving a \geq 4-point improvement in DLQI at Week 16.</p> <p>Safety outcomes: Proportion of patients experiencing AEs, SAEs and discontinuation of treatment due to AEs.</p> <p>Post-hoc outcome: PBS response criteria: composite measure of response EASI 50 and improvement in DLQI \geq4-points, at Week 16.</p>
Clinical claim	<p>Based on the indirect comparison for the composite outcome in the severe AD subgroup:</p> <p>LEB 250 mg Q2W \pm TCS is non-inferior to DUPI 300 mg Q2W \pm TCS for efficacy.</p> <p>LEB 250 mg Q2W \pm TCS is non-inferior to DUPI 300 mg Q2W \pm TCS for safety.</p> <p>LEB 250 mg Q2W \pm TCS is non-inferior to UPA 15 mg \pm TCS and UPA 30 mg \pm TCS for efficacy.</p> <p>LEB 250 mg Q2W \pm TCS is non-inferior to UPA 15 mg \pm TCS or 30 mg \pm TCS for safety.</p>

Source: Table 1.1-1, pp3-4 of the submission.

LEB = lebrikizumab; SC = subcutaneous; Q2W = every two weeks; Q4W = every four weeks; DUPI = dupilumab; UPA = upadacitinib; EASI = Eczema Area Severity Index; PGA/ IGA = Physician's / Investigator's Global Assessment; DLQI = Dermatology Life Quality Index; PBS = Pharmaceutical Benefits Scheme; AEs = adverse events; SAEs = serious adverse events; TCS = topical corticosteroids.

- 1.3 Though the submission nominated DUPI 200 mg every 2 weeks (Q2W) (for adolescents 30 kg to < 60 kg) as one of the comparators and included DUPI 200 mg Q2W in the CMA, the clinical claim and clinical evidence presented for the PBS population (severe AD) was based on DUPI 300 mg Q2W only.

2 Background

Registration status

- 2.1 The submission was lodged under the TGA-PBAC parallel process. At the time of PBAC consideration the Delegate's Overview was available. The proposed indication was:

“EBGLYSS is indicated for the treatment of adult and adolescent patients (12 years of age and older) with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy.”

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
LEBRIKIZUMAB					
Lebrikizumab (initial) 250 mg/2mL pre-filled pen autoinjector	\$█ published price TBD effective price (SPA)	4	4	2	Ebglyss
Lebrikizumab (continuing) 250 mg/2mL pre-filled pen autoinjector	\$█ published price TBD effective price (SPA)	1	1	5	Ebglyss
Lebrikizumab (extended induction (balance of supply)) 250 mg/2mL pre-filled pen autoinjector	\$█ published price TBD effective price (SPA)	2	2	1	Ebglyss

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; DUPI = dupilumab; LEB = lebrikizumab; SPA = special pricing arrangement; TBD = to be determined; UPA = upadacitinib; qty = quantity; rpts = repeats.

Note: The DPMQ provided by the submission was based on an AEMP of \$█. However, this DPMQ differed slightly to those calculated during the evaluation (using the 'Mark-ups v43 - eff 1 Jul 23 external' workbook). e.g., The DPMQ for 1 unit was \$█, compared to \$█ calculated during the evaluation.

The submission requested a SPA for LEB. The submission noted that a SPA currently applies to DUPI and UPA, and the SPA rebate for LEB (on the basis of a cost minimisation approach vs DUPI) could not be determined given the effective AEMPs are unknown to the sponsor.

Category / Program: General Schedule
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Episodicity: Chronic
Severity: Severe
Condition: Atopic Dermatitis
Indication: Chronic severe atopic dermatitis
Treatment Phase: Initial treatment of the whole body
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</p> <p>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</p> <p>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</p> <p>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</p> <p>Patient must have failed to achieve an adequate response to topical therapies (topical corticosteroids and/or topical calcineurin inhibitors); AND</p> <p>Patient must not have experienced an inadequate response to this therapy.</p>
Treatment criteria:
<p>Must be treated by a dermatologist; OR</p> <p>Must be treated by a clinical immunologist; AND</p>

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Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy with this PBS indication (combination with oral corticosteroids is permitted as these are not listed with the PBS indication: chronic severe atopic dermatitis).
Population criteria:
Patient must be 12 years of age or older.
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 Patient must have achieved an adequate response prior to this first continuing treatment authority application; 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 The treatment must be the sole PBS-subsidised biological medicine for this PBS indication.
Treatment criteria:
Must be treated by a dermatologist; OR Must be treated by a clinical immunologist; AND Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy with this PBS indication (combination with oral corticosteroids is permitted as these are not listed with the PBS indication: chronic severe atopic dermatitis).
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 State each of the current EASI and DLQI scores for this authority application.

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 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 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 Patient must have failed to achieve an adequate response to topical therapies (topical corticosteroids and/or topical calcineurin inhibitors); AND Patient must not have experienced an inadequate response to this therapy.
Treatment criteria:
Must be treated by a dermatologist; OR Must be treated by a clinical immunologist; AND Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy with this PBS indication (combination with oral corticosteroids is permitted as these are not listed with the PBS indication: chronic severe atopic dermatitis).

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Population criteria:
Patient must be 12 years of age or older.
Treatment Phase: Continuing or resuming treatment of the face and/or hands
Clinical criteria:
<p>Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the face and/or hands; AND</p> <p>Patient must have achieved an adequate response prior to this first continuing treatment authority application; OR</p> <p>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</p> <p>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</p> <p>The treatment must be the sole PBS-subsidised biological medicine for this PBS indication.</p>
Treatment criteria:
<p>Must be treated by a dermatologist; OR</p> <p>Must be treated by a clinical immunologist; AND</p> <p>Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy with this PBS indication (combination with oral corticosteroids is permitted as these are not listed with the PBS indication: chronic severe atopic dermatitis).</p>
Prescribing Instructions:
<p>For the purposes of this restriction, an adequate response to treatment of the face/hands is defined as:</p> <p>(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> <p>(ii) At least a 75% reduction in the skin area affected by this condition compared to baseline; and</p> <p>(b) An improvement in Dermatology Life Quality Index (DLQI) score of at least 4 points compared to baseline</p> <p>Document each qualifying response measure in the patient's medical records for PBS compliance auditing purposes.</p>
Treatment Phase: Extended induction (balance of supply)
Clinical criteria:
<p>Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis; AND</p> <p>Patient must not be undergoing each of: (i) commencing treatment through this treatment phase listing, (ii) treatment accessed through this treatment phase on more than 2 consecutive occasions; AND</p> <p>Patient has not achieved adequate treatment response during the initial treatment phase; AND</p> <p>In the opinion of the prescriber, continued treatment is likely to result in adequate response being achieved; AND</p> <p>The treatment must be the sole PBS-subsidised biological medicine for this PBS indication.</p>
Treatment criteria:
<p>Must be treated by a dermatologist; OR</p> <p>Must be treated by a clinical immunologist; AND</p> <p>Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy with this PBS indication (combination with oral corticosteroids is permitted as these are not listed with the PBS indication: chronic severe atopic dermatitis).</p>
Population criteria:
Patient must be 12 years of age or older.
Prescribing Instructions:
<p>For the purposes of this restriction, an adequate response to treatment is defined as:</p> <p>For treatment of the whole body:</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 Dermatology Life Quality Index (DLQI) score of at least 4 points compared to baseline</p>

For treatment of the face and/or hands:

- (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
- Document each qualifying response measure in the patient's medical records for PBS compliance auditing purposes.

- 3.1 The submission requested the listing of LEB for initial and continuing treatment of patients (aged 12 years or older) with severe AD affecting the whole body, or the face and/or hands. The proposed restrictions for LEB were consistent with those for DUPI and upadacitinib (UPA) in severe AD, with regards to eligibility and continuing criteria. The requested quantities would provide patients with up to 24 weeks of initial therapy (if adequate response is achieved and assessed at Week 16), and 24 weeks of continuing treatment.
- 3.2 For induction treatment the submission proposed a maximum quantity of 4 units, 2 repeats which would provide treatment for up to 18 weeks including loading doses and Q2W dosing. If response is assessed as being adequate at 16 weeks, the remaining dose can be given at 20 weeks, providing treatment up to 24 weeks. The PBAC noted a maximum quantity of 2 units (5 repeats) would require the patient to pay 2 co-payments for the first month, but then each repeat (2 doses) will allow for a month of treatment. This would still allow patients to receive doses up to 20-24 weeks of treatment in total. The PBAC considered that the maximum quantity of 4 units, 2 repeats (as proposed) was preferable for the induction period, such that the patient does not pay 2 copayments in the first month of induction treatment.
- 3.3 The submission additionally requested a listing for an extended induction period (balance of supply) for patients deemed to have achieved a less than adequate response to LEB ('slow responder') after 16 weeks. The proposed extended induction supply would provide an additional eight weeks of induction treatment at Q2W dosing and would last up to 28 weeks from the initial dose of LEB. The submission proposed that all patients who do not achieve the PBS response criteria at 16 weeks would be eligible for extended induction, with assessment of response between 24-28 weeks. However, this was not fully aligned to the TGA evaluator's recommendation that LEB should be discontinued in patients who show no evidence of clinical benefit after 16 weeks of treatment with 250 mg Q2W (TGA Clinical Evaluation Report) or the requested restriction's clinical criterion that "in the opinion of the prescriber, continued treatment is likely to result in adequate response being achieved". The PBAC noted that this approach is not consistent with induction and assessment of response for DUPI and UPA, but noted that it was consistent with the clinical data presented for LEB. The PBAC also noted that, in general, clinical practice with biologicals is moving towards a more extended induction period for assessment of response. The PBAC noted that there was potentially a higher cost associated with this approach as patients without adequate response are treated for a longer period before discontinuing treatment and slower responders receive additional doses

compared with patients who respond by week 16. The PBAC considered that inclusion of the extended induction period with assessment at 24 weeks, as proposed for the LEB restrictions, was reasonable, but the additional doses would need to be accounted for in the calculation of equi-effective doses applied in the cost-minimisation approach.

- 3.4 No grandfathering of patients was requested by the submission.
- 3.5 If listed, LEB would represent a third alternative treatment option in severe AD. The requested listing does not prevent the use of sequential treatment (i.e., patients who do not respond to DUPI would be eligible for LEB and vice versa) and there is potential for market growth in this treatment setting. The PBAC noted that switching is currently allowed between DUPI and UPA, and considered that allowing sequential treatment with an additional treatment (DUPI and/or UPA and LEB) was reasonable. The PBAC considered that allowing sequential treatment and switching between treatments is unlikely to substantially increase the uptake of treatments for severe AD as the number of patients ceasing treatment with DUPI/UPA has been relatively low. The PBAC noted that the pre-PBAC response also considered that the impact of sequential use on uptake was likely to be minimal.
- 3.6 The requested restriction was narrower than the proposed TGA indication. The proposed TGA indication did not restrict treatment with LEB to:
- Patients with severe AD (defined in the requested restriction as an EASI score ≥ 20 and a PGA score of 4);
 - The presence of lesions for at least 6 months from the time of initial diagnosis of chronic severe AD; and
 - Patients who have failed to achieve an adequate response to topical therapies (topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCIs).
- 3.7 The eligibility criteria of the included LEB trials were not aligned with the requested restriction as:
- All trials enrolled patients with moderate-to-severe AD, which was broader than the requested PBS population of severe AD and hence there may be potential for use outside the requested restriction;
 - Adolescent patients (aged ≥ 12 to < 18 years) weighing less than 40 kg were excluded in trials that enrolled adolescents (ADvocate 1, ADvocate 2, ADhere, ADhere J and ADvantage), but were not excluded from the requested PBS population. The safety and effectiveness of LEB in paediatric patients aged 12 years to less than 18 years who weigh less than 40 kg and paediatric subjects less than 12 years of age with moderate-to-severe AD have not been established (draft product information);
 - Patients who received prior treatment with immunosuppressive/immunomodulating drugs or phototherapy/photochemotherapy (within 4 weeks

prior to baseline) were excluded from all trials but not from the requested PBS population; and

- Patients who received treatment with DUPI (within 8 weeks of baseline visit for ADhere, ADhere J and ADvantage; within 3 months of baseline visit for KGAF) or other biologics (within five half-lives or 16 weeks prior to baseline visit, whichever is longer, in all trials) were excluded from trials but not from the requested PBS population.

The PBAC noted that the differences between the restriction criteria, TGA indication and the trial eligibility criteria were also generally present for DUPI and UPA and considered that the differences were reasonable.

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

4 Population and disease

- 4.1 AD is a chronic inflammatory disease characterised by dry skin, itching and extensive skin lesions. Symptoms may be continuous or of a relapsing-remitting nature. The clinical presentation of symptoms varies based on phase (chronic or acute) and severity of AD. Patients with severe AD have more frequent symptom flaring, and their disease is characterised by skin with pronounced dryness, red lesions, papulation, crusting and skin thickening. Patients can suffer from itchy painful skin, bleeding, sleep deprivation, an increased risk of skin infections, depression, anxiety and/or suicidal intentions.
- 4.2 LEB is an IgG4 monoclonal antibody that binds with high affinity and slow off-rate to the interleukin (IL)-13 cytokine, at an epitope that overlaps the binding site of the IL-4 receptor alpha (IL-4R α) subunit. This prevents heterodimerisation of the Type II receptor and selectively inhibits IL-13 signalling through the IL-4R α /IL-13 receptor alpha 1 (IL-13R α 1) pathway, thereby blocking the downstream effects of IL-13 with high potency. The submission claimed that emerging evidence has positioned IL-13 as a dominant driver of AD pathogenesis, and hence blocking IL-13 can have significant impacts on signalling pathways contributing to itch, skin inflammation, lichenification, infections and skin barrier defects.
- 4.3 The recommended dose of LEB (as per the draft product information) was an initial dose of 500 mg (two 250 mg injections) injected subcutaneously at Week 0 and Week 2, followed by 250 mg every two weeks (herein referred to as LEB 250 mg Q2W) until Week 16 or later, when adequate clinical response is achieved. The maintenance dose is 250 mg Q4W. However, in the TGA Clinical Evaluation Report, the evaluator recommended the PI state that treatment is administered until Week 16, and:
- For patients who achieve an adequate clinical response at Week 16, LEB 250 mg Q4W can be continued as a maintenance dose;
 - For patients who have had a less than adequate clinical response at Week 16, consideration may be given to continuing LEB 250 mg Q2W until an adequate

clinical response is achieved. Patients achieving an adequate clinical response can then continue maintenance treatment with LEB 250 mg Q4W; and

- LEB should be discontinued in patients who show no evidence of clinical benefit after 16 weeks of treatment.

- 4.4 The requested listing would place LEB as an alternative treatment option to DUPI and UPA for patients with severe disease who have failed to achieve an adequate response to topical therapy.

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

5 Comparator

- 5.1 There are currently two medicines listed on the PBS for the same population as requested for LEB – DUPI, a biologic IL-4 inhibitor, and UPA, a Janus Kinase (JAK) inhibitor.

- 5.2 The submission appropriately nominated DUPI as the main comparator. The main arguments provided in support of this nomination were:

- Both DUPI and LEB are biologics administered by subcutaneous injection and are close pharmacological analogues; and
- DUPI currently has the majority market share, positioning it as the medicine most likely to be replaced should LEB be PBS listed.

- 5.3 The submission appropriately nominated UPA (15 mg and 30 mg) as a secondary comparator due to its limited use within the Australian market (15.8% market share, compared to 84.2% market share for DUPI as claimed by the submission, though these values could not be verified during the evaluation). UPA was recommended by the PBAC for severe AD following the July 2021 meeting on a cost-minimisation basis to DUPI.

- 5.4 In the context of the CMA taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

- 5.5 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: DUPI, UPA.

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 (5), health care professionals (4) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the unmet need for individuals with AD who do not respond to current available treatment options, are contraindicated to, or experience side effects from available treatments. The comments noted that LEB may have fewer ocular side effects than DUPI and the benefits of monthly LEB injections, as opposed to fortnightly injections.

6.3 The PBAC noted the advice received from The Australasian College of Dermatologists in support of the LEB submission, noting that having an alternative treatment option is important for patients who have not achieved and maintained meaningful responses with DUPI or UPA or have experienced adverse events leading to discontinuation. The PBAC also noted the comments received from patient support groups (Eczema Association of Australasia Inc, Eczema Support Australia) in support of the LEB submission. Advice from Allergy & Anaphylaxis Australia – National Allergy Council also noted that there continues to be a high demand for treatments for severe AD and acknowledged the high budget impact of existing treatments for severe AD but emphasized the importance of having effective treatments available to patients with severe AD, noting the very severe impact of AD on affected patients and their families.

Clinical trials

6.4 No head-to-head trials comparing LEB and DUPI were available. Instead, an indirect treatment comparison (using placebo as the common comparator) was used to assess the submission's claim of non-inferior efficacy. The submission included:

- Seven randomised controlled trials (RCTs) of LEB vs placebo: Four LEB monotherapy trials (KGAF; ADvocate 1; ADvocate 2; ADOpt VA) and three LEB combination therapy trials (ADhere; ADhere J; ADvantage); and
- Nine RCTs of DUPI vs placebo: Six monotherapy trials (Study 1201; SOLO 1; SOLO2; SOLO Continue; Liberty AD ADOL; DUPI Chinese) and three DUPI combination therapy trials (CAFÉ; CHRONOS and JADE Compare). All DUPI trials except for DUPI Chinese have previously been considered by the PBAC.

6.5 The included LEB and DUPI trials enrolled patients with moderate-to-severe AD, which was broader than the proposed PBS population of severe AD patients (defined as an EASI score ≥ 20 and an IGA PGA score of 4). Therefore, the submission was based on *post-hoc* analyses of the severe AD subgroup of patients for the composite outcome

only. For LEB, this was informed by ADvocate 1, ADvocate 2, and ADhere, while for DUPI, this was informed by Study 1021, SOLO 1, SOLO 2, and CHRONOS (as reported in the DUPI Public Summary Document (PSD), March 2020 PBAC meeting). It was unclear why the submission only included ADvocate 1, ADvocate 2 and ADhere in their indirect treatment comparison for the severe AD subgroup even though data from other LEB trials (KGAF, ADhere J, and ADvantage) appear to have been available, particularly when there was a lack of sample size in the LEB combination trial in severe AD, with only one combination therapy trial (ADhere) included with small patient numbers in the severe AD subgroup (LEB=23; placebo=6).

- 6.6 While the proposed restrictions were for patients 12 years of age or older, the submission did not present an indirect comparison of LEB vs DUPI specifically for adolescents (aged 12 to <18 years) nor adults (aged ≥ 18 years) with severe AD. Among patients enrolled in ADvocate 1 and ADvocate 2, 10.7%-13.1% were adolescents between 12 to <18 years old. However, in the submission, results from patients aged 12 years or older from LEB trials were compared to DUPI trials which only enrolled adults (≥18 years). This represented a potential transitivity issue as it was unclear if patient age could be a treatment effect modifier. This was also inconsistent with the economic evaluation which included adolescent and adult population for DUPI.
- 6.7 The comparative effectiveness and safety of LEB and DUPI in the whole trial populations (i.e., moderate and severe AD patients) for outcomes at Week 16 was used by the submission as supportive evidence.
- 6.8 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Lebrikizumab trials		
KGAF (NCT03443024)	A randomised, Double Blind, Placebo Controlled, Dose ranging trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate to severe atopic dermatitis.	Clinical Study Report, 7 March 2018
	A randomised, Double Blind, Placebo Controlled, Dose ranging trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate to severe atopic dermatitis.	Protocol, 29 January 2018, 7 March 2018 (Amendment B)
	Guttman-Yassky et al. Efficacy and Safety of Lebrikizumab, a High Affinity Interleukin 13 Inhibitor, in Adults with Moderate to Severe Atopic Dermatitis A Phase 2b Randomized Clinical Trial.	<i>JAMA Dermatol</i> 2020;156 (4): 411-420.
ADvocate 1 (NCT04146363)	A randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate to severe atopic dermatitis.	Clinical Study Report, 20 May 2020
	A randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate to severe atopic dermatitis. Silverberg et al. (2023). Two Phase 3 Trials of Lebrikizumab for Moderate to Severe Atopic Dermatitis.	Protocol, 16 October 2019, 20 May 2020 (Amendment B) <i>N Engl Med</i> 2023; 388 (12): 1080-1091.
ADvocate 2 (NCT04178967)	A randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate to severe atopic dermatitis.	Clinical Study Report, 20 May 2020

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Trial ID	Protocol title/ Publication title	Publication citation
	A randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate to severe atopic dermatitis. Silverberg et al. (2023). Two Phase 3 Trials of Lebrikizumab for Moderate to Severe Atopic Dermatitis.	Protocol, 16 October 2019, 20 May 2020 (Amendment B). <i>N Engl Med</i> 2023; 388 (12): 1080 1091.
ADopt VA (NCT04626297)	A Phase 3, 16 week, Randomised, Double Blind, Placebo Controlled, Parallel Group Study to assess the impact of lebrikizumab on vaccine responses in adult patients with moderate to severe atopic dermatitis. A Phase 3, 16 week, Randomised, Double Blind, Placebo Controlled, Parallel Group Study to assess the impact of lebrikizumab on vaccine responses in adult patients with moderate to severe atopic dermatitis.	Clinical Study Report, 5 August 2020 Protocol, 5 August 2020
ADhere (NCT04250337)	A Randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of lebrikizumab when used in combination with topical corticosteroid treatment in patients with moderate to severe atopic dermatitis. A Randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of lebrikizumab when used in combination with topical corticosteroid treatment in patients with moderate to severe atopic dermatitis. Simpson et al. (2023). Efficacy and Safety of Lebrikizumab in Combination with Topical Corticosteroids in Adolescents and Adults with Moderate to Severe Atopic Dermatitis A Randomized Clinical Trial (ADhere)	Clinical Study Report, 13 May 2020 Protocol, 26 November 2019, 13 May 2020 (Amendment A) <i>JAMA Dermatol</i> 2023;159 (2):182 191.
ADhere J (NCT0470314)	A randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of Lebrikizumab when used in combination with topical corticosteroid treatment in Japanese patients with moderate to severe atopic dermatitis. A randomised, double blind, placebo controlled trial to evaluate the efficacy and safety of Lebrikizumab when used in combination with topical corticosteroid treatment in Japanese patients with moderate to severe atopic dermatitis.	Clinical Study Report, 19 November 2020 Protocol, 19 November 2020, 22 January 2021 (Amendment A)
ADvantage (NCT05149313)	A randomised, double blind, placebo controlled Phase 3 clinical trial to assess the efficacy and safety of lebrikizumab in combination with topical corticosteroids in adult and adolescent patients with moderate to severe atopic dermatitis that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable A randomised, double blind, placebo controlled Phase 3 clinical trial to assess the efficacy and safety of lebrikizumab in combination with topical corticosteroids in adult and adolescent patients with moderate to severe atopic dermatitis that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable	Clinical Study Report, September 2023 Protocol, 1 June 2021
Dupilumab trials		
Study 1021 (NCT01859988)	Thaçi et al. Efficacy and safety of dupilumab in adults with moderate to severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo controlled, dose ranging phase 2b trial. Simpson et al. Dupilumab therapy provides clinically meaningful improvement in patient reported outcomes (PROs): A phase IIb, randomized, placebo controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). Tofte et al. Efficacy and safety of dupilumab for the treatment of moderate to severe atopic dermatitis in adults: A pooled analysis of two phase 2 clinical trials.	<i>Lancet</i> 2016; 387 (10013): 40 52. <i>J Am Acad Dermatol</i> 2016; 75 (3): 506 515. <i>J Am Assoc Nurse Prac</i> 2018; 30 (9): 529 541.

Trial ID	Protocol title/ Publication title	Publication citation
SOLO 1 & SOLO 2 & SOLO Continue (NCT02277743; NCT02277769; NCT02395133)	Simpson et al. Two Phase 3 Trials of dupilumab versus placebo in atopic dermatitis. Thaçi et al. Efficacy and safety of dupilumab monotherapy in adults with moderate to severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). Simpson. Dupilumab Improves General Health Related Quality of Life in Patients with Moderate to Severe Atopic Dermatitis: Pooled Results from Two Randomized, Controlled Phase 3 Clinical Trials. Silverberg et al. Dupilumab provides important clinical benefits to patients with atopic dermatitis who do not achieve clear or almost clear skin according to the Investigator's Global Assessment: a pooled analysis of data from two phase III trials. Cork et al. Dupilumab improves patient reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health related quality of life in moderate to severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. Worm et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis.	<i>New Engl J Med</i> 2016; 375 (24): 2335 2348. <i>J Dermatol Science</i> 2019; 94 (2): 266 275. <i>Dermatol Ther</i> 2017; 7 (2): 243 248. <i>Br J Dermatol</i> 2019; 181 (1): 80 87. <i>J Dermatolog Treat</i> 2020; 31 (6): 606 614. <i>JAMA Dermatol</i> 2020; 156(2):131 143
Liberty AD ADOL (NCT03054428)	Simpson et al. Efficacy and Safety of Dupilumab in Adolescents with Uncontrolled Moderate to Severe Atopic Dermatitis A Phase 3 Randomized Clinical Trial.	<i>JAMA Dermatol</i> 2020;156 (1):44 56.
DUPI Chinese (NCT03912259)	Zhao et al. The efficacy and safety of dupilumab in Chinese patients with moderate to severe atopic dermatitis: a randomized, double blind, placebo controlled study.	<i>Br J Dermatol</i> 2022 Apr;186 (4):633 641.
CHRONOS (NCT02260986)	Blauvelt et al. Long term management of moderate to severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1 year, randomised, double blinded, placebo controlled, phase 3 trial. Thomson et al. Long term management of moderate to severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal.	<i>Lancet</i> 2017; 389 (10086): 2287 2303. <i>Br J Dermatol</i> 2018; 178 (4): 897 902.
CAFÉ (NCT02755649)	de Bruin-Weller et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ).	<i>Br J Dermatol</i> 2018; 178 (5): 1083 1101.
JADE Compare (NCT03720470)	Bieber et al. Abrocitinib versus placebo or Dupilumab for Atopic Dermatitis. Thyssen et al. Patient reported outcomes from the JADE COMPARE randomized phase 3 study of abrocitinib in adults with moderate to severe	<i>N Engl J Med</i> 2021; 384:1101 1112. <i>J Eur Acad Dermatol Venereol</i> 2022 Mar; 36 (3):434 443.

Source: Table 2.2-1, pp54-58 of the submission.

Blue shading indicates trials previously considered by the PBAC.

6.9 The key features of the included randomised LEB and DUPI trials are summarised in Table 3.

Table 3: Key features of the included evidence

Study	N	Design/duration	Bias	Relevant comparison	Population	Primary outcomes
Lebrikizumab trials						
KGAF	127 ^a	P2b, R, MC, DB, PC, 16wk, rescue therapy allowed	Low	LEB 250 mg Q2W ^b PBO Q2W	M-S AD; adults	% change in EASI at wk16
ADvocate 1	424	P3, R, MC, DB, PC, 16wk ^c , rescue therapy allowed	Low	LEB 250 mg Q2W ^b PBO Q2W	M-S AD; adults & adolescents	IGA 0/1 ^d & EASI 75 at wk16
ADvocate 2	427					
ADopt VA	247	P3, R, MC, DB, PC, 16wk, rescue therapy allowed	Low	LEB 250 mg Q2W ^b PBO Q2W	M-S AD; aged 18 to 55 years	Booster response to TT & +antibody response to MCV
ADhere	211	P3, R, MC, DB, PC, 16wk, rescue therapy allowed	Low	LEB 250 mg Q2W ^b + TCS PBO Q2W + TCS	M-S AD; adults & adolescents	IGA 0/1 ^d & EASI 75 at wk16
ADhere J	205 ^a	P3, R, MC, DB, PC, 16wk ^c , rescue therapy allowed	Low	LEB 250 mg Q2W ^b + TCS PBO Q2W + TCS	M-S AD; adults & adolescents	IGA 0/1 ^d & EASI 75 at wk16
ADvantage	331	P3, MC, R, DB, PC, 16 wk ^c , rescue therapy allowed	Low	LEB 250 mg Q2W ^b + TCS PBO Q2W + TCS	M-S AD; adults & adolescents	EASI 75 at wk16
Dupilumab trials						
Study 1021	125 ^a	P2b, R, MC, DB, PC 16wk, rescue therapy allowed	Low	DUPI 300 mg Q2W ^e PBO	M-S AD; adults	% change in EASI at wk16
SOLO 1	448 ^a	P3, R, MC, DB, PC 16wk, rescue therapy allowed	Low	DUPI 300 mg Q2W ^e PBO	M-S AD; adults	IGA 0/1 ^d & EASI 75 ^f at wk16
SOLO 2	469 ^a					
LIBERTY AD ADOL	167 ^a	P3, R, MC, DB, PC, AC 16wk, rescue therapy allowed	Low	DUPI 200/300 mg Q2W ^e PBO	M-S AD; adolescents	IGA 0/1 ^d & EASI 75 at wk16
DUPI Chinese	165	P3, R, MC, DB, PC 16wk, rescue therapy allowed	Low	DUPI 300 mg Q2W ^e PBO	M-S AD; adults	IGA 0/1 ^c
CAFÉ	215 ^a	P3, R, MC, DB, PC 16wk, rescue therapy allowed	Low	DUPI 300 mg Q2W ^e +TCS PBO +TCS	M-S AD; adults	EASI 75 at wk16
CHRONOS	421 ^a	P3, R, MC, DB, PC 52wk, rescue therapy > wk2	Low	DUPI 300 mg Q2W ^e +TCS PBO +TCS	M-S AD; adults	IGA 0/1 ^d and EASI 75 at wk16
JADE COMPARE	373 ^a	P3, R, MC, DB, DD, PC, AC 16wk, rescue therapy NP	Low	DUPI 300 mg Q2W ^e +TCS PBO +TCS	M-S AD; adults	IGA 0/1 ^d and EASI 75 at wk12

Source: Tables 2.2-3, 2.2-4, 2.2-5, 2.2-6, pp 61-63, 65, 66, 68-71, 73, 74 of the submission and Table 2, p 12 of the upadacitinib PSD, July 2021 PBAC meeting.

P2/3 = phase 2 or 3; DB = double blind; DD = double dummy; MC = multi-centre; R = randomised;; PC = placebo-controlled; AC = active control; LEB = lebrikizumab; TCS = topical corticosteroids; wk = week; TT = tetanus toxoid; DUPI = dupilumab; PBO = placebo; Q2W = once every 2 weeks; Q4W = once every 4 weeks; IGA = investigator's global assessment; EASI = Eczema Area and Severity Index; EASI 75 = improvement of at least 75% from baseline in Eczema Area and Severity Index; M-S = moderate-to-severe; NP = not permitted

a Excluding patients randomised to the treatment arms which are not relevant to the submission

b 'LEB 250 mg Q2W' comprised of 500 mg loading at baseline and Week 2, then 250 mg Q2W from Week 4 to Week 16.

c The following trials had a longer duration overall:

ADvocate 1 & 2: Patients were re randomised at week 16 and then continued for treatment for a further 36 weeks maintenance period (52 weeks in total)

ADhere J: 16-week induction period followed by a 52-week maintenance period (68 weeks in treatment duration)

ADvantage: two treatment periods – a 16-week double-blind induction period, followed by a 36-week open-label maintenance period

d Proportion of patients achieving IGA of 0 or 1 with a ≥ 2 -point improvement (i.e.: from a baseline of 3 or 4 on the 5-point IGA scale)

e 'DUPI 300 mg Q2W' comprised of 600 mg loading, then 300 mg every 2 weeks thereafter; 'DUPI 200 mg Q2W' comprised 400 mg loading, then 200 mg every two weeks thereafter.

f EASI 75 was a coprimary outcome in EU and Japan and a key secondary outcome elsewhere.

Blue shading indicates trials previously considered by PBAC

6.10 The submission included both monotherapy and combined therapy trials (which included the use of concomitant TCS). The PBAC has previously considered standard of care included concomitant TCS and considered that the trials that allowed ongoing use of TCS were the most relevant to Australian clinical practice, where TCS would be

expected to be continued in combination with other treatment (paragraph 6.10, UPA PSD, July 2021 PBAC meeting). All the LEB and DUPI trials included were double-blind, randomised, placebo-controlled trials which assessed primary/key secondary outcomes at Week 16.

- 6.11 The submission did not present the characteristics of the patients for the severe AD subgroup (nor the complement) even though the submission was seeking listing for this subgroup and relied on subgroup analyses for the proposed clinical claim. Therefore, it was unclear what these differences are and whether these differences may bias or confound the observed treatment effect. The characteristics of the requested PBS population (i.e., severe AD, defined as EASI score ≥ 20 and PGA score = 4) did not appear to be available within the Clinical Study Reports as it was not a pre-specified subgroup in any of the included trials.
- 6.12 The submission's claim of non-inferiority in the PBS population of severe AD was based on the proportion of patients who achieved the composite outcome of EASI 50 and DLQI improvement of ≥ 4 points from baseline at 16 weeks. This was not a prespecified outcome in any of the included trials and instead was constructed as a post-hoc outcome to align with the proposed (and the existing for DUPI and UPA) continuing criteria for treatment of severe AD affecting the whole body. The PBAC has previously considered EASI and DLQI outcomes as being key patient relevant outcomes for the treatment of AD; and accepted that for patients with AD affecting the whole body, an EASI 50 response combined with a DLQI improvement of ≥ 4 points were likely to be clinically reasonable and able to capture patients with a meaningful response to treatment (paragraph 7.4, DUPI PSD March 2020 PBAC meeting).
- 6.13 The submission's criteria for non-inferiority was an absence of a statistically significant difference in the indirect treatment comparisons for efficacy and safety. This was not stringent and may be insufficient to establish non-inferiority with a degree of certainty. As noted by the indirect comparison working group¹, "the formula for the confidence interval of an appropriately calculated indirect comparison involves two separate variances, leading to a wider confidence interval for the indirect comparison than that seen in either of the constituent direct comparisons" and "(t)he confidence intervals often encompass both clinically significant and non-significant differences, leading to indeterminate results". As such, it would be much more likely for an indirect comparison to report a lack of statistical significance and any conclusion of non-inferiority based on the lack of statistical difference alone should therefore be considered highly uncertain. No non-inferiority margins (for efficacy or safety) were proposed by the submission.

¹ Indirect comparison working group (2008) Report of the Indirect Comparisons Working Group to the Pharmaceutical Benefits Advisory Committee: assessing indirect comparisons. <https://www.pbs.gov.au/industry/useful-resources/pbac-technical-working-groups-archive/indirect-comparisons-working-group-report-2008.pdf>

- 6.14 A non-inferiority margin was not nominated in the submission for UPA 15 mg (against DUPI), considered at the July 2021 PBAC meeting. While the PBAC noted that the indirect comparison found no statistically significant difference between UPA 15 mg versus DUPI (paragraph 7.6, UPA PSD, July 2021 PBAC meeting), the PBAC's view that the clinical claim of non-inferiority was reasonably supported was based on the totality of evidence presented in the submission, and as such the lack of statistically significant difference alone may not be sufficient to demonstrate non-inferiority. A non-inferiority margin was not nominated for UPA 30 mg (against DUPI) given the submission's claim of superior efficacy.
- 6.15 AD affecting the face and/or hands was defined as at least 2 of the EASI subscores rated as severe or the condition must have affected at least 30% of the face/hands surface area. As there were no clinical trials of LEB (or the comparators) that enrolled patients specifically with severe AD affecting the face and/or hands, *post hoc* analyses of ADvocate 1, ADvocate 2 and ADhere were used by the submission as evidence that LEB is associated with improvements in AD affecting the face and hands. Efficacy was assessed based on a 4-point scale by the submission (from baseline to Week 16): cleared, improved, no change, or worsened.
- 6.16 It was unclear if this was a formal or validated scale and may carry a degree of uncertainty as an outcome measure. Comparatively, the basis for the extension of listing of DUPI to patients with disease affecting the face and/or hands was based on improvements in EASI score of DUPI in different body regions (head and neck, upper extremities, trunk, lower extremities) in patients enrolled in the DUPI clinical trials (paragraph 3.4, DUPI PSD, March 2020 PBAC meeting). Similarly, the evidence provided to support listing of UPA in patients with severe AD affecting the face and/or hands was based on post-hoc analysis from the HEADS UP trial (direct comparison of UPA 30 mg vs DUPI) of response rates across body regions captured in the EASI score (head and neck, upper extremities, lower extremities, trunk) (paragraph 6.19, UPA PSD, July 2021 PBAC meeting).
- 6.17 As not all outcomes were reported consistently across the LEB and DUPI trials, the submission relied on only select outcomes (EASI 50; DLQI \geq 4-point improvement; IGA 0/1 with at least 2-point improvement (abbreviated to IGA 0/1); and EASI 75) to inform the meta-analyses and indirect comparison for the whole trial population, which were used as supportive evidence for the submission's claim of non-inferior efficacy.
- 6.18 In ADvocate 1, ADvocate 2 and ADhere J, both LEB 250 mg Q2W and LEB 250 mg Q4W were used as maintenance therapy after Week 16. However, only the Q4W dosing frequency was proposed in the draft product information. The submission claimed that patients treated with Q2W had similar response rate to Q4W during the maintenance period and a Q4W dosing was used in both the economic and financial estimates.
- 6.19 In ADvocate 1 and ADvocate 2 and ADhere J, non-responders at Week 16 could enrol in an escape arm in which all patients received LEB 250 mg Q2W. Data from the escape

arm was relied upon by the submission to inform the proposed ‘slow responders’ (see Paragraph 3.3).

- 6.20 For the comparison with the secondary comparator UPA, indirect comparisons (with placebo as the common comparator) using results from ADvocate 1, ADvocate 2 and ADhere and five UPA trials (M16-048, MEASURE UP 1, MEASURE UP 2, AD UP and RISING UP) were presented. The PBAC has previously considered all of the included UPA trials.

Comparative effectiveness

Indirect treatment comparison (severe AD subgroup)

- 6.21 Table 4, Table 5 and Table 6 summarises the indirect treatment comparison between LEB and DUPI for the severe AD subgroup using placebo as the common comparator for the composite outcome (EASI 50 + DLQI ≥ 4-point improvement) and its individual components respectively.

Table 4: ITC in the severe AD subgroup for the composite outcome (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	DUPI 300 mg Q2W ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
ADvocate 1	46/82 (56.1)	4/41 (9.8)	-	5.8 (2.2, 14.9)	0.46 (0.32, 0.60)
ADvocate 2	35/75 (46.7)	6/42 (14.3)	-	3.3 (1.5, 7.1)	0.32 (0.17, 0.48)
ADhere	14/23 (60.9)	2/6 (33.3)	-	1.8 (0.6, 5.9)	0.28 (-0.15, 0.70)
LEB trials pooled	95/180 (52.8)	12/89 (13.5)	-	3.5 (1.9, 6.2)	0.39 (0.29, 0.50)
DUPI CsA experienced	-	25/178 (14.0)	91/152 (59.9)	4.3 (2.9, 6.3)	0.46 (0.37, 0.55)
DUPI CsA naive	-	49/246 (19.9)	99/166 (59.6)	3.0 (2.3, 4.0)	0.40 (0.31, 0.49)
DUPI trials pooled	-	74/424 (17.5)	190/318 (59.7)	3.5 (2.5, 4.9)	0.43 (0.36, 0.49)
Indirect treatment comparison: all trials pooled				0.99 (0.50, 1.96)	-0.03 (-0.16, 0.09)

Source: Table 2.6-4, p215 of the submission.

AD = atopic dermatitis; CI = confidence interval; CsA = ciclosporin; DLQI = dermatology life quality index; DUPI = dupilumab; EASI = eczema area and severity index; ITC = indirect comparison; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Blue shading indicates results previously considered by PBAC.

Table 5: ITC in the severe AD subgroup for EASI 50 (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	DUPI 300 mg Q2W ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
ADvocate 1	68/105 (64.8)	12/53 (22.6)	-	2.9 (1.7, 4.8);	0.42 (0.28, 0.57)
ADvocate 2	59/99 (59.6)	8/50 (16.0)	-	3.7 (1.9, 7.2)	0.44 (0.30, 0.58)
ADhere	20/29 (69.0)	4/9 (44.4)	-	1.6 (0.7, 3.4)	0.25 (-0.12, 0.61)
LEB trials pooled	147/233 (63.1)	24/112 (21.4)	-	2.7 (1.7, 4.2)	0.42 (0.32, 0.51)
DUPI CsA experienced	-	36/178 (20.2)	102/152 (67.1)	3.3 (2.4, 4.5)	0.47 (0.37, 0.56)
DUPI CsA naive	-	59/246 (24.0)	111/166 (66.9)	2.8 (2.2, 3.6)	0.43 (0.34, 0.52)
DUPI trials pooled	-	95/424 (22.4)	213/318 (67.0)	3.0 (2.5, 3.6)	0.45 (0.38, 0.51)
Indirect treatment comparison: all trials pooled				0.89 (0.54, 1.47)	-0.03 (-0.15, 0.09)

Source: Table 2.6-5, p217 of the submission.

AD = atopic dermatitis; CI = confidence interval; CsA = ciclosporin; DUPI = dupilumab; EASI = eczema area and severity index; ITC = indirect comparison; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Blue shading indicates results previously considered by PBAC.

Table 6: ITC in the severe AD subgroup for DLQI ≥ 4-point improvement (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	DUPI 300 mg Q2W ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
ADvocate 1	55/82 (67.1)	7/41 (17.1)	-	3.9 (2.0, 7.8)	0.50 (0.35, 0.65)
ADvocate 2	42/75 (56.0)	13/42 (31.0)	-	1.8 (1.1, 3.0)	0.25 (0.07, 0.43)
ADhere	18/23 (78.3)	4/6 (66.7)	-	1.2 (0.6, 2.1)	0.12 (-0.30, 0.53)
LEB trials pooled	115/180 (63.9)	24/89 (27.0)	-	2.0 (1.0, 3.9)	0.33 (0.11, 0.55)
DUPI CsA experienced	-	49/178 (27.5)	105/152 (69.1)	2.5 (1.9, 3.3)	0.42 (0.32, 0.51)
DUPI CsA naive	-	78/246 (31.7)	114/166 (68.7) ^a	2.2 (1.8, 2.7)	0.37 (0.28, 0.46)
DUPI trials pooled	-	127/424 (30.0)	249/318 (68.9)	2.3 (2.0, 2.7)	0.39 (0.32, 0.46)
Indirect treatment comparison: all trials pooled				0.87 (0.43, 1.75)	-0.06 (-0.29, 0.17)

Source: Table 2.6-6, p219 of the submission.

AD = atopic dermatitis; CI = confidence interval; CsA = ciclosporin; DLQI = dermatology life quality index; DUPI = dupilumab; ITC = indirect comparison; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

^a Erroneously reported by the submission (as 144). This was corrected during the evaluation from Table 9, DUPI PSD, March 2020 PBAC meeting.

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Blue shading indicates results previously considered by PBAC.

- 6.22 In the post hoc subgroup analysis of severe AD patients, there was no statistically significant difference (defined as 95% confidence interval (CI) including 1 for relative risk (RR) or 0 for risk difference (RD)) between LEB 250 mg Q2W and placebo in ADhere. As mentioned in paragraph 6.5, the number of patients in the severe AD subgroup in ADhere was small (LEB=23; placebo=6). Comparatively, all other trials reported statistically significant results favouring LEB or DUPI compared to placebo.
- 6.23 In the indirect comparison, there was no statistically significant difference between LEB and DUPI for the proportions of severe AD patients who achieved the composite outcome nor its individual components (EASI 50 or DLQI ≥ 4-point improvement). While results were not statistically significant, the reported point estimates were in favour of DUPI and the 95% CI was large, indicating large range of uncertainty associated with the indirect comparison. The upper and lower 95% CI for RR was 0.50 and 1.96 in the indirect comparison, suggesting that the proportion of patients treated with LEB who achieve the composite outcome could range from being half that of DUPI or nearly twice as high as DUPI.
- 6.24 The submission noted that the proportion of patients achieving the composite outcome and its components was generally lower in LEB monotherapy trials and higher in the LEB combination therapy trial ADhere, regardless of treatment (LEB or placebo) received. The submission described that the use of concomitant TCS was likely to be the reason for increased response rates in ADhere compared with the monotherapy trials. The magnitude of difference between the two arms was also smaller in the combination therapy trial i.e., the observed RR and RD for ADhere tended to be lower than those in reported in the monotherapy trials. This was consistent with PBAC observation for baricitinib where the benefit appeared to be somewhat attenuated in the trials that allowed concomitant TCS (paragraph 6.23, baricitinib PSD, July 2021 PBAC meeting). Given the PBAC has previously considered that TCS would be expected to be continued in combination with other treatment in

Australian clinical practice (paragraph 6.10, UPA PSD, July 2021 PBAC meeting), the observed pooled treatment effect for the composite outcome (RR=3.45, 95%CI: 1.91, 6.22) which included a majority of LEB monotherapy patients (157 out of 180 LEB patients with severe AD) may be overestimated compared to use in the proposed population. Further, the results of the indirect comparison may possibly be biased in favour of LEB if the ratio of patients treated with combination therapy (DUPI + TCS) in the pooled estimates for DUPI was higher than those observed for LEB, though this was unclear and could not be verified during the evaluation.

- 6.25 On balance, the clinical evidence presented by the submission indicates that LEB 250 mg Q2W ± TCS was likely better than placebo ± TCS. However, the evaluation considered the clinical evidence may not adequately support the submission’s claim that LEB 250 mg Q2W ± TCS was non-inferior to DUPI 300 mg Q2W ± TCS. Given the lower bound 95% CI for RR was 0.50 in the indirect comparison for the composite outcome, in order to accept that LEB is non-inferior to DUPI, the non-inferiority margin must be set as 0.50 or less i.e. willingness to accept that LEB may be half as good as DUPI but be considered non-inferior.

Indirect treatment comparison (whole trial population)

- 6.26 The pooled results of the meta-analyses for LEB and DUPI and indirect comparisons in the whole trial populations (i.e., moderate and severe AD patients) for the efficacy outcomes of EASI 75, EASI 50, DLQI ≥ 4-point improvement and IGA 0/1 at week 16 are presented in Table 7, Table 8, Table 9 and Table 10, respectively.

Table 7: Meta-analysis and indirect comparison (whole trial population) for EASI 75 (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	DUPI 300 mg ± TCS	RR (95% CI) Active treatment ± TCS vs PBO ± TCS	RD (95% CI)
Monotherapy trials					
LEB trials pooled	408/764 (53.4)	83/461 (18.0)	-	2.96 (2.27, 3.85)	0.36 (0.31, 0.42)
DUPI trials pooled ^a	-	87/689 (12.6)	333/685 (48.6)	3.82 (3.09, 4.71)	0.36 (0.31, 0.40)
ITC: monotherapy trials pooled ^a (corrected during the evaluation)				0.77 (0.55, 1.09)	0.00 (-0.07, 0.07)
ITC: monotherapy trials pooled (as presented in the submission)				0.87 (0.59, 1.27)	0.01 (-0.06, 0.08)
Combination therapy trials					
LEB trials pooled	310/488 (63.5)	82/259 (31.7)	-	2.04 (1.39, 2.98)	0.31 (0.24, 0.38)
DUPI trials pooled ^a	-	143/554 (25.8)	292/455 (64.2)	2.43 (1.92, 3.07)	0.38 (0.30, 0.46)
ITC: combination therapy trials pooled ^a (corrected during the evaluation)				0.84 (0.54, 1.31)	-0.07 (-0.18, 0.04)
ITC: combination therapy trials pooled (as presented in the submission)				0.80 (0.48, 1.33)	-0.09 (-0.23, 0.05)
All trials					
LEB all trials pooled	718/1252 (57.3)	165/720 (22.9)	-	2.53 (1.90, 3.38)	0.34 (0.30, 0.39)
DUPI all trials pooled	-	230/1243 (18.4)	625/1140 (54.8)	3.07 (2.49, 3.77)	0.37 (0.33, 0.40)
ITC: all trials pooled (estimated during the evaluation)				0.82 (0.58, 1.18)	-0.03 (-0.09, 0.03)
ITC: all trials pooled (as presented in the submission)				0.82 (0.58, 1.18)	-0.02 (-0.08, 0.04)

Source: Table 2.6-11, pp230-232 of the submission.

CI = confidence interval; DUPI = dupilumab; EASI = eczema area and severity index; LEB = lebrikizumab; OR = odds ratio; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

^a Indicates values corrected during the evaluation using random effects on StatsDirect v3, due to the re-classification of JADE Compare (as a combination therapy trial).

RR and RD were estimated using StatsDirect v3

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Table 8: Meta-analysis and indirect comparison (whole trial population) for EASI 50 (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	DUPI 300 mg ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
Monotherapy trials					
LEB trials pooled	533/764 (69.8)	155/461 (33.6)	-	2.1 (1.8, 2.4)	0.37 (0.32, 0.42)
DUPI trials pooled ^a	-	160/689 (23.2)	464/685 (67.7)	2.9 (2.5, 3.3)	0.45 (0.40, 0.49)
ITC: monotherapy trials pooled ^a (corrected during the evaluation)				0.73 (0.60, 0.89)	-0.08 (-0.15, -0.01)
ITC: monotherapy trials pooled (as presented in the submission)				0.80 (0.55, 1.17)	-0.04 (-0.13, 0.04)
Combination therapy trials					
LEB trials pooled	397/488 (81.4)	135/259 (52.1)	-	1.6 (1.1, 2.3)	0.30 (0.11, 0.49)
DUPI trials pooled ^a	-	236/547 (43.1)	371/445 (83.4)	1.82 (1.43, 2.33)	0.37 (0.27, 0.47)
ITC: combination therapy trials pooled ^a (corrected during the evaluation)				0.89 (0.57, 1.38)	-0.07 (-0.29, 0.15)
ITC: combination therapy trials pooled (as presented in the submission)				0.78 (0.53, 1.16)	-0.12 (-0.33, 0.08)
All trials					
LEB all trials pooled	930/1252 (74.3)	290/720 (40.3)	-	1.85 (1.48, 2.33)	0.34 (0.26, 0.42)
DUPI all trials pooled	-	396/1236 (32.0)	835/1130 (73.9)	2.39 (1.90, 3.01)	0.42 (0.37, 0.46)
ITC: all trials pooled				0.77 (0.56, 1.07)	-0.08 (-0.17, 0.01)

Source: Table 2.6-8, pp222-223 of the submission.

CI = confidence interval; DUPI = dupilumab; EASI = eczema area and severity index; LEB = lebrikizumab; NA = not applicable; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

^a Indicates values corrected during the evaluation using random effects on StatsDirect v3, due to the re-classification of JADE Compare (as a combination therapy trial).

RR and RD were estimated using StatsDirect v3

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Table 9: Meta-analysis and indirect comparison (whole trial population) for DLQI ≥ 4-point improvement (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	DUPI 300 mg ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
Monotherapy trials					
LEB trials pooled	342/516 (66.3)	87/283 (30.7)	-	2.14 (1.78, 2.58)	0.35 (0.27, 0.43)
Combination therapy trials					
LEB trials pooled	286/380 (75.3)	100/202 (49.5)	-	1.71 (0.97, 3.02)	0.28 (0.03, 0.52)
DUPI trials pooled ^a	-	242/514 (47.1)	357/433 (82.4)	1.70 (1.34, 2.17)	0.34 (0.21, 0.47)
ITC: combination therapy trials pooled ^a (corrected during the evaluation)				1.01 (0.54, 1.86)	-0.06 (-0.34, 0.22)
ITC: combination therapy trials pooled (as presented in the submission)				0.89 (0.51, 1.56)	-0.13 (-0.40, 0.13)
All trials					
LEB all trials pooled	628/896 (70.1)	187/485 (38.6)	-	1.89 (1.32, 2.71)	0.31 (0.19, 0.43)
DUPI all trials pooled	-	242/514 (47.1)	357/433 (82.4)	1.70 (1.34, 2.17)	0.34 (0.21, 0.47)
ITC: all trials pooled (as presented in the submission)				1.11 (0.73, 1.67)	-0.03 (-0.21, 0.15)

Source: Table 2.6-9, pp225-226 of the submission.

CI = confidence interval; DLQI = dermatology life quality index; DUPI = dupilumab; LEB = lebrikizumab; NA = not applicable; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

Note: Given the outcome of DLQI ≥ 4-point improvement, the N (denominator) should be the number of patients in the trial population with Baseline DLQI score of at least 4.

^a Indicates values corrected during the evaluation using random effects on StatsDirect v3, due to the re-classification of JADE Compare (as a combination therapy trial). For this outcome, values for ADvantage were corrected during the evaluation, which impacted the results.

RR and RD were estimated using StatsDirect v3

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Table 10: Meta-analysis and indirect comparison (whole trial population) for IGA 0/1 (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	DUPI 300 mg ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
Monotherapy trials					
LEB trials pooled	280/764 (36.6)	51/461 (11.1)	-	3.32 (2.52, 4.38)	0.26 (0.21, 0.30)
DUPI trials pooled ^a	-	50/689 (7.3)	230/685 (33.6)	4.45 (3.23, 6.12)	0.26 (0.22, 0.30)
ITC: monotherapy trials pooled ^a (corrected during the evaluation)				0.75 (0.49, 1.14)	0.00 (-0.06, 0.06)
ITC: monotherapy trials pooled (as presented in the submission)				0.83 (0.53, 1.29)	0.00 (-0.05, 0.06)
Combination therapy trials					
LEB trials pooled	189/488 (38.7)	45/259 (17.4)	-	2.32 (1.35, 3.97)	0.22 (0.15, 0.28)
DUPI trials pooled ^a	-	70/554 (12.6)	174/455 (38.2)	3.04 (2.35, 3.95)	0.26 (0.20, 0.31)
ITC: combination therapy trials pooled ^a (corrected during the evaluation)				0.76 (0.42, 1.39)	-0.04 (-0.13, 0.05)
ITC: combination therapy trials pooled (as presented in the submission)				0.76 (0.41, 1.42)	-0.05 (-0.14, 0.05)
All trials					
LEB all trials pooled	469/1252 (37.5)	96/720 (13.3)	-	2.80 (2.08, 3.78)	0.24 (0.21, 0.28)
DUPI all trials pooled ^a	-	402/1140 (35.4)	120/1243 (9.7)	3.61 (2.92, 4.46)	0.26 (0.23, 0.29)
ITC: all trials pooled ^a (calculated during the evaluation)				0.78 (0.54, 1.12)	-0.02 (-0.07, 0.03)
ITC: all trials pooled (as presented in the submission)				0.79 (0.54, 1.15)	-0.01 (-0.06, 0.04)

Source: Table 2.6-10, pp227-229 of the submission.

CI = confidence interval; DUPI = dupilumab; IGA = investigator's global assessment; LEB = lebrikizumab; NA = not applicable; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

^a Indicates values corrected during the evaluation using random effects on StatsDirect 3, due to the re-classification of JADE Compare (as a combination therapy trial). For this outcome, values for JADE Compare were corrected during the evaluation.

RR and RD were estimated using StatsDirect v3

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

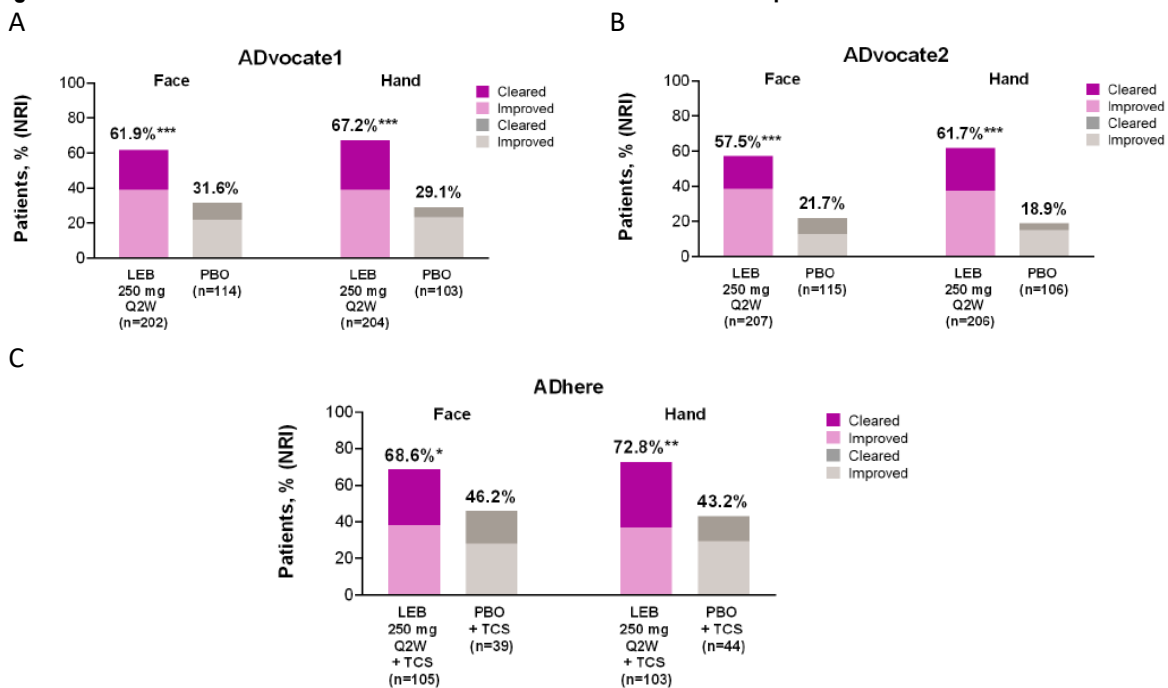
- 6.27 For the efficacy outcomes of EASI 75, EASI 50, DLQI \geq 4-point improvement and IGA 0/1, patients with moderate-to-severe AD (whole trial population) tended to respond more favourably with active treatment (LEB or DUPI) compared to placebo, with all trials achieving statistically significant results (95%CI did not include 1 or 0 for RR and RD respectively) against placebo, except in the LEB trial ADvantage for the outcome of DLQI \geq 4-point improvement (RR=1.1, 95% CI: 1.0, 1.3; RD=0.09, 95%CI: -0.02, 0.20). Once pooled (meta-analyses), results were also statistically significant, except for the LEB combination therapy trials for the outcome of DLQI \geq 4-point improvement (RR=1.71, 95%CI: 0.97, 3.02; though the RD was significant (RD=0.28, 95%CI: 0.03, 0.52)).
- 6.28 Results of the indirect treatment comparisons performed between LEB and DUPI mostly reported non statistically significant differences, with majority of point estimates favouring DUPI (except for the outcome of DLQI \geq 4-point improvement) though the 95% CIs were large. However, it was noted that the (all trials pooled) indirect treatment comparison for the outcome of DLQI \geq 4 points may have been biased against DUPI given monotherapy trials (which tended to have more favourable active treatment results) were included for LEB but not for DUPI. For the outcome of EASI 50, results statistically favoured DUPI (RR= 0.73, 95%CI: 0.60, 0.89; RD= -0.08, 95% CI: -0.15, -0.01) when only monotherapy trials were considered.
- 6.29 These results in the whole trial population were largely consistent with the findings in the previous analysis for the severe AD subgroup. Overall, the clinical evidence

presented by the submission indicates that LEB 250 mg Q2W ± TCS was likely superior to placebo ± TCS. However, the evaluation considered the evidence presented for the whole trial population may not adequately support the non-inferiority of LEB 250 mg Q2W ± TCS compared to DUPI 300 mg Q2W ± TCS given the point estimates were largely in favour of DUPI and the 95% CIs were large, indicating uncertainty associated with the estimates.

Face and/or hands

6.30 The analysis of patients who achieved cleared or improved responses are presented in Figure 1. LEB was associated with a statistically significantly higher proportion of patients with face AD achieving cleared or improved responses at Week 16 compared with placebo in ADvocate 1 (61.9% vs. 31.6%), ADvocate 2 (57.5% vs. 21.7%), and ADhere (68.6% vs. 46.2%). Similarly, LEB was associated with a statistically significantly higher proportion of patients with hand AD achieving cleared or improved responses at Week 16 compared with placebo in ADvocate 1 (67.2% vs. 29.1%), ADvocate 2 (61.7% vs. 18.9%), and ADhere (72.8% vs. 43.2). Overall, the response to LEB in the face and hands was largely consistent with the response to LEB in patients with moderate-to-severe AD of the whole body. However, it was unclear if the use of this 4-point scale as an outcome measure was validated and the may results not be entirely certain.

Figure 1: Patients with face and hand AD at baseline who had cleared or improved at Week 16



Source: Figure 2.6-1, p243 of the submission.

LEB = lebrikizumab; PBO = placebo; TCS = topical corticosteroids; Q2W = every 2 weeks; n=number of patients

Note: Patients who use rescue medication or discontinued treatment or with missing data were considered as non-responders; p-value is from Fisher's exact test.

*=p < 0.05, **= p < 0.01, *** = p < 0.001

- 6.31 The submission did not perform an indirect comparison for LEB vs DUPI for AD on the face and/or hands, however, outcomes reported in the included DUPI trials and the included LEB trials for the face and/or hands may not be comparable. As such the comparative efficacy of LEB and DUPI for severe AD of face and/or hands was unclear from the submission.

Maintenance (Q4W vs Q2W dosing)

- 6.32 The ADvocate 1, ADvocate 2 and ADhere J trials included a maintenance period in which both Q2W and Q4W LEB dosing frequency were used. During the maintenance period of ADvocate 1 and ADvocate 2 (i.e. from Week 16 to Week 52), the submission reported that numerically higher proportions of responders treated with LEB Q2W and LEB Q4W maintained the outcome of EASI 75 and IGA 0/1 in both trials compared with the corresponding placebo arms (LEB responders at Week 16 with treatment withdrawn). The submission's claim that patients treated Q2W had a similar response rate to those treated Q4W during the maintenance period appeared to be reasonable, as Q2W dosing generally had similar response rates to Q4W dosing during the maintenance period in ADvocate 1 and ADvocate 2. However, patients in ADhere J on Q4W dosing appeared to have more favourable response rates compared to those on Q2W dosing regarding improvement in DLQI scores, but not EASI 75 (74.9% (25/33) compared to 89.8% (26/29) respectively).

Week 16 escape arm

- 6.33 The submission's requested listing for extended induction beyond 16 weeks (balance of supply) for patients deemed to have achieved a less than adequate response to LEB ('slow responder') was based on the submission's claim that the results from the ADvocate 1 and ADvocate 2 escape arm showed a benefit of continued treatment in patients who had not achieved a protocol defined response (achieving an IGA 0/1 and/or an EASI 75 without use of rescue medication) at 16 weeks. ADhere J also included an escape arm and results for non-responders to LEB 250 mg Q2W from ADhere J were extracted during the evaluation for comparison and completeness.
- 6.34 While the proportion of patients achieving IGA 0/1, EASI 50 and EASI 75 appeared to be greater at Week 32 compared to Week 16, the proportion of patients reporting a DLQI \geq 4-point improvement from baseline (one of the components of the requested continuation criteria) actually decreased slightly at Week 32 compared to Week 16 in ADvocate 1 (61/82 to 60/82) and ADvocate 2 (75/99 to 71/99) and was similar in ADhere J at Week 16 (32/45) and Week 32 (34/45) when the total number of patients who entered the escape arm were considered in the denominator (as in an ITT analysis). Therefore, it may be concluded that if patients failed to meet the criteria of DLQI \geq 4-point improvement at Week 16, it was unlikely that the extended induction treatment to Week 24 would increase the number of responders. However, in patients who did not meet the EASI 50 criteria at Week 16 (but did meet the DLQI \geq 4-point improvement criteria), the additional extended induction may increase the number of responders at Week 24.

6.35 The response rates for the composite outcome or the severe AD subgroup were not presented by the submission, and it was unclear what the expected response rate would be for continuing treatment in the PBS population. Moreover, evidence based on escape arm data is not supported by any formal statistical analysis and should therefore be interpreted with caution.

Indirect treatment comparison with secondary comparator, UPA

6.36 The submission presented indirect comparisons of LEB 250 mg Q2W± TCS versus UPA 15 mg ± TCS and 30 mg ± TCS (using placebo as the common comparator) in the severe AD subgroup for the composite outcome (EASI50 and DLQI ≥ 4-point improvement from baseline at Week 16), informed by:

- LEB: monotherapy trials ADvocate 1 and ADvocate 2, and combination therapy trial, ADhere; and
- UPA: monotherapy trials Measure UP 1 and Measure UP 2, and combination therapy trial, AD Up (as reported in the UPA PSD, July 2021 PBAC meeting; these trials have previously been considered by the PBAC in the July 2021 submission for UPA).

6.37 Results of this *post-hoc* analysis are presented in Table 11 and Table 12.

Table 11: ITC in the severe AD subgroup for the composite outcome (all trials pooled, UPA 15 mg; Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	UPA 15 mg ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
ADvocate 1	46/82 (56.1)	4/41 (9.8)	-	5.8 (2.2, 14.9)	0.46 (0.32, 0.60)
ADvocate 2	35/75 (46.7)	6/42 (14.3)	-	3.3 (1.5, 7.1)	0.32 (0.17, 0.48)
ADhere	14/23 (60.9)	2/6 (33.3)	-	1.8 (0.6, 5.9)	0.28 (-0.15, 0.70)
LEB trials pooled	95/180 (52.8)	12/89 (13.5)	-	3.45 (1.91, 6.22)	0.39 (0.29, 0.50)
MEASURE UP 1 ^a	-	1/21 (4.8)	15/26 (57.7)	12.1 (1.7, 84.4)	0.53 (0.32, 0.74)
MEASURE UP 2 ^a	-	2/43 (4.7)	30/41 (73.2)	15.7 (4.0, 61.7)	0.69 (0.54, 0.83)
AD UP ^a	-	9/34 (26.5)	23/31 (74.2)	2.8 (1.5, 5.1)	0.48 (0.26, 0.69)
MEASURE UP 1 ^b	-	15/75 (20.0)	53/76 (69.7)	3.5 (2.2, 5.6)	0.50 (0.36, 0.63)
MEASURE UP 2 ^b	-	15/73 (20.5)	47/72 (65.3)	3.2 (2.0, 5.1)	0.45 (0.30, 0.59)
AD UP ^b	-	31/98 (31.6)	67/91 (73.6)	2.3 (1.7, 3.2)	0.45 (0.37, 0.53)
UPA trials pooled	-	73/344 (21.2)	235/337 (69.7)	3.38 (2.30, 4.96)	0.51 (0.42, 0.59)
Indirect treatment comparison: all trials pooled				1.02 (0.50, 2.06)	-0.11 (-0.25, 0.02)

Source: Table 2a.6-1, p323 of the submission.

AD = atopic dermatitis; CI = confidence interval; DLQI = dermatology life quality index; EASI = eczema area and severity index; LEB = lebrikizumab; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids; UPA = upadacitinib

^a Cyclosporin A experienced patients

^b Cyclosporin A naïve patients

Blue shading indicates trials previously considered by PBAC.

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Table 12: ITC in the severe AD subgroup for the composite outcome (all trials pooled, UPA 30 mg; Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	UPA 30 mg ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
ADvocate 1	46/82 (56.1)	4/41 (9.8)	-	5.8 (2.2, 14.9)	0.46 (0.32, 0.60)
ADvocate 2	35/75 (46.7)	6/42 (14.3)	-	3.3 (1.5, 7.1)	0.32 (0.17, 0.48)
ADhere	14/23 (60.9)	2/6 (33.3)	-	1.8 (0.6, 5.9)	0.28 (-0.15, 0.70)
LEB trials pooled	95/180 (52.8)	12/89 (13.5)	-	3.45 (1.91, 6.22)	0.39 (0.29, 0.50)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	UPA 30 mg ± TCS	RR (95% CI)	RD (95% CI)
				Active treatment ± TCS vs PBO ± TCS	
MEASURE UP 1 ^a	-	1/21 (4.8)	16/20 (80.0)	16.8 (2.5, 115.2)	0.75 (0.55, 0.95)
MEASURE UP 2 ^a		2/43 (4.7)	26/32 (81.3)	17.5 (4.5, 68.3)	0.77 (0.62, 0.92)
AD UP ^a	-	9/34 (26.5)	22/27 (81.5)	3.1 (1.7, 5.5)	0.55 (0.34, 0.76)
MEASURE UP 1 ^b	-	15/75 (20.0)	70/85 (82.4)	4.1 (2.6, 6.5)	0.62 (0.50, 0.75)
MEASURE UP 2 ^b	-	15/73 (20.5)	68/85 (80.0)	3.9 (2.5, 6.2)	0.59 (0.47, 0.72)
AD UP ^b	-	31/98 (31.6)	76/95 (80.0)	2.5 (1.9, 3.4)	0.48 (0.36, 0.61)
UPA trials pooled	-	73/344 (21.2)	278/344 (80.8)	3.97 (2.63, 6.00)	0.62 (0.53, 0.71)
Indirect treatment comparison: all trials pooled				0.87 (0.42, 1.78)	-0.23 (-0.37, -0.09)

Source: Table 2a.6-1, p323 of the submission.

AD = atopic dermatitis; CI = confidence interval; DLQI = dermatology life quality index; EASI = eczema area and severity index; LEB = lebrikizumab; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroid; UPA = upadacitinib

^a Cyclosporin A experienced patients

^b Cyclosporin A naïve patients

Blue shading indicates trials previously considered by PBAC.

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

6.38 Results in the indirect comparison in the severe AD subgroup reported:

- No statistically significant difference was observed between LEB 250 mg Q2W ± TCS and UPA 15 mg ± TCS, however the 95% CIs were large; and
- The proportion of patients who achieved the composite outcome was statistically significantly lower with LEB 250 mg Q2W ± TCS than UPA 30 mg ± TCS in terms of RD (RD= -0.23; 95% CI: -0.37, -0.09) but not RR (RR 0.87; 95% CI: 0.42, 1.78).

6.39 While the results of the indirect comparison between LEB 250 mg Q2W ± TCS and UPA 15 mg ± TCS met the submission's nominated criteria for non-inferiority based on an absence of a statistically significant difference, the evaluation considered the submission's claim of non-inferior efficacy may not be supported given lack of an established non-inferiority margin and uncertainty associated with the observed 95% CIs derived from an indirect comparison. Further, the nominated criteria for non-inferiority of LEB and UPA 30 mg was not met.

Comparative harms

6.40 Table 13 summarises the adverse events (AEs) reported in the included LEB trials. Results for individual trials were statistically not significant (95%CI included 1 or 0 for RR and RD respectively).

Table 13: Summary and meta-analysis of any adverse events reported in the included LEB trials (Week 16)

	LEB 250 mg Q2W ± TCS	PBO ± TCS	RR (95% CI)	RD (95% CI)
			Active treatment ± TCS vs PBO ± TCS	
Monotherapy trials				
KGAF	46/75 (61.3)	24/52 (46.2)	1.3 (0.9, 1.9)	0.15 (-0.02, 0.33)
ADvocate 1	129/282 (45.7)	73/141 (51.8)	0.9 (0.7, 1.1)	-0.06 (-0.16, 0.04)
ADvocate 2	150/281 (53.4)	96/145 (66.2)	0.8 (0.7, 0.9)	-0.13 (-0.22, -0.03)
ADopt VA	48/125 (38.4)	42/122 (34.4)	1.1 (0.8, 1.6)	0.04 (-0.08, 0.16)
LEB trials pooled	373/763 (48.9)	235/460 (51.1)	0.97 (0.79, 1.19)	-0.02 (-0.12, 0.09)
Combination therapy trials				
ADhere	63/145 (43.4)	23/66 (34.8)	1.2 (0.8, 1.8)	0.09 (-0.05, 0.23)
ADhere J	93/123 (75.6)	52/82 (63.4)	1.2 (1.0, 1.4)	0.12 (-0.01, 0.25)
ADvantage	136/220 (61.8)	59/111 (53.2)	1.2 (0.9, 1.4)	0.09 (-0.03, 0.20)
LEB trials pooled	292/488 (59.8)	134/259 (51.7)	1.19 (1.04, 1.35)	0.10 (0.03, 0.17)
All trials				
LEB all trials pooled	665/1251 (53.2)	369/719 (51.3)	1.06 (0.91, 1.24)	0.03 (-0.05, 0.11)

Source: Table 2.6-12, pp233-235 of the submission.

AE = adverse events; CI = confidence interval; LEB = lebrikizumab; NA = not applicable; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; TCS = topical corticosteroids

6.41 The indirect comparisons for any AEs, serious adverse events (SAEs) and AEs leading to discontinuation (all trials pooled) reported over 16 weeks are presented in Table 14. CHRONOS was not included in the indirect treatment comparison given only Week 52 safety results were available.

Table 14: Indirect treatment comparisons of safety outcomes (Week 16)

	RR (95% CI)	RD (95% CI)
AEs		
LEB 250 mg Q2W ±TCS vs DUPI 300 mg ± TCS	1.07 (0.90, 1.26)	0.04 (-0.05, 0.13)
SAEs		
LEB 250 mg Q2W ±TCS vs DUPI 300 mg ± TCS	1.68 (0.63, 4.49)	0.02 (0.00, 0.04)
AEs leading to discontinuation		
LEB 250 mg Q2W ±TCS vs DUPI 300 mg ± TCS	1.20 (0.47, 3.05)	0.01 (-0.01, 0.02)

Source: Table 2.6-12, 2.6.113 & 2.6-14, pp233-235, 236-238 & 239-241 of the submission.

AE = adverse event; CI = confidence interval; DUPI = dupilumab; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; RD = risk difference; RR = relative risk; SAEs = serious adverse events; TCS = topical corticosteroids

6.42 All safety results were not significantly different in the indirect treatment comparisons of LEB versus DUPI (all trials pooled) and therefore met the submission's criteria for non-inferiority. However, the point estimates tended to favour DUPI and the 95%CI for SAEs and AEs leading to discontinuations were large (noting the relatively low number of observations for these outcomes).

6.43 Based on the Development Safety Update Report (DSUR) (reporting period: 23 September 2021 to 22 September 2022), the following events were determined to be adverse drug reactions (of interest) of LEB: conjunctivitis; keratitis; injection site reactions; herpes zoster; and blood eosinophilia. These AEs were extracted from the included trials during the evaluation and the RR and RD were calculated for each condition. Overall, the results indicated that patients enrolled in the LEB arms of the included trials had a higher risk of experiencing conjunctivitis clusters compared to patients enrolled in the placebo arms (pooled RR=3.67, 95%CI: 2.36, 5.70; pooled RD=0.08, 95%CI: 0.04, 0.12). This was also observed with DUPI (a biologic that is a

close pharmacological analogue to LEB, as DUPI is an IL-4 and IL-13 inhibitor whereas LEB is an IL-13 inhibitor), where patients treated with DUPI in the included trials reported a higher incidence of conjunctivitis compared to patients treated with placebo (paragraph 6.35, DUPI PSD, July 2018 PBAC meeting).

- 6.44 There was a lack of long-term safety outcomes for LEB available, however, Guttman-Yassky² reported no new safety signals were noted in up to two years of treatment³ with LEB in ADjoin (long-term extension study in responders from ADvocate 1, ADvocate 2 and ADhere).

Benefits/harms

- 6.45 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.46 The submission described LEB 250 mg Q2W as non-inferior compared with DUPI 300 mg Q2W in terms of effectiveness. Although the results of the indirect treatment comparison between LEB and DUPI in the severe AD subgroup were not statistically significant (RR=0.99, 95%CI: 0.50, 1.96; RD=-0.03, 95%CI: -0.16, 0.09), the evaluation considered the therapeutic conclusion presented in the submission may not be adequately supported by the evidence presented by the submission because:

- The submission's non-inferiority claim was based on an absence of a statistically significant difference in the indirect treatment comparisons. However, the 95% CI for RR was wide and the absence of a statistically significant difference based on an indirect comparison may be insufficient to support a claim of non-inferiority. A more stringent approach may be to apply an established non-inferiority margin to reduce uncertainty; however, a non-inferiority margin was not nominated by the submission;
- The PBAC has previously considered that trials that allowed ongoing use of TCS were the most relevant to Australian clinical practice, where TCS would be expected to be continued in combination with other treatment (paragraph 6.10, UPA PSD, July 2021 PBAC meeting). However, the majority of patients treated with LEB were enrolled in monotherapy trials, and as such the pooled LEB benefit reported carried a degree of uncertainty with regards to the applicability to the proposed PBS population. Further, the magnitude of benefit of treatment in the LEB combination therapy trial ADhere was lower than the benefit of LEB in the monotherapy trials. As such, the results of the indirect comparison may be biased

² Guttman-Yassky E, et al. Efficacy and Safety of Lebrikizumab is Maintained to Two Years in Patients with Moderate-to-Severe Atopic dermatitis. Fall Clinical Dermatology Conference. <https://jofskin.org/index.php/skin/article/view/2382/1916>

³ However, it was unclear what the average length of exposure was.

in favour of LEB if the ratio of patients treated with combination therapy (DUPI + TCS) in the pooled estimates for DUPI was higher than those observed for LEB; and

- The point estimates of the indirect treatment comparison were consistently in favour of DUPI, though the 95% CIs were large, indicating a substantial degree of uncertainty associated with the estimates.
- 6.47 No comparative evidence for LEB and DUPI in adolescent patients (aged ≥ 12 to < 18 years) with severe AD was presented by the submission. As such, the comparative efficacy of LEB versus DUPI in the adolescent PBS population was uncertain.
- 6.48 The submission described LEB 250 mg Q2W as non-inferior compared with DUPI 300 mg Q2W in terms of safety. The submission's claim of non-inferiority may be reasonable and plausible given the similarities in the respective mechanisms of action (DUPI is an IL-4 and IL-13 inhibitor whereas LEB is an IL-13 inhibitor), though it was difficult to determine with certainty given the relatively low observations for SAEs and AEs leading to discontinuations. There was a lack of long-term safety outcomes available for LEB though no new safety signals were noted at up to two years of treatment.
- 6.49 Additionally, the submission described LEB 250 mg Q2W \pm TCS as non-inferior in terms of effectiveness compared with UPA 15 mg \pm TCS and compared with UPA 30 mg \pm TCS. While the results of the indirect comparison between LEB 250 mg Q2W \pm TCS and UPA 15 mg \pm TCS met the submission's nominated criteria for non-inferiority based on an absence of a statistically significant difference, the submission's claim of non-inferior efficacy may not be supported given lack of an established non-inferiority margin and uncertainty associated with the observed 95% CIs derived from an indirect comparison. The nominated criteria for non-inferiority of LEB and UPA 30 mg was not met as the proportion of patients who achieved the composite outcome was statistically significantly lower with LEB 250 mg Q2W \pm TCS than UPA 30 mg \pm TCS in terms of RD (RD= -0.23; 95% CI: -0.37, -0.09).
- 6.50 The PBAC considered that the claim of non-inferior comparative effectiveness to DUPI was reasonable, as was the claim of non-inferior comparative effectiveness to UPA.
- 6.51 The PBAC considered that the claim of non-inferior comparative safety to DUPI was reasonable, as was the claim of non-inferior comparative effectiveness to UPA.

Economic analysis

- 6.52 The submission presented a CMA which compared LEB 250 mg for adult and adolescent patients aged 12 years and over, with DUPI 300 mg for adult patients and DUPI 200 mg for adolescent patients weighing < 60 kg, over a two-year time horizon, including a 16 week induction period. Only data from adult patients receiving DUPI 300 mg were presented in the submission's clinical evaluation for the severe AD subgroup with no comparative evidence for LEB and DUPI 200 mg in adolescent patients (aged ≥ 12 to < 18 years) with severe AD presented.

- 6.53 The submission's approach of comparing drug costs over a two-year period was consistent with the CMA of UPA and DUPI, which was previously accepted by the PBAC (paragraph 6.52, UPA PSD, July 2021 PBAC meeting). The submission did not include any cost offsets in the CMA.
- 6.54 The equi-effective doses of LEB and DUPI estimated by the submission were:
- For adults and adolescents ≥ 60 kg: LEB 500 mg SC at Week 0 and 2, followed by LEB 250 mg SC Q2W until Week 16, followed by LEB 250 mg Q4W thereafter = DUPI 600 mg SC at Week 0, followed by DUPI 300 mg SC Q2W thereafter; and
 - For adolescents < 60 kg: LEB 500 mg SC at Week 0 and 2, followed by LEB 250 mg SC Q2W until Week 16, followed by LEB 250 mg Q4W thereafter = DUPI 400 mg SC at Week 0, followed by DUPI 200 mg SC Q2W thereafter.
- 6.55 The equi-effective doses were derived from the treatment regimens in the included LEB and DUPI trials and were consistent with the respective draft or approved product information. The recommended dosing for LEB in the draft product information was based on patients who weigh at least 40 kg. For DUPI, the dosing for adolescents < 60 kg was consistent with the recommended dose in the approved product information (p3) for adolescent patients who weigh between 30 kg - < 60 kg.
- 6.56 Even though the submission requested a listing for extended induction (balance of supply) for 'slow responders', neither the equi-effective dose nor an economic evaluation for these patients was provided by the submission. The evaluation considered this was inappropriate and would lead to an underestimate of the number of LEB doses used over two years. A CMA in 'slow responders' was conducted during the evaluation, in which 'slow responders' were assumed to use LEB 250 mg Q2W until week 24, after which they will use a maintenance dose of LEB 250 mg Q4W.
- 6.57 The results of the CMAs are presented below. As DUPI is subject to a special pricing arrangement (SPA) and the effective AEMP was not known to the submission, the CMA was performed using the published AEMP for DUPI in severe AD.
- 6.58 Table 15 shows the results based on responders at Week 16 (presented by the submission). Table 16 shows the results of the CMA performed during the evaluation for the extended induction (balance of supply) listing for 'slow responders'; and lastly, given a proportion of patients would be expected to respond at Week 16 and a proportion of patients would be 'slow responders', the cost of LEB per pack should be weighted accordingly - a revised CMA using a weighted approach performed during the evaluation is presented in Table 17. The proportion of slow responders (34.48%, 55 of 145 total responders) was approximated based on pooled EASI 75 results and the proportion of patients in the week 16 escape arm who achieved response by week 24 (58.6% as per pooled Advocate 1 and 2 data). It was assumed 95/180 patients responded by week 16 and a further 50 of the remaining patients (50/85) responded between week 16 and week 24.

6.59 The pre-PBAC response stated that the sponsor is willing to adjust the cost-minimisation approach to include additional doses for extended induction on the condition that the proposed extended induction response rate (80.5%) for LEB is accepted in the financial estimates, and that the additional responders are included in the Risk Sharing Arrangements (RSA).

Table 15: Results of the cost-minimisation approach (responders at Week 16)

Component	Lebrikizumab 250 mg	Dupilumab 200/300 mg
Pack size	1	2
Cost per pack (published AEMP)	\$█	\$1,609.86
Total doses over two years	32	53
Total medicine cost over two years	\$█	\$42,661.29

Source: Table3.4-1, p374 of the submission.

AEMP = approved ex-manufacturer price

Table 16: Results of the cost-minimisation approach (extended induction; balance of supply)

Component	Lebrikizumab 250 mg	Dupilumab 200/300 mg
Pack size	1	2
Cost per pack (published AEMP)	\$█	\$1,609.86
Total doses over two years	34	53
Total medicine cost over two years	\$█	\$42,661.29

Source: Constructed during the evaluation.

AEMP = approved ex-manufacturer price

Table 17: Results of the cost-minimisation approach (weighted by the proportion of responders at Week 16 and 'slow responders')

Component	Lebrikizumab 250 mg	Dupilumab 200/300 mg
Pack size	1	2
Cost per pack (published AEMP)	\$█	\$1,609.86
Total doses over two years	32.69 ^a	53
Total medicine cost over two years	\$█	\$42,661.29

Source: Constructed during the evaluation.

AEMP = approved ex-manufacturer price

^a Calculated by: 65.52% (95/145) of patients expected to respond at Week 16 thereby requiring 32 doses, and 34.48% (50/145) expected to be 'slow responders' thereby requiring 34 doses. The submission expected that, from a cohort of 180 patients with severe AD treated with LEB, 95 would be responders at Week 16 (based on the composite outcome) and there would be 50 additional 'slow responders' (based on pooled EASI 75 results of placebo and LEB 250 mg Q2W patients who 'escaped') between Week 16 and 24, totalling 145 responders.

Drug cost/patient/year

6.60 The drug cost per patient per year was \$█ (assuming standard induction/response at Week 16) based on the submission's requested published DPMQ⁴. This calculation was based on three initial scripts, followed by seven continuing scripts in year 1. It is anticipated that there will be 13 scripts for LEB required from Year 2 onwards at a cost of \$█ per year.

6.61 Assuming an extended induction to 24 weeks, the drug cost per patient per year is \$█ based on the submission's requested published DPMQ⁴. This calculation was based on

⁴ The DPMQ provided by the submission was based on an AEMP of \$█, and was calculated to be \$█, \$█, and \$█ for 4 (initial), 2 (balance of supply) and 1 (continuing) unit(s), respectively. However, this DPMQ differed slightly to those calculated during the evaluation (using the 'Mark-ups v43 - eff 1 Jul 23 external' workbook). e.g., The DPMQ for 1 unit was \$█, compared to \$█ calculated during the evaluation.

three initial scripts, followed by two extended induction/balance of supply scripts, and six continuing scripts in year 1. It is anticipated that there will be 13 scripts for LEB required from Year 2 onwards at a cost of \$ per year.

Estimated PBS usage & financial implications

- 6.62 This submission was considered by DUSC. An epidemiological approach was employed to estimate the financial impact of listing LEB for the treatment of severe AD on the PBS. The submission argued that an epidemiological approach was necessary given both DUPI and UPA were only recently listed on the PBS and as such there were limited data to inform a market share approach. However, the submission utilised PBS sample data to inform the uptake (extrapolation) of advanced systemic therapies in the financial estimates. The PBAC guidelines V5.0 (p101) notes that “a market-share approach might be preferred if the submission indicates a noninferior therapeutic conclusion”. The Pre-Sub-Committee Response (PSCR) stated that the current submission sought to provide more certain data to determine the eligible population as well as uptake of advanced systemic therapies to provide a basis to revise the RSA expenditure caps. DUSC considered that a market-share approach, with growth factored in, would be more appropriate than an epidemiological approach.
- 6.63 The proposed restrictions do not prevent sequential treatment for non-response or intolerance to DUPI or UPA. In the financial estimates treatment switching was only applied to responders, non-responders to DUPI/UPA were not assumed to receive treatment with lebrikizumab. However, the number of patients ceasing treatment for DUPI/UPA has been below predicted and the potential impact on total numbers is likely to be small. The pre-PBAC response provided revised estimates incorporating sequential treatment for patients who do not achieve a response to their initial therapy, which increased the net financial implications by approximately 1% per year. The PBAC agreed with the evaluation and pre-PBAC response that the impact of sequential use in non-responders was likely to be minimal (see also paragraph 6.74 regarding increase to caps for sequential use).
- 6.64 Key data sources, parameters and assumptions used to estimate the financial impact of listing LEB, and evaluation and DUSC comments on these values are summarised in Table 18.

Table 18: Key inputs for financial estimates

Data	Value and Source		Comment	
Eligible population				
Prevalent patients (with AD)		Adolescents (12-17 yrs)	Adults (≥ 18 yrs)	DUSC commented that the estimated current prevalence (past 2 years) of atopic dermatitis was 6.3% and estimated lifetime prevalence of atopic dermatitis was 16.4% in the Australian general practice population (Chidwick, 2020).
	Yr 1	1	2	
	Yr 2	1	2	
	Yr 3	1	2	
	Yr 4	1	3	
	Yr 5	1	3	
	Yr 6	1	3	
	Source: Calculated by applying a prevalence of 9% (as used in the DUPI submission; Table 19, DUPI		DUSC considered that overall, the prevalence assumptions were reasonable noting that	

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Data	Value and Source	Comment
	PSD, March 2020) to the Australian population aged ≥ 18 years and the Australian population aged 12 to 17 years.	there is limited Australian data to draw on to inform the assumptions.
Patients (aged 12 to 17 years) with severe AD affecting whole body	5.84% Source: Based on a cross-sectional, international epidemiologic study in the paediatric population (Silverberg et al 2021).	The definition of AD and severity were both self-reported and thus may not align with PGA=4 DUSC noted that the proportion of patients with severe AD by country ranges from 1.1% in Japan to 25.2% in Israel (Canada, 7.5%, US 8.7%, UK 7.2%).
Patients (aged ≥ 18 years) with severe AD affecting whole body	Aged ≥ 18 years: 5.00% Source: Previously used in the submission for DUPI (Table 19, DUPI PSD, March 2020).	The evaluation for DUPI (Table 19, DUPI PSD, March 2020) previously noted that this value was based on a sponsor-commissioned survey (METIS 2019a) and the definition of severe disease may not align with PGA=4. DUSC noted that there is an absence of good data in this area. DUSC considered that this is uncertain and potentially underestimated, considering the actual use of DUPI versus predicted.
Patients aged ≥ 12 years with severe AD affecting whole body with EASI ≥ 20	95.00% Source: Previously used in the submission for DUPI (Table 19, DUPI PSD, March 2020).	The evaluation for DUPI (Table 19) previously noted that this was reasonable (for the whole body).
Patients aged ≥ 12 years who are uncontrolled on TCS	80.00% Source: Sponsor's market research data; from a survey of dermatologists (n = 30) and immunologists (n = 7) in Australia who treated patients with severe AD in 2021	This was uncertain but fell within the range of previously proposed values for DUPI (68% used in the DUPI submission (Table 19, DUPI PSD, March 2020), which was revised to 100% in later resubmissions (paragraph 6.1, DUPI PSD, July 2023)). DUSC noted that this was tested by the submission in their sensitivity analyses (using 68% (-\$15m) and 90% (+\$12.5m).
Patients aged ≥ 12 years with severe AD affecting face and/or hands as a proportion of those with severe AD affecting whole body	20.68% (2,420/11,700) as a ratio of patients with severe AD affecting the whole body (17.14% (2,420/14,120) of total patients treated) Source: Prospection 10% PBS sample data (Attachment 8.1 to the submission).	This was in line with script data utilisation for DUPI in which 17.6% (March 2021-August 2022) and 19% (March 2021-March 2023) of patients treated with DUPI for severe AD were qualifying under the hands/face only criteria (paragraph 6.3, DUPI PSD, July 2023).
Engagement with specialist	Was not included by the submission given that the predicted use for LEB was informed by the total treated prevalent pool of patients with severe AD and patients would be necessarily already engaged with a specialist. Thereby implicitly assumed to be 100%.	DUSC noted that the eligible population was based on an epidemiological approach, and to be eligible patients need to engage with a specialist.

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Data	Value and Source	Comment																																								
Treatment utilisation																																										
Uptake rate of advanced systemic therapies (DUPI, UPA and LEB)	<p>Yr -2: 5.6% Yr -1: 8.5% Yr 0: 9.5% Yr 1: 11.0% Yr 2: 11.5% Yr 3: 12.0% Yr 4: 12.5% Yr 5: 13.0% Yr 6: 13.5%</p> <p>Source: The uptake rate was informed by initiations of DUPI and UPA in 2021 and 2022 which were extrapolated from 2023 to 2029 and was adjusted to reach a 'cumulative uptake' of 73.5% over the six-years analysis period (i.e., the addition of rates from Yr1-6 resulted in 73.5%).</p>	<p>This was a source of uncertainty. DUSC noted that the Sum Yr-2 to Yr 0 = 23.6% aligns with the September 2023 DUSC report of a 25% market share. DUSC considered the cumulative uptake from Yr -2 to Yr 6 (97%) to be overestimated, noting that access to specialists, remoteness and socioeconomic status would impact on uptake.</p> <p>The PSCR (pp3-4) stated that the IPSOS market research (p390) showed that after 3.5 years, approximately 90% of eligible patients with moderate to severe AD are receiving a biologic or JAKi. DUSC disagreed with the PSCR that this is the best available evidence, noting that the sample only included dermatologists treating 20+ AD patients in past 3 months with at least 1 on biologic in the 3 month period. The pre-PBAC response noted that no alternative data sources were identified</p>																																								
Uptake of LEB as % of patients treated with advanced systemic therapies	<p>Yr 1: ██████ % Yr 2: ██████ % Yr 3: ██████ % Yr 4: ██████ % Yr 5: ██████ % Yr 6: ██████ %</p> <p>Source: Assumption; sponsor anticipated uptake rate.</p>	<p>The relative uptake of LEB should not have a large impact on the financial estimates if the CMA price was accurate.</p>																																								
Response rates and persistence	<table border="1" data-bbox="395 1256 906 1491"> <thead> <tr> <th></th> <th>DUPI</th> <th>UPA 15</th> <th>UPA 30</th> <th>LEB</th> </tr> </thead> <tbody> <tr> <td>Response</td> <td>59.6%</td> <td>69.6%</td> <td>80.80%</td> <td>80.5%</td> </tr> <tr> <td colspan="5">Persistence</td> </tr> <tr> <td>Wk 52</td> <td>95.7%</td> <td>95.7%</td> <td>95.7%</td> <td>95.7%</td> </tr> <tr> <td>Yr 2</td> <td>83.2%</td> <td>83.2%</td> <td>83.2%</td> <td>83.2%</td> </tr> <tr> <td>Yr 3</td> <td>79.9%</td> <td>79.9%</td> <td>79.9%</td> <td>79.9%</td> </tr> <tr> <td>Yr 4</td> <td>77.2%</td> <td>77.2%</td> <td>77.2%</td> <td>77.2%</td> </tr> <tr> <td>Yr 5</td> <td>74.8%</td> <td>74.8%</td> <td>74.8%</td> <td>74.8%</td> </tr> </tbody> </table> <p>Source: Response for DUPI and UPA were based on those used in the respective submissions (Table 19, DUPI PSD, March 2020; Table 16, UPA PSD, July 2021). Persistence rate was based on those previously used in submissions for DUPI and UPA (Table 19, DUPI PSD, March 2020; Table 16, UPA PSD, July 2021).</p> <p>Response rate for LEB was based the combined response rate of patients at 16 weeks plus response rate of patients at 24 weeks who did not respond at 16 weeks (discussed in para 6.65)</p>		DUPI	UPA 15	UPA 30	LEB	Response	59.6%	69.6%	80.80%	80.5%	Persistence					Wk 52	95.7%	95.7%	95.7%	95.7%	Yr 2	83.2%	83.2%	83.2%	83.2%	Yr 3	79.9%	79.9%	79.9%	79.9%	Yr 4	77.2%	77.2%	77.2%	77.2%	Yr 5	74.8%	74.8%	74.8%	74.8%	<p>The PBAC previously did not accept that assuming a difference in response (for UPA vs DUPI) was reasonable (Table 16, UPA PSD), given the claim of non-inferiority of UPA 15 mg vs DUPI, and given the PBAC did not accept the submission's claim that UPA 30 mg was superior to DUPI in terms of response (paragraph 7.1, UPA PSD).</p> <p>The overall response rate used by the submission for LEB was inappropriate and was inconsistent with the submission's claim of non-inferiority to DUPI.</p> <p>The submission applied the same persistence estimates as assumed by the DUPI March 2020 and UPA July 2021 submissions. In the 10% PBS sample, for the 2022 calendar year, 75.10% of patients who initiated DUPI, continued with treatment and 56.40% of patients who initiated with UPA continued treatment. DUSC also noted that the persistence rates are higher than observed in the Prospecion analysis and considered that utilisation might be overestimated based on persistence rates.</p>
	DUPI	UPA 15	UPA 30	LEB																																						
Response	59.6%	69.6%	80.80%	80.5%																																						
Persistence																																										
Wk 52	95.7%	95.7%	95.7%	95.7%																																						
Yr 2	83.2%	83.2%	83.2%	83.2%																																						
Yr 3	79.9%	79.9%	79.9%	79.9%																																						
Yr 4	77.2%	77.2%	77.2%	77.2%																																						
Yr 5	74.8%	74.8%	74.8%	74.8%																																						

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Data	Value and Source	Comment
LEB distribution of standard versus extended induction	Standard induction: 52.8% (proportion of responders at Week 16) Extended induction: 47.2% (proportion of non-responders at Week 16) Source: Pooled analysis of LEB clinical trials at Week 16 (based on the composite outcome of EASI 50 and DLQI improvement \geq 4 points) and analysis of escape arm at Week 24.	The PBAC considered that the additional cost for extended induction should be accounted for in the cost-minimisation approach. As such there should be no overall additional cost for LEB compared with DUPI and UPA.

Source: Tables 4.1-1, 4.1-2, 4.1-3, 4.1-4, 4.1-6, 4.1-7, 4.1-8, 4.1-12, pp378-382, 386,387 & 392 of the submission.

AD = atopic dermatitis; DLQI = dermatology life quality index; DUPI = dupilumab; EASI = eczema area and severity index; PGA = physician's global assessment; LEB = lebrikizumab; PBS = Pharmaceutical Benefits Scheme; Q2W = every 2 weeks; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; UPA = upadacitinib; Yr = year

The redacted values correspond to the following ranges:

¹ 100,000 to < 200,000

² 1,000,000 to < 2,000,000

³ 2,000,000 to < 3,000,000

6.65 The response rate for LEB used in the financial estimates was based on the combined response rate of patients at 16 weeks plus response rate of patients at 24 weeks who did not respond at 16 weeks and was inconsistent with the submission's claim of non-inferior efficacy against DUPI. The response rate at 16 weeks was based on a pooled analysis of LEB at Week 16 for the composite outcome of EASI 50 and DLQI \geq 4-point improvement (52.8%; 95/180, see Table 4), leaving 85 patients (47.2%, 85/180) who were not responders at week 16. Response at 24 weeks among patients who did not respond at 16 weeks was based on the proportion of pooled patients who achieved an EASI 75 response (58.6%; 255/435) between Week 16 and 24 of the 'Week 16 escape' arms of ADvocate 1 and ADvocate 2. The submission then estimated that 50 patients (58.6% of 85 patients) who did not respond at week 16 will become responders at week 24. These two responder numbers were added to obtain an overall response rate at Week 24 of 80.5% ((95+50)/180).

6.66 Table 19 presents the estimated net financial implications for the proposed listing of LEB for treatment of severe AD (including whole body and AD affecting the face and/or hands only) over the first 6 years.

Table 19: Estimated use and financial implications (based on published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS and RPBS)						
Prevalent AD population (12-17 yrs)	1	1	1	1	1	1
Prevalent AD population (\geq 18 yrs)	2	2	2	3	3	3
Total eligible pts w/whole body AD ^a	4	4	4	4	4	4
Pts w/hand and/or face AD (20.68%)	5	5	5	5	5	5
Total eligible pts w/severe AD	6	6	1	1	1	1
Pts initiating advanced systemic trt	5	5	5	5	5	5
Total pts initiating LEB trt	7	7	8	8	8	8

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Pts continuing LEB trt in Yr 1 (80.5%)	7	7	7	8	8	8
Pts continuing LEB trt in Yr 2+	9	7	8	8	5	5
Number of scripts						
Initial (std induction)	8	5	5	10	10	10
Initial (extd induction)	7	7	8	8	8	8
Continuing Yr 1+ (std induction)	8	5	5	10	10	10
Continuing Yr 1+ (extd induction)	8	5	5	5	5	5
Continuing Yr 2+	9	10	11	11	11	12
Total scripts	10	11	11	11	12	12
PBS/RPBS cost less co-pay						
LEB total (pub) ^b	13	14	15	16	17	17
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
Number of scripts offset by LEB						
DUPI (200 & 300 mg)	-10	-18	-11	-1	-1	-1
UPA (15 & 30 mg)	-5	-10	-18	-19	-4	-1
Total	-	-11	-1	-1	-12	-12
PBS/RPBS cost less co-pay						
DUPI (200 & 300 mg)	20	20	20	20	20	20
UPA (15 & 30 mg)	20	20	20	20	20	20
Total (pub) ^b	20	20	20	20	20	20
Estimated financial implications for the PBS/RPBS and the health budget						
Net cost to PBS/RPBS / budget (pub)	21	22	23	24	25	14

Source: Tables 4.2-1, 4.2-2, 4.2-6, 4.3-1, 4.3-4, 4.4-1, 4.5-1, 4.5-2, pp393-396, 398 & 399 of the submission.

AD = atopic dermatitis; DPMQ = dispensed price for maximum quantity; DUPI = dupilumab; extd = extended; LEB = lebrikizumab; PBS = Pharmaceutical Benefits Scheme; pt = patients; pub = published; RPBS = Repatriation Pharmaceutical Benefits Scheme; std = standard; trt = treatment UPA = upadacitinib; w/ = with; Yr = year

a multiplied by the proportion of: patients with severe AD (5.84% for adolescents; 5% for adults); patients with EASI ≥ 20 (95%); and patients uncontrolled on TCS (80%).

b The DPMQ provided by the submission differed slightly to those calculated during the evaluation (using the 'Mark-ups v43 - eff 1 Jul 23 external' workbook). The financial estimates were not updated during the evaluation given the small difference in published prices, e.g., LEB 1 pen: \$ reported by the submission, compared to \$ calculated during the evaluation.

c The number of prescriptions for UPA (15 and 30 mg) varied (5 repeats for continuing; 3 repeats for continuing – dose change). The submission assumed 5 repeats for all UPA continuing patients and therefore the estimated net change in prescriptions may not be entirely accurate. Data from sheet '2e: scripts-market' show that approximately 10% of total UPA services were dose changes.

The redacted values correspond to the following ranges:

- ¹ 100,000 to < 200,000
- ² 1,000,000 to < 2,000,000
- ³ 2,000,000 to < 3,000,000
- ⁴ 80,000 to < 90,000
- ⁵ 10,000 to < 20,000
- ⁶ 90,000 to < 100,000
- ⁷ 500 to < 5,000
- ⁸ 5,000 to < 10,000
- ⁹ < 500
- ¹⁰ 20,000 to < 30,000
- ¹¹ 70,000 to < 80,000
- ¹² 200,000 to < 300,000
- ¹³ \$70 million to < \$80 million
- ¹⁴ \$100 million to < \$200 million
- ¹⁵ \$200 million to < \$300 million
- ¹⁶ \$300 million to < \$400 million
- ¹⁷ \$400 million to < \$500 million

¹⁸ 40,000 to < 50,000

¹⁹ 60,000 to < 70,000

²⁰ net cost saving

²¹ \$20 million to < \$30 million

²² \$50 million to < \$60 million

²³ \$60 million to < \$70 million

²⁴ \$80 million to < \$90 million

²⁵ \$90 million to < \$100 million

6.67 The following points were noted regarding the submission's financial model:

- DUSC considered that the prevalence rates may be underestimated, but data informing prevalence for Australia are limited.
- The response rates used were inconsistent with previous PBAC advice (for UPA) and inconsistent with the submission's claim of non-inferiority of LEB vs DUPI. The use of an inflated response rate for LEB (80.5%) resulted in a higher proportion of patients continuing LEB than DUPI and hence resulted in an overestimation of the net financial impact of listing LEB.
- The uptake rate of advanced systemic therapies was a source of uncertainty. DUSC considered the cumulative uptake from Yr -2 to Yr 6 (97%) to be overestimated, noting that access to specialists, remoteness and socioeconomic status would impact on uptake.

6.68 Overall, the PBAC considered the financial impact estimated by the submission was likely highly overestimated, due to the overestimation of continuing patients for LEB compared with DUPI, and overestimated uptake rates. The submission's estimates also included a net cost for additional doses for extended induction, however the PBAC noted that there should be no additional cost for additional doses as the cost-minimised price for LEB should account for these additional doses.

Quality Use of Medicines

6.69 The sponsor plans to implement a range of activities to support the quality use of medicines in the treatment of AD, and the appropriate use of LEB, in accordance with the registered indication and proposed PBS listing. These activities include, but are not limited to, health care providers and patient resources to support treatment initiation; and educational meetings or symposia held in conjunction with relevant national events.

Financial Management – Risk Sharing Arrangements

6.70 The submission noted that there is currently an RSA in place for DUPI and UPA. The submission argued that the estimates used to inform the RSA and agreed expenditure caps have significantly underestimated actual use and that without revision, the current RSA subsidisation caps are anticipated to result in an average selling price that is commercially unviable for LEB. The ESC noted that as there is no change in indication this, in and of itself, is not a justification for increasing the RSA caps. The pre-PBAC

response further stated that a PBAC recommendation for substantial uplift to the existing RSA caps and/or a substantial reduction in the required rebate of expenditure above the cap, will be necessary to ensure commercial viability and enable the sponsor to proceed with listing LEB on the PBS.

- 6.71 The PBAC recalled its advice provided at the November 2024 meeting that “renegotiation of any Deed arrangements was ultimately a matter for the Commonwealth”, however the PBAC provided advice for consideration at time of negotiation of any future RSA (paragraph 6.1, Review of cost-effectiveness of AD drugs PSD, November 2023 PBAC meeting). The PBAC also recalled its advice regarding the cost-effectiveness and subsidisation caps for DUPI and UPA “that any renegotiation of the Deed arrangements increasing the cap would also need to consider a substantially lower price to be consistent with the basis of the Committee’s original recommendation” (paragraph 6.18, Review of cost-effectiveness of AD drugs PSD, November 2023 PBAC meeting). Overall, the PBAC considered dupilumab would likely be cost-effective with a price reduction in the order of 50% (paragraph 6.14, Review of cost-effectiveness of AD drugs PSD, November 2023 PBAC meeting).
- 6.72 The sponsor proposed that the subsidisation caps are increased to \$ [REDACTED] million in the first year of listing of lebrikizumab (2024) and to \$ [REDACTED] million in Year 6 (based on the published prices).
- 6.73 The uptake rate used by the submission for the analysis of their proposed subsidisation caps was a source of uncertainty, which had the potential to have a sizable impact on the resulting estimates. In July 2022 and July 2023, the sponsor for DUPI submitted Category 3 submissions requesting an increase in the financial caps for the current RSA to reflect the higher than estimated use of DUPI for severe chronic AD, and an increase to the current caps was recently recommended by the PBAC to account for the proportion of patients with AD of the hand/face only (paragraphs 6.4 and 6.7, DUPI PSD, July 2023 PBAC meeting).
- 6.74 The PBAC recalled its advice that when UPA was recommended: “a small increase in the financial caps may be reasonable given the different mechanism of action and route of administration of UPA and DUPI may lead to differences in tolerability and response resulting in sequential use being appropriate in some patients...The PBAC considered that an increase in the caps of a magnitude greater than this would need to be supported by clinical evidence and an assessment of the cost-effectiveness of sequential use” (paragraph 7.16, UPA PSD, July 2021 PBAC meeting). The PBAC noted that no evidence regarding sequential use was presented. The PBAC considered that allowing sequential use or switching between DUPI/UPA and LEB is unlikely to substantially increase the overall uptake of treatments for severe AD as the number of patients ceasing treatment for DUPI/UPA has been relatively low and LEB does not provide a different route of administration. Therefore, the PBAC considered that no increase to the RSA caps was justified on the basis of switching or sequential use of DUPI/UPA and LEB.

- 6.75 The PBAC noted the pre-PBAC response stated that the sponsor is willing to adjust the cost-minimisation approach to include additional doses for extended induction on the condition that the proposed extended induction response rate (80.5%) for LEB is accepted in the financial estimates, and that the additional responders are included in the RSA. The PBAC recalled its previous advice when UPA was recommended: “The sponsor requested that if the RSA in place for DUPI was to include UPA that the financial caps should be increased to reflect the superior response of UPA 30 mg (and the higher proportion of patients who remain on treatment)... the PBAC did not accept the claim of superior efficacy of UPA 30 mg and therefore considered that increasing the caps in this way was not justified” (paragraph 7.15, upadacitinib PSD, July 2021 PBAC meeting). The PBAC noted that no claim of superior efficacy for LEB had been proposed in the submission and considered that an increase to the financial estimates and caps, on the basis of a CMA, was not supported.
- 6.76 The pre-PBAC also noted the sponsor’s concern regarding the level of rebate required for expenditure over the RSA caps in this indication. The sponsor proposed a significant reduction in the rebate of expenditure over the caps. The PBAC considered that the renegotiation of the level of rebate required was also ultimately a matter for the Commonwealth, and could be considered at the time of negotiation of any future RSA.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of lebrikizumab (LEB) for adult and adolescent patients (12 years of age and older) with severe atopic dermatitis. The PBAC acknowledged the clinical need for additional systemic treatments for severe AD and considered that LEB provides an overall clinical benefit similar to the primary comparator dupilumab (DUPI) and the additional comparator upadacitinib (UPA). The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost effectiveness of LEB would be acceptable if it were cost-minimised to the lowest cost alternative therapy of DUPI or UPA.
- 7.2 The PBAC considered that inclusion of an extended induction period, as proposed for the LEB restrictions, was reasonable, but the additional doses for a proportion of ‘slow responders’ would need to be accounted for in the calculation of equi-effective doses applied in the cost-minimisation approach. The PBAC considered the equi-effective doses, assuming equivalent drug costs over a two-year period are:

For adults and adolescents ≥ 60 kg:

- For ‘slow responders’ requiring extended induction (34.48% of patients) - LEB 500 mg at week 0 and 2, followed by LEB 250 mg Q2W until week 24, followed by a maintenance dose of LEB 250 mg Q4W; and for week 16 responders (65.52% of patients) - LEB 500 mg at week 0 and 2, followed by 250 mg Q2W until week 16,

followed by a maintenance dose of LEB 250 mg Q4W and

- DUPI 600 mg at week 0, followed by a maintenance dose of 300 mg Q2W.

For adolescents < 60 kg:

- For 'slow responders' requiring extended induction (34.48% of patients) - LEB 500 mg at week 0 and 2, followed by LEB 250 mg Q2W until week 24, followed by a maintenance dose of LEB 250 mg Q4W; and for week 16 responders (65.52% of patients) – LEB 500 mg at week 0 and 2, followed by 250 mg Q2W until week 16, followed by a maintenance dose of LEB 250 mg Q4W; and
- DUPI 400 mg at week 0, followed by a maintenance dose of 200 mg Q2W.

- 7.3 The PBAC noted the previously determined equi-effective doses for UPA and DUPI could be used to inform equi-effective doses for LEB and UPA for the purpose of determining the lowest cost alternative therapy (paragraph 7.12, UPA PSD, July 2021 PBAC Meeting).
- 7.4 The PBAC noted that consumer comments from individuals and organisations described the unmet need for individuals with AD who do not respond to current available treatment options, or experience side effects from available treatments. The comments noted that LEB may have fewer ocular side effects than DUPI and the benefits of monthly LEB injections, as opposed to fortnightly injections. The PBAC noted that LEB has a mechanism of action somewhat different to DUPI as it blocks IL-13 alone, whereas DUPI blocks both IL-4 and IL-13. The PBAC considered it would be beneficial for patients who have failed to achieve an adequate response to topical therapy to have access to an alternative treatment for severe AD.
- 7.5 The PBAC noted that the proposed restrictions for LEB were consistent with those for DUPI and UPA in severe AD, with regards to eligibility and continuing criteria and considered this was appropriate. The submission additionally requested a listing for an extended induction period (balance of supply) for patients deemed to have achieved a less than adequate response to LEB ('slow responder') after 16 weeks. The proposed extended induction supply would provide an additional eight weeks of induction treatment at Q2W dosing, with response assessed between 24-28 weeks. The PBAC noted that this approach is not consistent with induction and assessment of response for DUPI and UPA, but noted that it was consistent with the clinical data presented for LEB. The PBAC also noted that, in general, clinical practice in a variety of indications, is moving towards a more extended induction period for assessment of response. The PBAC noted that there was potentially a higher cost associated with this approach as non-responders and 'slow responders' receive additional doses compared with patients who respond by 16 weeks. The PBAC considered that inclusion of the extended induction period, as proposed for the LEB restrictions, was reasonable, but the additional doses would need to be accounted for in the calculation of equi-effective doses applied in the cost-minimisation approach.
- 7.6 The PBAC noted that the requested listing does not prevent the use of sequential

treatment (i.e., patients who do not respond to DUPI would be eligible for LEB and vice versa). The PBAC noted that switching and sequential use are currently allowed between DUPI and UPA, and considered that allowing sequential treatment with an additional treatment (DUPI and/or UPA and LEB) was reasonable. The PBAC considered that allowing sequential treatment and switching between treatments is unlikely to substantially increase the uptake of treatments for severe AD as the number of patients ceasing treatment with DUPI/UPA has been relatively low. The PBAC noted that the pre-PBAC response also considered that the impact of sequential use on uptake was likely to be minimal.

- 7.7 The PBAC noted the submission nominated DUPI 300 mg SC Q2W as the main comparator and UPA (15 mg and 30 mg, taken once daily orally) as a secondary comparator UPA. The PBAC recalled that UPA was recommended for severe AD on a cost-minimisation basis to DUPI, following its July 2021 meeting. The PBAC considered that the nominated comparators were appropriate.
- 7.8 The PBAC noted that no head-to-head trials comparing LEB and DUPI were available, so an indirect treatment comparison (using placebo as the common comparator) was presented to support the submission's claim of non-inferior efficacy. The PBAC noted that the indirect comparison included nine RCTs of DUPI compared with placebo and seven RCTs of LEB compared with placebo. The PBAC noted that there were uncertainties associated with the indirect comparison presented because: the trials used a mix of monotherapy and TCS combination therapy; the comparison was based on post hoc analyses of the severe subgroup; the comparison did not include all available LEB trials; there was no comparison presented specifically for adolescents; and no non-inferiority margin was specified. The PBAC noted that in the indirect comparison, there was no statistically significant difference between LEB and DUPI for the proportions of severe AD patients who achieved the composite outcome nor its individual components (EASI 50 or DLQI \geq 4-point improvement). The PBAC noted that the 95% confidence intervals were wide, indicating a substantial degree of uncertainty associated with the estimates. However, the PBAC considered that LEB appeared similar to DUPI, including for the comparison of the composite responder outcome (EASI 50 + DLQI \geq 4 point improvement at week 16 (RR 0.99 (95%CI: 0.50, 1.96))), and considered that the claim of non-inferiority with DUPI was reasonable.
- 7.9 The PBAC noted that the submission also presented indirect comparisons of LEB with UPA 15 mg and UPA 30 mg (using placebo as the common comparator) for the composite outcome (EASI50 and DLQI \geq 4-point improvement at Week 16). While the results of the comparison with UPA 15 mg showed no statistically significant difference, there was a statistically significant difference in favour of UPA 30 mg. The PBAC recalled it previously did not accept the claim of superior efficacy for UPA 30 mg compared with DUPI, though acknowledged that it may have a faster onset of response, offset by an increase in treatment related adverse events (paragraph 7.11, upadacitinib PSD, July 2021 PBA meeting). Overall, the PBAC considered that the claim of non-inferior efficacy for LEB compared with UPA 15 mg and 30 mg was reasonable.

- 7.10 The PBAC noted that overall safety results (SAEs, any AEs and AEs leading to discontinuations) were not significantly different in the indirect treatment comparisons of LEB versus DUPI (all trials pooled). The PBAC noted that patients enrolled in the LEB arms of the included trials had a higher risk of experiencing conjunctivitis clusters compared to patients enrolled in the placebo arms (pooled RR=3.67, 95%CI: 2.36, 5.70; pooled RD=0.08, 95%CI: 0.04, 0.12). However, this was also observed with DUPI. Overall, the PBAC considered the submission's claim of non-inferiority to DUPI was reasonable and plausible given the similarity in the mechanism of action.
- 7.11 The submission presented a CMA which compared LEB 250 mg for adult and adolescent patients aged 12 years and over, with DUPI 300 mg for adult patients and DUPI 200 mg for adolescent patients weighing <60 kg, over a two-year time horizon (including a 16 week induction period), with no cost-offsets. The PBAC noted that this approach was consistent with the CMA it had previously accepted for UPA versus DUPI (paragraph 6.52, UPA PSD, July 2021 PBAC meeting). The PBAC noted that the LEB equi-effective dose proposed in the submission did not include additional doses for patients who were slow responders and required additional doses during the induction phase. The PBAC considered this was inappropriate and would lead to an underestimate of the number of LEB doses used over two years. The PBAC noted that the evaluation conducted a weighted CMA that accounted for additional doses in slow responders (34.48% of patients), who were assumed to use LEB 250 mg Q2W until week 24, followed by a maintenance dose of LEB 250 mg Q4W. The PBAC considered that the approach to estimating the proportion of slow responders was reasonable and that the CMA approach proposed in the evaluation accounting for slow responders (as presented in Table 17) was appropriate.
- 7.12 The PBAC noted that the pre-PBAC response stated that the sponsor is willing to adjust the cost-minimisation approach to include additional doses for extended induction on the condition that the proposed extended induction response rate (80.5%) for LEB is accepted in the financial estimates, and that the additional responders are included in the RSA. The PBAC considered that, if the clinical claim is a higher response rate that would be associated with an increased financial impact, a cost utility analysis would be the appropriate approach for the economic analysis.
- 7.13 The PBAC considered the cost of LEB should also be no greater than the cost of UPA over a two year time horizon informed by the previously accepted CMA for UPA versus DUPI (paragraph 7.12, UPA PSD, July 2021 PBAC meeting).
- 7.14 The PBAC noted the submission presented financial estimates based on an epidemiological approach, using PBS sample data to inform the uptake of advanced systemic therapies. DUSC considered that a market-share approach, with growth factored in, would be more appropriate than an epidemiological approach. The PBAC noted that there are almost three years of utilisation data available and considered that the epidemiological approach presented in the submission introduced additional uncertainty. Overall, the PBAC considered the financial impact estimated by the

submission was highly uncertain and likely to be substantially overestimated, due to the assumption of higher rates of continuation for LEB compared to DUPI, and overestimated uptake rates. The submission's estimates also included a net cost for additional doses for extended induction. However, the PBAC noted that there should be no additional cost for extended induction doses as the cost-minimised price for LEB should account for these additional doses.

- 7.15 The submission noted that there is an RSA with subsidisation caps in place for DUPI and UPA for severe AD, and noted that LEB would need to join these arrangements. The submission argued that the estimates used to inform the RSA and agreed caps have significantly underestimated actual use and that without revision, the current RSA subsidisation caps are anticipated to result in an average selling price that is commercially unviable for LEB. The sponsor stated that the intent of the financial estimates provided in the submission was to provide more certain data to determine the eligible population as well as uptake of advanced systemic therapies, to provide a basis to revise the RSA expenditure caps. The PBAC considered that the financial estimates presented in the submission were not useful for this purpose as the approach did not provide a reliable basis for estimation of the utilisation and costs for the severe AD market.
- 7.16 The PBAC also recalled its advice provided at the November 2023 meeting that "renegotiation of any Deed arrangements was ultimately a matter for the Commonwealth". However, the PBAC provided advice for consideration at the time of negotiation of any future RSA (paragraph 6.1, Review of cost-effectiveness of AD drugs PSD, November 2023 PBAC meeting). The PBAC also recalled its advice regarding the cost-effectiveness and subsidisation caps for DUPI and UPA "that any renegotiation of the Deed arrangements increasing the cap would also need to consider a substantially lower price to be consistent with the basis of the Committee's original recommendation" (paragraph 6.18, Review of cost-effectiveness of AD drugs PSD, November 2023 PBAC meeting). Overall, the PBAC considered dupilumab would likely be cost-effective with a price reduction in the order of 50% (paragraph 6.14, Review of cost-effectiveness of AD drugs PSD, November 2023 PBAC meeting). The PBAC considered that this advice was also relevant to the LEB price that would be considered cost-effective in the context of any substantial renegotiation of the Deed arrangements. The pre-PBAC response also noted the sponsor's concern regarding the level of rebate required for expenditure over the RSA caps in this indication. The PBAC considered that renegotiation of the level of rebate required was also ultimately a matter for the Commonwealth, and could be considered at the time of negotiation of any future RSA.
- 7.17 The PBAC recommended that LEB should not be treated as interchangeable on an individual patient basis with DUPI or UPA.
- 7.18 The PBAC advised that LEB is not suitable for prescribing by nurse practitioners.
- 7.19 The PBAC recommended that the Early Supply Rule should apply for continuing

treatment only.

- 7.20 The PBAC noted that the administrative advice that includes links to EASI and PGA scores is not consistent between the listings for UPA and DUPI and considered these should be aligned for UPA, DUPI and LEB. No other flow-on restriction changes to DUPI or UPA were identified resulting from the listing for LEB.
- 7.21 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because LEB is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over DUPI, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.22 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands and manufacturer
LEBRIKIZUMAB					
lebrikizumab 250 mg/2 mL injection, 2 mL pen device	New MP	4	4	2	Ebglyss Eli Lilly Australia Pty Ltd
Category / Program: GENERAL – General Schedule (Code GE)					
Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Administrative Advice: The Eczema Area and Severity Index (EASI) referenced in this restriction is that described in the following literature publications: Chalmers JR et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). <i>British Journal of Dermatology</i> 2014 December;171(6):1318-25. Schmitt J et al. HOME initiative collaborators. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. <i>The Journal of Allergy and Clinical Immunology</i> 2014 October;134(4):800-7					
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: The Physician's Global Assessment (5-point scale) referenced in this restriction is that described in the following literature					

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publication: Fatumura M et al. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD trials: Many options, no standards <i>Journal of the American Academy of Dermatology</i> 2016; 674(2): 288-94 The overall appearance of dermatitis lesions is rated as 4 (severe) if the lesions are best described as featuring: deep/dark red erythema, with marked and extensive induration/papulation; excoriation and oozing/crusting are present.
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.
Variant of Restriction Summary 12498 / Treatment of Concept: 12497: Authority Required
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: 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
Treatment criteria: The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
AND
Population criteria: Patient must be 12 years of age or older
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.

<p>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.</p>
<p>Document the details of the medium to high potency topical corticosteroids (or calcineurin inhibitors) initially trialled in the patient's medical records.</p>
<p>Prescribing Instructions: At the time of assessment of response, i.e., within 16 weeks of initial treatment, if adequate response hasn't been achieved, the prescriber can apply for an extended induction treatment (up to further 8 weeks of therapy) where there has been a partial response and the prescriber considers that extended induction doses could result in achieving adequate response.</p>
<p>Variant of Restriction Summary 12506 / ToC: 12507: Authority Required</p>
<p>Indication: Chronic severe atopic dermatitis</p>
<p>Treatment Phase: Initial treatment of the face and/or hands</p>
<p>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</p>
<p>AND</p>
<p>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</p>
<p>AND</p>
<p>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</p>
<p>AND</p>
<p>Clinical criteria: The treatment must be the sole PBS-subsidised biological medicine for this PBS indication</p>
<p>AND</p>
<p>Clinical criteria: Patient must not have experienced an inadequate response to this biological medicine in this PBS indication</p>
<p>AND</p>
<p>Treatment criteria: Must be treated by a dermatologist; or Must be treated by a clinical immunologist</p>
<p>AND</p>
<p>Population criteria: Patient must be 12 years of age or older</p>
<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:</p>

<p>(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 trialed are in the patient's medical records.</p>																							
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Restriction Summary new 1 / Treatment of Concept: new 2: Authority Required
Indication: Chronic severe atopic dermatitis
Treatment Phase: Extended induction treatment (further 8 weeks of initial treatment of the whole body or 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 under the initial treatment phase of the whole body or the face and/or hands
AND
Clinical criteria: Patient must not be undergoing each of: (i) commencing treatment through this treatment phase listing, (ii) treatment accessed through this treatment phase more than once;
AND
Clinical criteria: Patient must not have achieved adequate response after 16 weeks of initial treatment with this drug in this PBS indication;
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
Prescribing Instructions: Prescriber must only apply for this treatment phase if the patient has had a partial response to treatment and the prescriber considers that further induction treatment (further 8 weeks of therapy) with this drug is likely to result in an adequate response.
Prescribing Instructions: For the purposes of this restriction, an adequate response to treatment of whole body 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 State each of the current EASI and DLQI scores for this authority application.
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 Document each qualifying response measure in the patient's medical records for PBS compliance auditing purposes
Prescribing Instructions: A second assessment of response must be conducted between 24 to 28 weeks from the first administered dose of this drug to determine the patient's eligibility for continuing treatment. Where an assessment is not undertaken, the patient will not be eligible for ongoing treatment.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands and manufacture r
LEBRIKIZUMAB					
lebrikizumab 250 mg/2 mL injection, 2 mL pen device	New MP	1	1	5	Ebglyss Eli Lilly Australia Pty Ltd
Category / Program: GENERAL – General Schedule (Code GE)					
Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Administrative Advice: The Eczema Area and Severity Index (EASI) referenced in this restriction is that described in the following literature publications: Chalmers JR et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). <i>British Journal of Dermatology</i> 2014 December;171(6):1318-25. Schmitt J et al. HOME initiative collaborators. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. <i>The Journal of Allergy and Clinical Immunology</i> 2014 October;134(4):800-7					
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: The Physician's Global Assessment (5-point scale) referenced in this restriction is that described in the following literature publication: Fatumura M et al. <i>Journal of the American Academy of Dermatology</i> 2016; 64(2): 288-94 The overall appearance of dermatitis lesions is rated as 4 (severe) if the lesions are best described as featuring: deep/dark red erythema, with marked and extensive induration/papulation; excoriation and oozing/crusting are present.					
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.					
Variant of Restriction Summary 11374 / ToC: 11374: Authority Required					
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 prior to this first continuing treatment authority application; 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					

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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
Prescribing Instructions:
For the purposes of this restriction, an adequate response to treatment of the whole body 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 State each of the current EASI and DLQI scores for this authority application.
Variant of Restriction Summary 11377 / ToC: 11377: Authority Required
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 prior to this first continuing treatment authority application; 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
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 State the current EASI ratings or the percentage of face/hand surface area affected by the condition. Also state the DLQI score for this authority application.

Flow on changes to UPA and DUPI for atopic dermatitis:

Align the administrative advice of access EASI and PGA scores between the listings for UPA, DUPI and LEB. That includes amending the current AA in dupilumab (PBS item codes 12291X and 12292Y) to:

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>

The Eczema Area and Severity Index (EASI) referenced in this restriction is that described in the following literature publications:

Chalmers JR et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). British Journal of Dermatology 2014 December;171(6):1318-25.

Schmitt J et al. HOME initiative collaborators. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. The Journal of Allergy and Clinical Immunology 2014 October;134(4):800-7

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

The Physician's Global Assessment (5-point scale) referenced in this restriction is that described in the following literature publication:

Fatumura M et al. Journal of the American Academy of Dermatology 2016; 64(2): 288-94

The overall appearance of dermatitis lesions is rated as 4 (severe) if the lesions are best described as featuring: deep/dark red erythema, with marked and extensive induration/papulation; excoriation and oozing/crusting are present.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

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.