

An addendum has been included at the end of the document.

## 6.08 UPADACITINIB, Tablet 15 mg, Tablet 30 mg, Rinvoq<sup>®</sup>, AbbVie Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested Authority Required (Telephone) PBS listing for upadacitinib (UPA) 15 mg and 30 mg tablets for initial and continuing treatment of adults and adolescents with severe atopic dermatitis (AD).
- 1.2 Listing was requested on the basis of a cost-minimisation analysis (for UPA 15 mg) and a cost utility analysis (for UPA 30 mg) versus dupilumab (DUPI), which is a subcutaneously (SC) administered interleukin-4 (IL-4) inhibitor currently listed on the PBS for severe AD. The PBAC noted that UPA is a novel medicine, as no other Janus Kinase (JAK) inhibitor is available on the PBS for AD. The PBAC also considered an application for listing of baricitinib (another JAK inhibitor) for severe AD at the July 2021 meeting.

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

Component	Description
Population	Patients aged 12 years or older with severe atopic dermatitis, affecting the whole body or the face and hands, who are inadequately controlled on topical therapies (as per the criteria for the listing of DUPI)
Intervention	UPA 15 mg or 30 mg tablet, orally, once daily The recommended dose in adults is 15 mg or 30 mg once daily, and 15 mg once daily for adolescents.
Comparator	Primary: - In adults and adolescents ≥ 60 kg: DUPI 600 mg SC injection as a loading dose followed by 300 mg SC injection once every fortnight. - In adolescents <60 kg: DUPI 400 mg SC injection as a loading dose, followed by 200 mg SC injection once every fortnight. Supplementary (near-market comparators): - Baricitinib 2 mg and 4 mg, orally, once daily; - Abrocitinib 100 mg and 200 mg, orally once daily; and - Tralokinumab 300 mg SC injection, once every fortnight.
Outcomes	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 ≥ 2-point improvement at Week 16. Secondary outcomes: EASI 50, ≥ 4 point improvement in DLQI. PBS response criteria (post-hoc outcome): composite measure of response EASI 50 and improvement in DLQI ≥4, at Week 16.
Clinical claim	- In the treatment of patients aged 12 years or older with severe AD, UPA 30 mg is <b>more effective</b> than DUPI at improving disease activity outcomes (EASI 50 + DLQI ≥4; EASI 75; IGA 0/1), and <b>no worse</b> in terms of safety. - In the treatment of patients aged 12 years or older with severe AD, UPA 15 mg is <b>no worse</b> than DUPI at improving disease activity outcomes (EASI 50 + DLQI ≥4; EASI 75; IGA 0/1), and <b>no worse</b> in terms of safety.

Source: Table 1-1, p28 of the submission.

DLQI = Dermatology Life Quality Index; DUPI = dupilumab; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; D = once daily; SC = sub-cutaneous; UPA = upadacitinib.

## **2 Background**

### ***Registration status***

- 2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration the TGA Round 1 Clinical Evaluation Report (CER) was available. The TGA delegate's overview was not available prior to PBAC consideration of UPA. The proposed TGA indication is: "RINVOQ® is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy."
- 2.2 The proposed TGA indication is broader than the proposed PBS listing, given the TGA indication is for moderate-to-severe disease but the requested PBS listing restricts treatment to severe disease (PBS definition below).
- 2.3 The Updated Product Information (PI) provided with the Pre-Sub-Committee Response (PSCR) included information about UPA patient groups and dosing, specifically that (i) UPA 15 mg is recommended for adolescents and patients ≥ 65 years of age (ii) the lowest effective dose for maintenance should be considered, (iii) a starting dose of UPA 30 mg may be appropriate for some patients, such as those with high disease burden, and (iv) a dose of UPA 30 mg may be appropriate for patients with an inadequate response to UPA 15 mg. The pre-PBAC response noted that the requested PBS population are those with severe disease and therefore a high disease burden, for whom a starting dose of 30 mg may be appropriate.

### ***Previous PBAC consideration***

- 2.4 This was the first PBAC submission for UPA in this indication. UPA is currently PBS listed for rheumatoid arthritis. UPA was recommended by the PBAC for use in severe psoriatic arthritis and ankylosing spondylitis at the March 2021 PBAC meeting.

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

## **3 Requested listing**

- 3.1 The sponsor's requested listing is presented below.

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Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
UPADACITINIB					
15 mg tablet, 28	1	28	4 (initial listings) 5 (continuing and grandfather listings)	Published: \$1786.73 Effective: \$ [REDACTED]	RINVOQ® AbbVie Pty Ltd
30 mg tablet, 28	1	28	4 (initial listings) 5 (continuing and grandfather listings)	Published: \$2157.16 Effective: \$ [REDACTED]	

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>Condition:</b>	Severe atopic dermatitis
<b>PBS indication</b>	Severe AD patients inadequately controlled on topical therapies
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required - Telephone
<b>Treatment phase:</b>	Initial treatment of the whole body
<b>Treatment criteria:</b>	Must be treated by a dermatologist; OR Must be treated by a clinical immunologist
<b>Clinical criteria:</b>	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 corticosteroid therapy of medium to high potency for at least 28 days; AND Patient must have an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical corticosteroids of medium to high potency 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 corticosteroid therapy of medium to high potency for at least 28 days; AND The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands; AND The treatment must be the sole PBS-subsidised biological medicine for this PBS indication; AND Patient must not have experienced an inadequate response to this biological medicine in this PBS indication.
<b>Population criteria:</b>	Patient must be aged 12 years or older
<b>Treatment phase:</b>	Continuing or resuming treatment of the whole body
<b>Clinical criteria:</b>	Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the whole body; AND Patient must have achieved an adequate response within the first 16 weeks of treatment; OR Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; OR Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. 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
<b>Prescriber instructions:</b>	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
<b>Treatment phase:</b>	Transitioning from non-PBS to PBS-subsidised supply - treatment of the whole body (Grandfather listing)

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<b>Clinical criteria:</b>	<p>Patient must have been receiving treatment with this biological medicine for this PBS indication prior to 1 October 2021, AND</p> <p>Patient must have had a Physicians Global Assessment (PGA) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical corticosteroid therapy of medium to high potency for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine; AND</p> <p>Patient must have had an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical corticosteroid therapy of medium to high potency for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine; 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 corticosteroid therapy of medium to high potency for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; OR</p> <p>Patient must have, where the above baseline DLQI was not recorded in the patient's medical records, a current age-appropriate DLQI score (of any value) measured; AND</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, prior to commencing non-PBS-subsidised therapy with this biological medicine; AND</p> <p>Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological medicine; AND</p> <p>The treatment must be the sole PBS-subsidised biological medicine for this PBS indication; AND</p> <p>Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine.</p>
<b>Prescriber instructions:</b>	<p>A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p> <p>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria</p>
<b>Treatment phase:</b>	Initial treatment of the face and/or hands
<b>Clinical criteria:</b>	<p>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 corticosteroid therapy of medium to high potency for at least 28 days; OR</p> <p>The condition must have affected at least 30% of the face/hands surface area despite treatment with daily topical corticosteroid therapy of medium to high potency 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 corticosteroid therapy of medium to high potency 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>The treatment must be the sole PBS-subsidised biological medicine for this PBS indication; AND</p> <p>Patient must not have experienced an inadequate response to this biological medicine in this PBS indication.</p>
<b>Population criteria:</b>	Patient must be aged 12 years or older
<b>Treatment phase:</b>	Continuing or resuming treatment of the face and/or hands
<b>Clinical criteria:</b>	<p>Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the face/hands, AND</p> <p>Patient must have achieved an adequate response within the first 16 weeks of treatment; 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>

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<b>Prescriber instructions:</b>	For the purposes of this restriction, an adequate response to treatment 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
<b>Treatment phase:</b>	Transitioning from non-PBS to PBS-subsidised supply - treatment of the face and/or hands (Grandfather listing)
<b>Clinical criteria:</b>	Patient must have been receiving treatment with this biological medicine for this PBS indication prior to 1 October 2021, AND The condition must have had at least 2 of the following Eczema Area and Severity Index (EASI) symptom sub-scores for erythema, oedema/papulation, excoriation, lichenification rated as severe despite treatment with daily topical corticosteroid therapy of medium to high potency for at least 28 days, prior to commencing non-PBS-subsidised therapy with this biological medicine; OR The condition must have affected at least 30% of the face/hands surface area despite treatment with daily topical corticosteroid therapy of medium to high potency for at least 28 days corticosteroid therapy, prior to commencing non-PBS-subsidised therapy with this biological medicine, AND Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical corticosteroid therapy of medium to high potency for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; OR Patient must have, where the above baseline DLQI was not recorded in the patient's medical records, a current age-appropriate DLQI score (of any value) measured, AND The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, prior to commencing non-PBS-subsidised therapy with this biological medicine, AND Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological medicine, AND The treatment must be the sole PBS-subsidised biological medicine for this condition, AND Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine.
<b>Prescriber instructions:</b>	A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

Source: Attachment 2 of the submission; Table ES-11, pXXIV of the submission; '20210305-pb11a-UPA.pdf', Table 1.4-1, p35 of the submission.

\* The submission requested a special pricing arrangement, and presented 'proxy' effective DPMQs for UPA (\$██████ for UPA 15 mg and \$██████ for UPA 30 mg) based on a proxy effective DPMQ for DUPI (\$██████), which was estimated from the modelled economic evaluation assuming an ICER=\$75,000 to < \$95,000/QALY for DUPI versus best supportive care.

3.2 The sponsor requested an Authority Required (Telephone) listing of UPA 15 mg and 30 mg tablets for initial and continuing treatment of adults and adolescents with severe AD affecting the whole body, or hands and face. The restriction allows clinicians to commence treatment on UPA 15 mg or UPA 30 mg based on individual patient presentation, with continuing treatment conditional on meeting the response criteria within the first 16 weeks of treatment. The requested quantities would provide for 20 weeks of initial treatment (5 packs) and 24 weeks of continuing treatment (6 packs). The restriction was consistent with the current PBS listing of DUPI, as it proposed the same eligibility and response criteria.

- 3.3 The submission sought transitioning arrangements to provide continuing treatment for an estimated 250 patients ('grandfather' patients) enrolled in a planned Patient Familiarisation Program, which will be launched upon TGA registration. The eligibility and continuation criteria for the program will be identical to the proposed PBS restriction.
- 3.4 The submission requested a special pricing arrangement (SPA), with an effective price for UPA 15 mg based on a cost-minimisation analysis and for UPA 30 mg based on a cost-effectiveness analysis (to account for superior efficacy) versus the current effective price for DUPI. As the sponsor was unaware of the current effective price for DUPI, the submission estimated 'proxy' effective prices based on assumed cost-effectiveness for DUPI versus best supportive care (BSC) with prices to be updated when the approved ICER and the effective price for DUPI is known.
- 3.5 The same criteria would apply to both UPA doses, including population criteria ('patient must be aged 12 or older'), but the recommended dose in the draft PI is UPA 15 mg once daily for adolescents weighing at least 40 kg and patients aged  $\geq 65$  years and the 30 mg dose is not recommended in adolescents. The PBAC considered that the listing should limit prescription of UPA 30 mg tablets to patients aged  $\geq 18$  years and  $< 65$  years, or be consistent with the PI once it is finalised.
- 3.6 The restriction does not explicitly consider how clinicians may titrate the dose of UPA in adults, assuming that the TGA PI does not require patients to commence on the lowest effective dose. The PSCR stated that dose selection should be based on clinician judgement and aligned with the TGA approved PI. The submission did not present any evidence to inform the impacts of dose titration on response. The PBAC considered that it may be useful for the restriction to provide administrative advice regarding dose titration and how this would be managed in the context of assessing whether patients have met response criteria to qualify for ongoing treatment on the PBS. The pre-PBAC response stated that the restriction should have sufficient flexibility to allow clinicians to titrate the dose up or down dependent on the clinical characteristics of each patient. The ESC noted that full response to UPA appeared to be reached within around 8 weeks, therefore it may be sufficient for dose titration and assessment of response to have occurred within the proposed 16 week timeframe for initial treatment and assessment of response. The PBAC agreed with the ESC that this approach to assessment of response appears to be appropriate, but that this may be further informed by finalisation of conditions in the TGA Product Information and further clinician input.
- 3.7 Under the proposed listing, patients who fail to respond to treatment with DUPI would be eligible for UPA and vice versa; and therefore sequential use of these two AD treatments would be permitted under the proposed listing. The submission acknowledged this and proposed an increase in the financial caps of the risk sharing arrangements to accommodate sequential use following failure to prior DUPI. The PBAC considered that it would be likely that clinicians would want to treat patients with UPA if they have not responded to DUPI as there are no further drug treatment

options in severe disease, however noted that the submission did not present any data to assess efficacy in this group of patients.

- 3.8 The PBAC noted that UPA is not strictly a biological medicine and that the proposed restriction refers to UPA as a biological medicine since the restriction is based on the restriction for DUPI, which is a biological medicine. Further consideration may be required regarding how to most accurately refer to both UPA and DUPI.
- 3.9 The proposed listing incorporates 3 diagnostic tools by reference: the Physicians Global Assessment (PGA), Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI). The sponsor will need to work with the Department to address how these indices would be provided to clinicians or the public in the context of an UPA listing.

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

## **4 Population and disease**

- 4.1 AD is a chronic, systemic, inflammatory disease that affects skin and is characterised by persistent itch and marked redness. Altered immune responses render AD patients at increased risk of bacterial, viral, and fungal skin infections. AD is also associated with comorbid conditions affecting sleep, pain, psychologic domains, and physical and social functioning.
- 4.2 The requested listing would place UPA as an alternative orally administered treatment option to DUPI SC injections, for adults and adolescents with severe AD who have failed to achieve an adequate response to topical therapy. Poor tolerability and safety profiles limit the long-term use of conventional oral therapies such as ciclosporin (CsA).
- 4.3 UPA is a reversible JAK1 inhibitor. The JAK family of enzymes (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) are associated with key cytokines/interleukins (such as IL-13, IL-4, IL-31, and IL-22) and play an important role in the pathogenesis of AD. Selective inhibition of JAK1 controls inflammatory responses whilst minimising effects on non-inflammatory pathways mediated by the other JAK protein family members.

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

## **5 Comparator**

- 5.1 The submission nominated DUPI as the comparator because it is the treatment most likely to be replaced by UPA.
- 5.2 The submission also identified three potential near market comparators: baricitinib (JAK1/2 inhibitor), abrocitinib (JAK1 inhibitor) and tralokinumab (IL-13 inhibitor). The clinical evidence presented in the submission included supplementary comparisons between UPA and the near-market comparators (baricitinib, abrocitinib and tralokinumab) based on available published data. The PBAC also considered a

submission for the PBS listing of baricitinib for the treatment of severe AD at the July 2021 meeting.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the burden of disease in terms of the stigma associated with the appearance of AD, purulence, pain and burning that leads to sleep disturbance and impacts on mental health, social interactions and the capacity to work. Citing Boeri (2020)<sup>1</sup>, the clinician noted that not all patients respond to dupilumab and patients express a preference for rapid onset of action, fully clear skin and the option of oral administration.
- 6.2 The clinician noted that in the direct head to head trial, UPA had superior efficacy in terms of EASI 90 and EASI 100 (almost/complete clearance of AD) and also more rapid improvement in terms of itch. The clinician noted that for UPA there were slightly higher rates of AEs and drug-related AEs. Acne and folliculitis AEs were not severe and rates of skin infections were not higher than DUPI or other therapies used for AD. The clinician stated that overall, dermatologists were comfortable with the UPA safety profile particularly when compared to other treatments used for AD (such as prednisolone, azathioprine, CsA, methotrexate). The clinician emphasised that UPA is a selective JAK inhibitor which should be considered different to pan-JAK inhibitors from a safety perspective.
- 6.3 Regarding dosing, the clinician stated that it was preferable to start with the 30 mg dose and then reduce to 15 mg where possible to minimise exposure, consistent with dosing of other treatments for AD (prednisolone, CsA). The clinician stated that access to the 15 mg dose would be needed for patients aged <18 and >65 years and the ability to increase the dose to 30 mg would be needed if need clinicians are required to initiate patients on the 15 mg dose.

### ***Consumer comments***

- 6.4 The PBAC noted and welcomed the input from individuals (10), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website.
- 6.5 The PBAC noted the advice received from AD support groups: Eczema Association of Australasia Inc (EAA), Eczema Support Australia and Allergy & Anaphylaxis Australia (A&AA). Comments from EAA described the very high disease burden for patients with severe AD and their families, describing the impact from itch, sleep disruption, pain

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<sup>1</sup> Boeri M et al. *J Dermatolog Treat* 2020.

and infections, and the resulting effects on their ability to work and in social situations, and the detrimental impact on mental health. EAA also noted the cost of managing AD and the long-term comorbidities associated with AD. Both Eczema Support Australia and A&AA noted that patients with AD vary in response to treatments as well as contraindications and side effects from treatments and therefore access to alternatives to DUPI are highly valued by patients and clinicians.

- 6.6 Eczema Support Australia noted that disease management is complex, and currently patients with AD classified as moderate do not qualify for treatment with DUPI despite fluctuating disease severity/disease flares. Some patients with AD classified as moderate may remain on CsA (which has a poor AE profile) or would need to cease treatment, allowing their AD to worsen, in order to qualify for treatment with DUPI. Both Eczema Support Australia and A&AA requested that the PBAC consider the issues involved in living with AD and consider including patients with moderate to severe AD, noting the disease burden and unmet need for patients with moderate AD. The PBAC noted that advice from all support groups was supportive of the evidence provided in the submission.
- 6.7 Comments from consumers noted the impact of AD on their quality of life. Consumers reported having inadequate response to DUPI or experiencing side effects from treatment with DUPI and were therefore supportive of access to alternative treatments for AD such as UPA.

### ***Clinical trials***

- 6.8 The submission was based on one head-to-head randomised trial comparing UPA to DUPI, five randomised trials comparing UPA to placebo (PBO), and seven randomised trials comparing DUPI to PBO:

- UPA vs DUPI, as monotherapy: HEADS UP;
- UPA vs PBO, as monotherapy: MEASURE UP 1, MEASURE UP 2, M16-048;
- UPA vs PBO, in combination with TCS: AD UP, and RISING UP;
- DUPI vs PBO, as monotherapy: SOLO 1, SOLO 2, LIBERTY AD ADOL, Study 1021;
- DUPI vs PBO, in combination with TCS: CAFÉ, CHRONOS, JADE COMPARE.

The PBAC has previously considered evidence from five of the seven DUPI trials (SOLO 1, SOLO 2, CAFÉ, CHRONOS, Study 1021<sup>2</sup>).

- 6.9 HEADS UP did not include the UPA 15 mg dosing regimen or capture the Dermatology Life Quality Index (DLQI), which is a patient relevant outcome used to assess response on the PBS. Therefore, the submission relied on the results of an indirect treatment

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<sup>2</sup> referred to as 'Phase IIb' in previous DUPI submissions

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comparison (using PBO as a common reference) to inform the clinical claim, economic model and financial estimates.

- 6.10 The ESC recalled that the PBAC previously considered standard of care includes concomitant TCS, (para 5.1, DUPI Public Summary Document (PSD), July 2018 PBAC meeting) 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 UPA. The pre-PBAC response argued that the efficacy of UPA as a monotherapy remains relevant and important to patients and represents a reduced treatment burden for patients, and for the health system more broadly.
- 6.11 Table 2 provides citation details of the trials presented in the submission.

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**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>UPA vs DUPI</b>		
HEADS UP: M16-046	A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis,	February 2021.
<b>UPA vs PBO</b>		
MEASURE UP 1: M16-045	A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis.	September 2020
MEASURE UP 2: M18-891	A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis.	September 2020
M16-048	A Phase 2b Multicenter, Randomized, Placebo-Controlled, Double-Blind Dose-Ranging Study to Evaluate ABT-494 (Upadacitinib) in Adult Subjects with Moderate to Severe Atopic Dermatitis. Guttman-Yassky E, Thaci D, Pangan A et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial.	January 2020  J Allergy Clin Immunol 2020; 145: 877-884.
RISING UP: M17-377	Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects in Japan.	April 2020
AD UP: M16-047	A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis.	September 2020
<b>DUPI vs PBO</b>		
SOLO 1	Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.	N Engl J Med. 2016 Dec 15;375(24):2335-2348.
SOLO 2	Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.	N Engl J Med. 2016 Dec 15;375(24):2335-2348.
LIBERTY AD ADOL	Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis.	JAMA Dermatol 2020; 156(1): 44-56.
Study 1021	Thaci D, Simpson EL, Beck LA 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.	Lancet 2016; 387:40-52.
CAFÉ	de Bruin-Weller M, Gadkari A, Simpson E et al. Dupilumab improves patient-reported outcomes in atopic dermatitis inadequately controlled, intolerant, or inadvisable for cyclosporine-A. Annals of Allergy, Asthma and Immunology 2017; 119(5S1):S94-S95.	Annals of Allergy, Asthma and Immunology 2017; 119(5S1):S94-S95.
CHRONOS	Blauvelt A, Bruin-Weller M, Gooderham M 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.	Lancet. 2017; 389:2287-303.
JADE COMPARE	Thaci D, Bieber T, Simpson EL et al. A phase 3 study to investigate the efficacy and safety of abrocitinib and dupilumab in comparison with placebo in adults with moderate-to-severe atopic dermatitis.	29 <sup>th</sup> EADV Congress; October 28-November 1 2020.

Only main publications have been reported in this table.

Source: Table 2-3, pp43-45 of the submission.

6.12 Table 3 presents the key features of the included randomised trials.

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Table 3: Key features of the included evidence

Trial	N	Design/duration	Bias	Relevant comparison	Patient population	Primary outcome(s)
<b>UPA trials</b>						
HEADS UP	692	P3, R, MC, DB 24wk (+OL 52wk), rescue therapy <sup>^</sup>	Low	UPA 30 mg D DUPI 300 mg Q2W <sup>†</sup>	M-S AD; adults	EASI 75 at Wk16
MEASURE UP 1	847	P3, R, MC, DB, PC 16wk (BE <sup>a</sup> to 136wk), rescue therapy <sup>^</sup>	Low	UPA 15 mg D UPA 30 mg D PBO	M-S AD; adults and adolescents	EASI 75 & IGA of 0 or 1 <sup>c</sup> at Wk16
MEASURE UP 2	836	P3, R, MC, DB, PC 16wk (BE <sup>a</sup> up to 136wk), rescue therapy <sup>^</sup>	Low	UPA 15 mg D UPA 30 mg D PBO	M-S AD; adults and adolescents	EASI 75 & IGA of 0 or 1 <sup>c</sup> at Wk16
M16-048	167*	P3, R, MC, DB 16wk, PC (BE <sup>b</sup> to 88wk), no rescue therapy <sup>^^</sup>	Low	UPA 15 mg D UPA 30 mg D PBO	M-S AD; adults	% change in EASI
AD UP	901	P3, R, MC, DB, PC 16wk (BE <sup>a</sup> to 136wk), rescue therapy <sup>^</sup>	Low	UPA 15 mg D + TCS UPA 30 mg D + TCS PBO + TCS	M-S AD; adults and adolescents	EASI 75 & IGA of 0 or 1 <sup>c</sup> at Wk16
RISING UP	272	P3, R, MC, DB, PC 16wk (BE <sup>a</sup> /OL to 136wk), rescue therapy <sup>^</sup>	Low	UPA 15 mg D + TCS UPA 30 mg D + TCS PBO + TCS	M-S AD; adults and adolescents	Safety
<b>DUPI trials</b>						
Study 1021	125*	P2b, R, MC, DB, PC 16wk, rescue therapy <sup>^</sup>	Low	DUPI 300 mg Q2W <sup>†</sup> PBO	M-S AD; adults	% change in EASI at wk16
SOLO 1	448*	P3, R, MC, DB, PC 16wk, rescue therapy <sup>^</sup>	Low	DUPI 300 mg Q2W <sup>†</sup>	M-S AD; adults	IGA of 0 or 1 <sup>c</sup> & EASI 75 <sup>§</sup> at wk16
SOLO 2	469*		Low	PBO		
LIBERTY AD ADOL	215	P3, R, MC, DB, PC, AC 16wk, rescue therapy allowed <sup>^</sup>	Low	DUPI 200/300 mg Q2W <sup>†</sup> PBO	M-S AD; adolescents	IGA of 0 or 1 <sup>c</sup> & EASI 75 at wk16
CAFÉ	215	P3, R, MC, DB, PC 16wk, rescue therapy allowed <sup>^</sup>	Low	DUPI 300 mg Q2W <sup>†</sup> +TCS PBO +TCS	M-S AD; adults	EASI 75 at wk16
CHRONOS	421	P3, R, MC, DB, PC 52wk, rescue therapy > wk2	Low	DUPI 300 mg Q2W <sup>†</sup> +TCS PBO +TCS	M-S AD; adults	IGA of 0 or 1 <sup>c</sup> and EASI 75 at wk16
JADE Compare	373*	P3, R, MC, DB, DD, PC, AC 16wk, rescue therapy NR	Low	DUPI 300 mg Q2W +TCS PBO +TCS	M-S AD; adults	IGA of 0 or 1 <sup>c</sup> and EASI 75 at wk12

Source: Tables 2-7, pp57-60 of the submission, and related publications/CSRs.

P2/3 = phase 2 or 3; BE = blinded extension; DB = double blind; DD = double dummy; MC = multi-centre; R = randomised; OL = open-label; PC = placebo-controlled; AC = active control; SOC = standard-of-care; TCS = topical corticosteroids; wk = week; DUPI = dupilumab; PBO = placebo; UPA = upadacitinib; D = once daily; Q2W = once every 2 weeks; IGA = investigator's global assessment; EASI = Eczema Area and Severity Index; EASI 50/75 = improvement of at least 50/75% from baseline in Eczema Area and Severity Index; NR = not reported; M-S = moderate to severe.

<sup>a</sup> At Week 16, subjects in the placebo group were re-randomised to receive UPA 30 mg or UPA 15 mg in the BE period. Subjects originally randomised to UPA were to continue UPA at the same dose.

<sup>b</sup> M16-048: At Week 16, subjects who completed the first 16-week double-blind period (Period 1) were re-randomised into a 72-week double-blind, PBO-controlled treatment period (Period 2), at the same UPA dose as Period 1. PBO patients in Period 1 were re-randomised to receive UPA 30 mg daily or PBO in Period 2.

<sup>c</sup> Proportion of patients achieving IGA of 0 or 1 with a  $\geq 2$ -point improvement (i.e.: from a baseline of 3 or 4 on the 5-point IGA scale)

\* Excluding patients randomised to the following treatment arms: UPA 7.5 mg, DUPI 300 mg weekly/200mg every 2 weeks/100 mg every 4 weeks or abrocitinib 100 or 200 mg daily.

<sup>†</sup> 'DUPI 300 mg Q2W' comprised 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.

<sup>§</sup> EASI 75 was a coprimary outcome in EU and Japan and a key secondary outcome elsewhere.

<sup>^</sup> Protocols allowed investigators to rescue patients who were experiencing unacceptable or worsening of symptoms. Patients who received rescue therapy were discontinued from study treatment and considered non-responders.

<sup>^^</sup>M16-048: Period 1 was a 16-week randomised, double-blind, placebo-controlled period. Rescue therapy was allowed at the Week 20 visit (4 weeks after re-randomisation into Period 2).

- 6.13 All trials were multicentre, randomised, placebo and/or active controlled, parallel group with a double-blind phase of at least 16 weeks. Patients had moderate-to-severe AD and were required to have experienced an inadequate response to TCS or topical calcineurin inhibitors (TCIs). Most trials measured the primary endpoint at week 16 with treatment response defined according to the Eczema Area and Severity Index (EASI) and/or the Investigator's Global Assessment (IGA). Most trials also allowed rescue therapy during the double-blind phase, but patients who received rescue therapy were considered non-responders for the primary endpoint (and other categorical outcomes).
- 6.14 The selection criteria were broadly similar across the UPA and DUPI trials with a key exception being age, as some trials enrolled adults, adolescents or both. Overall, baseline characteristics were balanced between treatment arms within trials (with the exception of some characteristics in M16-048, a relatively small trial) and are representative of patients with moderate-to-severe AD, with mean EASI of 28-36 at baseline and approximately half (45.8% to 55.3%) with IGA of 4. As more of the UPA trials enrolled adolescents compared to the DUPI trials, there were slight differences in age-related characteristics across the two sets of trials. Overall, these differences are unlikely to be important, particularly when controlling for age ( $\geq 18$  years and 12-17 years).
- 6.15 Under the requested restriction, patients are required to meet different eligibility and response criteria depending on the affected area.
- For patients with severe AD affecting the whole body, initial treatment requires a Physicians Global Assessment (PGA) score of 4 and an EASI score  $\geq 20$ , and continuing treatment requires a  $\geq 50\%$  improvement from baseline in EASI (i.e. EASI 50) and an improvement from baseline in DLQI  $\geq 4$  points.
  - For patients with severe AD affecting the face/palm of hands, initial treatment requires  $\geq 2$  of the EASI symptom sub-scores (i.e. erythema, oedema/papulation, excoriation, lichenification) rated as severe or  $\geq 30\%$  surface area of the face/hands affected, and continuing treatment requires  $\geq 3$  of the EASI symptom sub-scores rated as mild or none or  $\geq 75\%$  reduction in the skin area affected compared to baseline, and an improvement from baseline in DLQI  $\geq 4$  points.
- 6.16 The PBAC has previously considered EASI (marker of lesions) and DLQI outcomes (patient impact) 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  $\geq 4$  points are likely to be clinically reasonable and able to capture patients with a meaningful response to treatment (para 7.4, DUPI PSD March 2020 PBAC meeting). The PBAC also considered that it would be clinically appropriate for a separate listing in patients with AD affecting the face and hands, who would not be eligible under the whole body criteria due to the relatively small body surface area involved. The PBAC previously agreed that listing for these patients

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should include improvement in DLQI as a criterion for continuing treatment (para 7.5, DUPI PSD March 2020 PBAC meeting).

6.17 Table 4 summarises the primary and key secondary/exploratory endpoints measured across trials, which included EASI 50 response and DLQI  $\geq 4$  at 16 weeks.

**Table 4: Primary (1°), key secondary (2°) and other secondary/exploratory/post-hoc (✓) outcomes reported at Week 16 (unless otherwise indicated)**

Trials	EASI 50 <sup>a</sup>	EASI 75 <sup>a</sup>	EASI 90 <sup>a</sup>	% change EASI <sup>b</sup>	IGA of 0 or 1 <sup>c</sup>	DLQI $\geq 4$ <sup>d</sup>	DLQI 0/1 <sup>e</sup>	Change DLQI or CDLQI <sup>f</sup>
<b>UPA trials</b>								
HEADS UP		1°	2°					
MEASURE UP 1	✓	1°	2°	2°	1°	2°	✓	
MEASURE UP 2	✓	1°	2°	2°	1°	2°	✓	
RISING UP	✓	✓	✓	✓	✓			
AD UP	✓	1°	2°	2°	1°	✓	✓	
M16-048	2°	2°	2°	1°	2°		2°	✓2°
<b>DUPI trials</b>								
Study 1021	2°	2°	2°	1°	2°			✓
SOLO 1	✓	1° / 2° <sup>g</sup>	✓	✓	1° / 2° <sup>g</sup>	✓		✓
SOLO 2	✓	1° / 2° <sup>g</sup>	✓	✓	1° / 2° <sup>g</sup>	✓		✓
CAFÉ	2°	1°	2°	2°	2°	✓		2°
CHRONOS	✓	1°	✓	✓	1°	✓		
JADE Compare	✓	1° (Wk12) 2° (Wk16)	✓		1° (Wk12) 2° (Wk16)			✓
LIBERTY AD ADOL	✓	1°	✓	2°	1°			✓

Source: Compiled during evaluation with reference to Table 2.4-8 of the submission and related CSRs/protocols.

CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index.; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment

<sup>a</sup> At least 50/75/90% improvement/reduction from baseline in EASI score.

<sup>b</sup> % change from baseline in EASI score.

<sup>c</sup> Proportion of patients achieving IGA of 0 or 1 with a  $\geq 2$ -point improvement (i.e.: from a baseline of 3 or 4 on the 5-point IGA scale).

<sup>d</sup> Proportion of patients achieving an improvement (reduction) in DLQI  $\geq 4$ .

<sup>e</sup> Proportion of patients achieving DLQI score of 0/1 for patients with a DLQI score  $> 1$  at baseline.

<sup>f</sup> Mean change or absolute and percentage change from baseline in the DLQI total scores.

<sup>g</sup> EASI 75 was a co-primary outcome in Europe and Japan and a key secondary outcome elsewhere.

6.18 The trials provide clinical evidence for patients with AD affecting the whole body (as none of the trials enrolled patients with AD exclusively affecting the face and hands), and neither the PBS response criteria (i.e. EASI 50 **and** DLQI  $\geq 4$ ) nor the PBS population (i.e. severe AD, defined as EASI score  $\geq 20$  **and** PGA score =4) were pre-specified analyses in any of the trials.

6.19 The submission did not provide any evidence to support listing of UPA in patients with severe AD affecting the face and hands, but argued that it is biologically plausible that UPA is effective across all anatomical regions. For DUPI, the decision to extend listing to patients with disease affecting the face and hands was based on a post-hoc analysis indicating similar and statistically significant improvements in EASI score for all body areas assessed, including head & neck, trunk, upper limbs, lower limbs (para 3.4, DUPI PSD March 2020 PBAC meeting). The PSCR provided a post-hoc analysis of response rates across body regions captured in the EASI score (head and neck, upper

extremities, lower extremities, trunk) from the HEADS UP trial. The results showed similar improvements across all body regions with UPA compared with DUPI. The ESC considered this was in line with the evidence presented for DUPI to justify the additional restriction.

## Comparative effectiveness

### Initial response: direct evidence

6.20 Table 5 shows the primary and key secondary outcomes in HEADS UP in the ITT population, comparing UPA 30 mg directly to DUPI 300 mg.

Table 5: Primary and key secondary outcomes in HEADS UP trial (ITT)

Outcome	UPA 30 mg	DUPI 300 mg	UPA 30 mg vs DUPI 300 mg	
	Point-estimate (95%CI)		Diff. (95%CI)	Multiplicity adjusted
EASI 75, Wk 16	71.0% (66.2,75.8)	61.1% (55.9,66.2)	10.0% (2.9,17.0)	p<0.05
Worst Pruritus NRS, Δ BL to Wk16	-66.88 (-70.59,-63.17)	-49.04 (-52.87,-45.22)	-17.84 (-23.17,-12.50)	p<0.05
EASI 100, Wk 16	27.9% (23.2,32.6)	7.6% (4.8,10.4)	20.3% (14.9,25.8)	p<0.05
EASI 90, Wk 16	60.6% (55.4, 65.7)	38.8% (33.6, 43.9)	21.8% (14.5, 29.1)	p<0.05
Worst Pruritus NRS, Δ BL to Wk4	-59.49 (-63.76, -55.21)	-31.73 (-36.11, -27.34)	-27.76 (-33.88, -21.64)	p<0.05
EASI 75, Wk 2	43.6% (38.4, 48.8)	17.5% (13.5, 21.5)	26.0% (19.5, 32.6)	p<0.05
Worst Pruritus NRS, Δ BL to Wk1	-31.44 (-34.86, -28.02)	-8.76 (-12.26, -5.27)	-22.68 (-27.56, -17.79)	p<0.05
Worst Pruritus NRS, Δ BL to Wk16 ≥4	55.2% (49.9, 60.5)	35.9% (30.7, 41.0)	19.3% (11.9, 26.7)	p<0.05

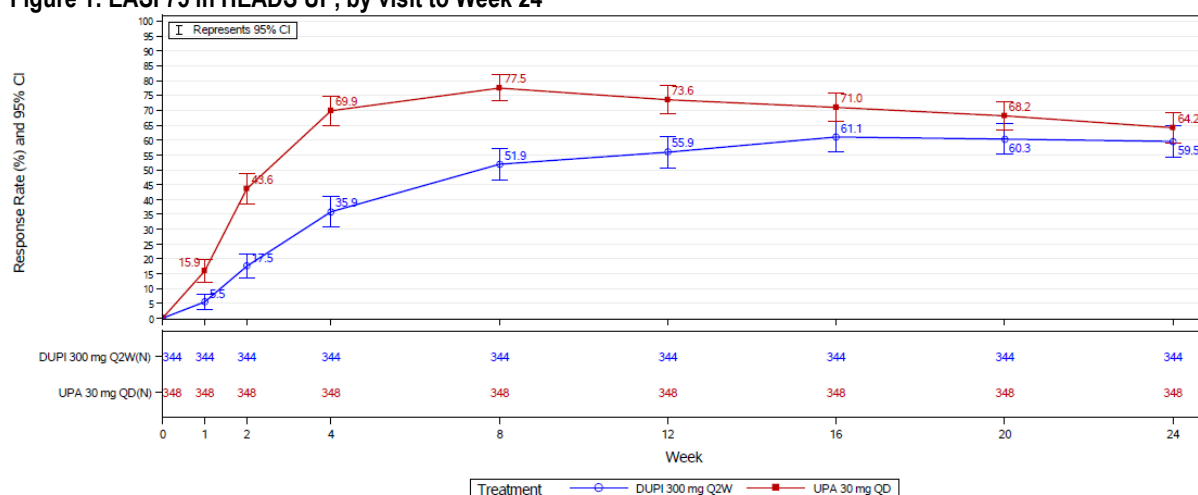
Source: Table 14.2\_1 p614 of CSR M16046

BL = baseline; EASI = Eczema Area and Severity Index; NRS = Numerical Rating Scale; DUPI = dupilumab; UPA = upadacitinib.

6.21 The results demonstrated a significantly larger proportion of patients achieved EASI 75 at Week 16 with UPA 30 mg compared to DUPI, and superiority of UPA 30 mg was demonstrated in all pre-specified ranked secondary endpoints.

6.22 Figure 1 shows the proportion of patients with EASI 75 in HEADS UP by visit.

Figure 1: EASI 75 in HEADS UP, by visit to Week 24



Source: Figure 2.9, p93 of the submission

EASI = Eczema Area and Severity Index.

- 6.23 The results indicated that the statistically significant treatment difference observed at Week 16 disappeared by Week 24. The submission (p92) claimed that the modest downward trend observed in the UPA 30 mg arm after Week 16 is largely owing to some patients receiving rescue TCS and being classified as non-responders. A higher proportion of patients on DUPI had received rescue therapy at Week 16 compared to UPA 30 mg (who were therefore classified as non-responders), but the proportions rescued were similar at Week 24. Given rescue therapy (i.e. topical or other systemic treatments) is commonly used in practice and would not disqualify patients from PBS treatment with UPA, it was unclear whether the difference observed in the trial outcome would translate to practice. The ESC considered that these results appeared to show that patients treated with UPA tended to respond to treatment faster than patients treated with DUPI, however beyond 16 weeks the difference in EASI 75 response between UPA and DUPI was not statistically significant.
- 6.24 As noted above, the submission relied on the results of an indirect comparison over the direct evidence because HEADS UP did not measure the DLQI. However, the trial did measure IGA and EASI at baseline (i.e. the criteria used to identify the PBS subgroup in the other trials, EASI score  $\geq 20$  and IGA score = 4) and the change in EASI score at Week 16 (where EASI 50 is one component of the PBS response criteria). In the PSCR, the sponsor provided this post-hoc analysis to reduce uncertainty around the magnitude of the estimated treatment difference, noting the limitations of this analysis. The ESC noted that the outcome of EASI 50 was numerically but not statistically significantly different between UPA and DUPI at 16 weeks (76.3% vs 68.9% respectively, RR=1.11 95%CI: 0.97, 1.27), but otherwise outcomes were consistent with the primary outcome. The PSCR also noted that EASI 75, 90 and 100 were significantly superior for UPA at 16 weeks but at 24 weeks only EASI 100 (complete skin clearance) remained significantly different from DUPI.

**Initial response: indirect treatment comparisons**

- 6.25 The submission presented a series of indirect treatment comparisons at Week 16 comparing UPA 15 mg and UPA 30 mg versus DUPI (using PBO as a common comparator) in the PBS subgroup (i.e. severe AD, defined as EASI score  $\geq 20$  and IGA score =4 at baseline) and the ITT population (i.e. moderate-to-severe AD).
- 6.26 For the PBS subgroup, the submission presented post-hoc results in adult patients from the UPA trials to match limited data reported for DUPI. Data in the DUPI PSD cited the proportion of patients who met the PBS response criteria (EASI 50 and DLQI  $\geq 4$ ) in the PBS subgroup by prior CsA treatment pooled across monotherapy and combination therapy trials (Table 9, DUPI PSD March 2020 PBAC meeting). Given the limitations of these analyses and the post-hoc nature of the PBS criteria and subgroup, the submission also presented indirect comparisons for other efficacy outcomes in the ITT populations.
- 6.27 Table 6 presents results of the PBS response outcome in the PBS subgroup in the PBO-controlled trials.

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Table 6: PBS response (i.e. EASI-50 AND DLQI 4) at Week 16 in PBS adult population (i.e. severe AD defined as IGA=4 AND EASI ≥20 at baseline)

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
<b>CsA Naive</b>					
<b>UPA 15 mg ± TCS v PBO ± TCS</b>					
MEASURE UP 1	53/76 (69.7)	15/75 (20.0)	<b>3.49 (2.17,5.61)</b>	<b>0.50 (0.36,0.63)</b>	2 (2,3)
MEASURE UP 2	47/72 (65.3)	15/73 (20.5)	<b>3.18 (1.96,5.14)</b>	<b>0.45 (0.30,0.59)</b>	2 (2,3)
AD UP	67/91 (73.6)	31/98 (31.6)	<b>2.33 (1.70,3.19)</b>	<b>0.42 (0.29,0.55)</b>	2 (2,3)
Meta-analysis UPA 15 mg v PBO	167/239 (69.9)	61/246 (24.8)	<b>2.79 (2.15,3.62)</b>	<b>0.45 (0.37,0.53)</b>	2 (2,3)
<b>UPA 30 mg ± TCS v PBO ± TCS</b>					
MEASURE UP 1	70/85 (82.4)	15/75 (20.0)	<b>4.12 (2.59,6.54)</b>	<b>0.62 (0.50,0.75)</b>	2 (1,2)
MEASURE UP 2	68/85 (80.0)	15/73 (20.5)	<b>3.89 (2.45,6.19)</b>	<b>0.59 (0.47,0.72)</b>	2 (1,2)
AD UP	76/95 (80.0)	31/98 (31.6)	<b>2.53 (1.86,3.44)</b>	<b>0.48 (0.36,0.61)</b>	2 (2,3)
Meta-analysis UPA 30 mg v PBO	214/265 (80.8)	61/246 (24.8)	<b>3.31 (2.35,4.64)</b>	<b>0.57 (0.48,0.65)</b>	2 (2,2)
<b>DUPI 300 mg ± TCS v PBO ± TCS</b>					
1021	NR	NR	NR	NR	NR
SOLO 1	NR	NR	NR	NR	NR
SOLO 2	NR	NR	NR	NR	NR
CHRONOS	NR	NR	NR	NR	NR
Meta-analysis DUPI 300 mg v PBO	99/166 (59.6)	49/246 (19.9)	<b>2.99 (2.26,3.96)</b>	<b>0.40 (0.31,0.49)</b>	3 (2,3)
<b>CsA Experienced</b>					
<b>UPA 15 mg ± TCS v PBO ± TCS</b>					
MEASURE UP 1	15/26 (57.7)	1/21 (4.8)	<b>12.12 (1.74,84.38)</b>	<b>0.53 (0.32,0.74)</b>	2 (1,3)
MEASURE UP 2	30/41 (73.2)	2/43 (4.7)	<b>15.73 (4.01,61.66)</b>	<b>0.69 (0.54,0.83)</b>	1 (1,2)
AD UP	23/31 (74.2)	9/34 (26.5)	<b>2.80 (1.54,5.09)</b>	<b>0.48 (0.26,0.69)</b>	2 (1,4)
Meta-analysis UPA 15 mg v PBO	68/98 (69.4)	12/98 (12.2)	<b>7.13 (1.63,31.18)</b>	<b>0.58 (0.45,0.72)</b>	2 (1,2)
<b>UPA 30 mg ± TCS v PBO ± TCS</b>					
MEASURE UP 1	16/20 (80.0)	1/21 (4.8)	<b>16.80(2.45,115.19)</b>	<b>0.75 (0.55,0.95)</b>	1 (1,2)
MEASURE UP 2	26/32 (81.3)	2/43 (4.7)	<b>17.47 (4.47,68.30)</b>	<b>0.77 (0.62,0.92)</b>	1 (1,2)
AD UP	22/27 (81.5)	9/34 (26.5)	<b>3.08 (1.71,5.54)</b>	<b>0.55 (0.34,0.76)</b>	2 (1,3)
Meta-analysis UPA 30 mg v PBO	64/79 (81.0)	12/98 (12.2)	<b>8.46 (1.79,39.97)</b>	<b>0.70 (0.57,0.83)</b>	1 (1,2)
<b>DUPI 300 mg ± TCS v PBO ± TCS</b>					
1021	NR	NR	NR	NR	NR
SOLO 1	NR	NR	NR	NR	NR
SOLO 2	NR	NR	NR	NR	NR
CHRONOS	NR	NR	NR	NR	NR
Meta-analysis DUPI 300 mg SC v PBO	91/152 (59.9)	25/178 (14.0)	<b>4.26 (2.90,6.27)</b>	<b>0.46 (0.37,0.55)</b>	2 (2,3)
<b>Indirect comparisons</b>					
<b>CsA Naive</b>					
UPA 15 mg v DUPI 300 mg Wk 16			0.93 (0.64,1.37)	0.05 (-0.07,0.17)	-
UPA 30 mg v DUPI 300 mg Wk 16			1.11 (0.71,1.72)	<b>0.17 (0.05,0.29)</b>	6 (3,20)
<b>CsA Experienced</b>					
UPA 15 mg v DUPI 300 mg Wk 16			1.67 (0.36,7.69)	0.12 (-0.04,0.28)	-
UPA 30 mg v DUPI 300 mg Wk 16			1.99 (0.41,9.56)	<b>0.24 (0.08, 0.40)</b>	4 (3,13)

Source: Table 4.1 of Attachment 8 of the submission; Table 2-30-31, p107 of the submission.

DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; CsA = ciclosporin A; NR = not reported; DUPI = dupilumab; PBO = placebo; TCS = topical corticosteroid; UPA = upadacitinib.

Note: that the results presented in Table 6 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for any of the above mentioned studies. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.28 The results demonstrated that a significantly larger proportion of patients achieved the PBS composite outcome at Week 16 with active treatment (UPA 15 mg, UPA 30 mg or DUPI) compared to PBO, for CsA-naïve or -experienced patients. The indirect treatment comparisons found no statistically significant differences between UPA 15 mg versus DUPI, but a statistically significant difference in favour of UPA 30 mg versus DUPI using the risk difference (RD) statistic, irrespective of prior CsA.
- 6.29 Table 7 presents a summary of results for the indirect treatment comparisons between UPA and DUPI, in the ITT populations (for adults and adolescents separately). The results presented in the table below were estimated during the evaluation to control for potential age-related differences.

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Table 7: Summary of results for indirect treatment comparisons for other response outcomes at Week 16 for UPA vs DUPI via PBO, in the ITT population (adults and adolescents presented separately)

Outcome & population	RR (95%CI)	RD (95%CI)
<b>ADULTS</b>		
<b>EASI-75 response</b>		
<b>Monotherapy</b>		
UPA 15 mg v DUPI 300 mg <sup>†</sup>	1.13 (0.82,1.56)	<b>0.13 (0.06,0.20)</b>
UPA 30 mg v DUPI 300 mg <sup>†</sup>	1.34 (0.98,1.84)	<b>0.25 (0.18,0.32)</b>
<b>Combination therapy</b>		
UPA 15 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	1.14 (0.80,1.61)	0.04 (-0.06,0.14)
UPA 30 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	1.30 (0.95,1.78)	<b>0.14 (0.04,0.24)</b>
<b>EASI-50 response</b>		
<b>Monotherapy</b>		
UPA 15 mg v DUPI 300 mg <sup>†</sup>	0.96 (0.77,1.20)	0.04 (-0.03,0.11)
UPA 30 mg v DUPI 300 mg <sup>†</sup>	1.07 (0.86,1.33)	<b>0.12 (0.05,0.19)</b>
<b>Combination therapy</b>		
UPA 15 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	1.31 (0.86,1.99)	0.11 (-0.05,0.27)
UPA 30 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	1.36 (0.93,1.98)	<b>0.14 (0.01,0.27)</b>
<b>vIGA score of 0 or 1 and ≥2-grades improvement</b>		
<b>Monotherapy</b>		
UPA 15 mg v DUPI 300 mg <sup>†</sup>	1.56 (0.95,2.57)	<b>0.08 (0.001,0.16)</b>
UPA 30 mg v DUPI 300 mg <sup>†</sup>	<b>1.98 (1.20,3.26)</b>	<b>0.21 (0.15,0.27)</b>
<b>Combination therapy</b>		
UPA 15 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	1.30 (0.82,2.05)	0.04 (-0.04,0.12)
UPA 30 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	<b>1.77 (1.17,2.69)</b>	<b>0.19 (0.11,0.27)</b>
<b>DLQI≥4-point improvement</b>		
<b>Monotherapy</b>		
UPA 15 mg v DUPI 300 mg <sup>†</sup>	1.08 (0.83,1.42)	0.06 (-0.06,0.18)
UPA 30 mg v DUPI 300 mg <sup>†</sup>	1.18 (0.90,1.54)	0.12 (-0.01,0.25)
<b>Combination therapy</b>		
UPA 15 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	1.03 (0.83,1.26)	0.00 (-0.11,0.11)
UPA 30 mg +TCS v DUPI 300 mg <sup>†</sup> +TCS	1.07 (0.87,1.31)	0.03 (-0.08,0.14)
<b>ADOLESCENTS</b>		
<b>EASI-75 response</b>		
<b>Monotherapy</b>		
UPA 15 mg v DUPI 200/300 mg <sup>†#</sup>	1.23 (0.45,3.38)	<b>0.27 (0.10,0.44)</b>
UPA 30 mg v DUPI 200/300 mg <sup>†#</sup>	1.41 (0.50,3.97)	<b>0.36 (0.16,0.56)</b>
<b>EASI-50 response</b>		
<b>Monotherapy</b>		
UPA 15 mg v DUPI 200/300 mg <sup>†#</sup>	<b>0.47 (0.24,0.92)</b>	-0.06 (-0.25,0.13)
UPA 30 mg v DUPI 200/300 mg <sup>†#</sup>	0.52 (0.27,1.00)	0.01 (-0.18,0.20)
<b>vIGA score of 0 or 1 and ≥2-grades improvement</b>		
<b>Monotherapy</b>		
UPA 15 mg v DUPI 200/300 mg <sup>†#</sup>	0.65 (0.11,3.69)	0.13 (-0.03,0.29)
UPA 30 mg v DUPI 200/300 mg <sup>†#</sup>	1.11 (0.20,6.15)	<b>0.39 (0.23,0.55)</b>

Source: related CSRs : Table 14.2\_2.2.1 3.1.1, 14.2\_6.1.1 of CSR M16045 (MEASURE UP 1), Table 14.2\_2.2.1, 14.3.1.1, 14.2\_6.1.1 of CSR M18891 (MEASURE UP 2), Table 14.2\_1.5, 14.2\_1.2.3, 14.2\_1.3.1 of CSR M16048, Table 14.2\_2.2.1, 14.2\_6.1.1 of CSR M16047 (AD UP), Table 14.2\_3.1, 14.2\_1.1, 14.2\_7.1 of CSR M17377 (RISING UP), Table A.1.1 and A.1.2 of Attachment 8 'ITC Report Dataanalytics'; <https://www.clinicaltrials.gov/ct2/show/results/NCT03720470?term=NCT03720470&draw=2&rank=1> (JADE COMPARE).

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DUPI = dupilumab; PBO = placebo; TCS = topical corticosteroids; UPA = upadacitinib; RR = relative risk; RD = risk difference; CI = confidence interval; EASI = Eczema Area and Severity Index; DLQI = Dermatology Life Quality Index; vIGA = validated Investigator Global Assessment; EASI 50/75 = 50/75% improvement/reduction in the EASI score from baseline; IGA score of 0 or 1 and  $\geq 2$ -point improvement=achievement of a score of 0 or 1 from a baseline of 3 or 4 on the 5-point IGA scale;  $DLQI \geq 4$ =at least 4-point improvement in DLQI from baseline.

Bold = statistically significant results. Italics = calculated during evaluation.

† DUPI dosing comprised 600mg loading, then 300mg every 2 weeks thereafter.

# DUPI patients weighing < 60kg received 200mg DUPI every 2 weeks (400mg loading dose), patients weighing  $\geq 60$ kg received 300mg DUPI every 2 weeks (600mg loading dose)

- 6.30 The results in the ITT population were generally consistent with the PBS subgroup, where the indirect comparisons found similar efficacy between UPA 15 mg versus DUPI and statistically favoured UPA 30 mg versus DUPI for most outcomes (except  $DLQI \geq 4$  point improvement).
- 6.31 The submission presented evidence that disease severity in the PBO-controlled trials, defined by the PBS eligibility criteria, was not a treatment effect modifier, and therefore evidence for the ITT population was applicable to the PBS population. The Commentary considered this was reasonable and supported by subgroup data in HEADS UP by baseline severity (IGA 3 vs 4, and EASI < median score vs  $\geq$  median score).
- 6.32 In trials that enrolled adolescents and adults, active treatment was equally effective versus PBO in adolescents and adults. Interpretation of the indirect comparisons for adolescents is however problematic, given the small patient numbers and differences in the PBO response rates (particularly for EASI 50). Overall, there was insufficient evidence to suggest that the treatment benefit for UPA 30 mg versus DUPI was dissimilar in adolescents compared to adults, noting that the draft PI indicated that the 30 mg dose is not recommended in adolescents.

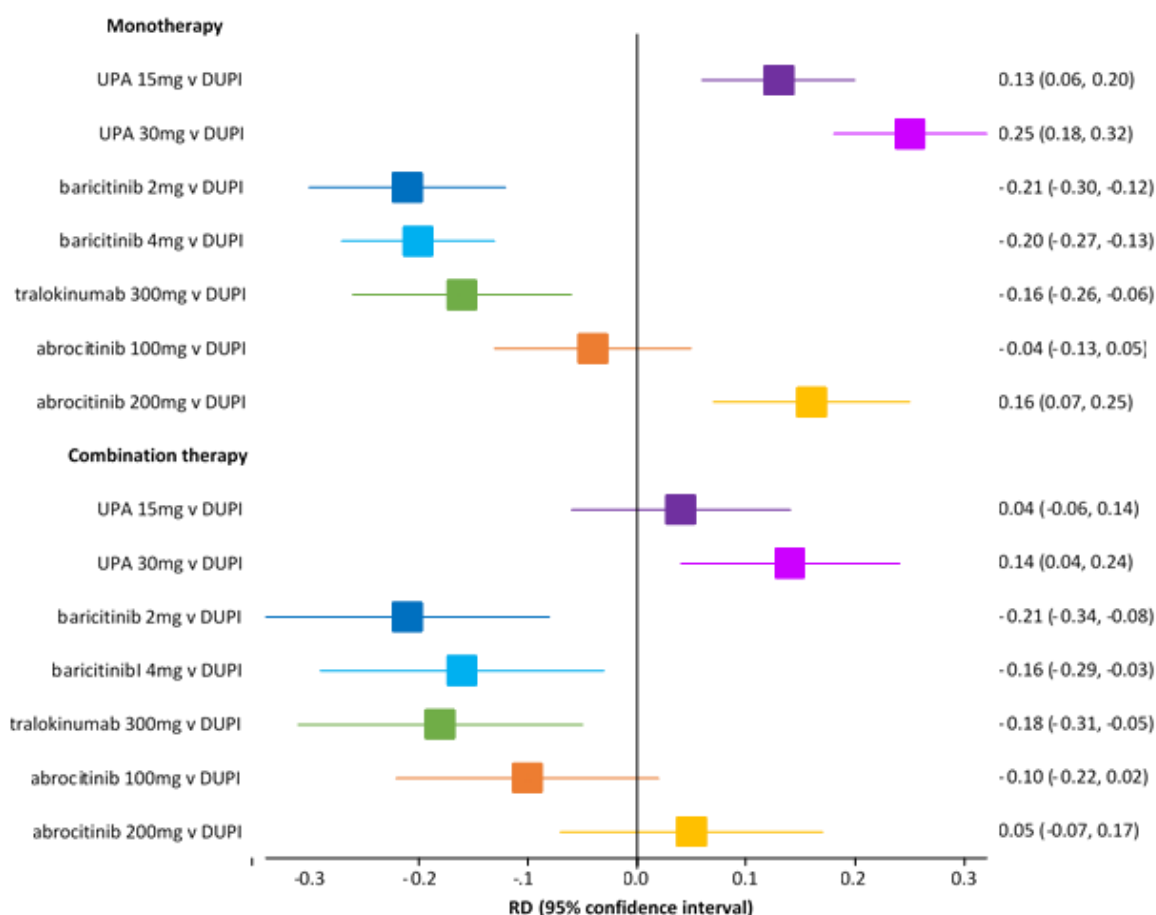
### Near market comparators

- 6.33 The submission presented several supplementary indirect treatment comparisons between UPA and the nominated near market comparators baricitinib, tralokinumab and abrocitinib, based on a further twelve PBO-controlled trials. The analyses used all available data (i.e. ITT population including adults and adolescents) for the different doses investigated.
- 6.34 The results of the indirect comparison for EASI 75, the most commonly reported outcome, were recalculated during the evaluation using results from the DUPI trials (excluding LIBERTY AD ADOL) as a reference to aid interpretation in the Australian context, summarised in Figure 2. The figure illustrates the relatively heterogeneous treatment effects over the range of comparators and doses, with potentially different conclusions being drawn depending on monotherapy versus combination therapy trials. The PBAC previously considered standard of care includes concomitant TCS, indicating that the results from the ‘combination’ trials are more applicable to practice (para 5.1, DUPI PSD July 2018 PBAC meeting). The ESC noted that the difference between DUPI and the JAK inhibitors appeared to be somewhat attenuated in the trials that allowed concomitant TCS. The ESC considered that in the PBS population

TCS use may reduce differences between UPI and DUPA seen up to 16 weeks in the HEADS UP trial (see Figure 1) and the difference at 16 weeks may also be less notable.

6.35 Overall, the data indicates that at 12 or 16 weeks baricitinib (2 mg and 4 mg) and tralokinumab are the least efficacious and UPA 30 mg is the most efficacious, with the other treatments somewhere in-between.

Figure 2: Indirect treatment comparison between UPA, baricitinib, tralokinumab and abrocitinib versus DUPI for EASI 75 response at Week 12 or 16



Source: constructed during the evaluation.  
EASI = Eczema Area and Severity Index; DUPI = dupilumab; UPA = upadacitinib.

### Comparative harms

6.36 Tables 8 and 9 summarise treatment emergent adverse events (TEAEs) reported in HEADS UP (comparing UPA 30 mg directly to DUPI 300 mg) and the PBO-controlled trials for UPA (pooled across monotherapy and combination therapy trials), respectively.

**Table 8: Summary of TEAEs in HEADS UP trial at Week 24 - UPA 30 mg daily vs DUPI 300 mg Q2W**

Safety outcome	UPA 30 mg n/N (%)	DUPI 300 mg n/N (%)	RR (95% CI)	RD (95% CI)
Any AEs	271/348 (77.9)	230/344 (66.9)	<b>1.16 (1.06, 1.28)</b>	<b>0.11 (0.04, 0.18)</b>
Drug-related AEs <sup>a</sup>	170/348 (48.9)	129/344 (37.5)	<b>1.30 (1.09, 1.55)</b>	<b>0.11 (0.04, 0.19)</b>
Severe AEs	31/348 (8.9)	15/344 (4.4)	<b>2.04 (1.12, 3.72)</b>	<b>0.05 (0.01, 0.08)</b>
Serious AEs	14/348 (4.0)	7/344 (2.0)	1.98 (0.81, 4.84)	0.02 (-0.01, 0.05)
Discontinuation from AEs	11/348 (3.2)	4/344 (1.2)	2.72 (0.87, 8.45)	0.02 (-0.00, 0.04)
Deaths	1 <sup>b</sup> /348 (0.3)	0/344 (0.0)	2.97 (0.12, 72.55)	0.00 (-0.01, 0.01)
TEAE of special interest				
Any serious infection	4/348 (1.1)	2/344 (0.6)	1.98 (0.36, 10.72)	0.01 (-0.01, 0.02)
Herpes zoster	12/348 (3.4)	4/344 (1.2)	2.97 (0.97, 9.10)	0.02 (0.00, 0.05)
Hepatic disorder	12/348 (3.4)	5/344 (1.5)	2.37 (0.84, 6.66)	0.02 (0.00, 0.04)
Neutropenia	6/348 (1.7)	2/344 (0.6)	2.97 (0.60, 14.59)	0.01 (0.00, 0.03)
Malignancy	1/348 (0.3)	1/344 (0.3)	0.99 (0.06, 15.74)	-0.00 (-0.01, 0.01)
CPK elevation	26/348 (7.5)	11/344 (3.2)	<b>2.34 (1.17, 4.65)</b>	<b>0.04 (0.01, 0.08)</b>
MACE	0/348 (0)	0/344 (0)	-	0.00 (-0.01, 0.01)
VTE	0/348 (0)	0/344 (0)	-	0.00 (-0.01, 0.01)

Source: Table 2-22, p100 of the submission, Table 10, p70 of HEADS UP (M16-046) CSR.

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; AE = adverse events; TEAE = treatment emergent adverse events; DUPI = dupilumab; UPA = upadacitinib; D = once daily; Q2W = once every two weeks.

<sup>a</sup> Investigator assessed as having a reasonable possibility of being related to study drug.

<sup>b</sup> Investigator assessed as having a reasonable possibility of being related to study drug. The autopsy report determined the death to be due to pneumonia associated with methicillin-resistant staphylococcal infection, influenza A, and beta hemolytic streptococcal infection (p78 of HEADS UP CSR).

6.37 In HEADS UP, a statistically higher proportion of patients experienced a TEAE with UPA 30 mg compared to DUPI 300 mg, including higher rates of drug-related AEs, severe AEs and elevated creatine phosphokinase (CPK). The submission stated, over half of the severe AEs observed with UPA 30 mg were investigations into elevations of alanine aminotransferase or CPK, and the difference compared to DUPI was unlikely to be clinically meaningful. The PSCR noted that these differences in AEs did not lead to a statistically significant difference in discontinuation rates between UPA and DUPI. The ESC noted that there were numerically more serious infections for patients treated with UPA than DUPI, though the difference was not statistically significant (RR=1.98, 95%CI: 0.36-10.72).

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Table 9: Summary of pooled TEAEs at Week 16 reported in the PBO-controlled trials of UPA (MEASURE UP1, MEASURE UP2, M16-048, AD UP, RISING UP), safety population (adults & adolescents)

Trial ID	UPA 15 mg n/N (%)	UPA 30 mg n/N (%)	PBO n/N (%)	RD (95% CI)		
				UPA 15 mg vs PBO	UPA 30 mg vs PBO	UPA 30 mg vs UPA 15 mg
Any AE	625/990 (63.1)	688/997 (69.0)	565/992 (57.0)	<b>0.06 (0.02, 0.10)</b>	<b>0.12 (0.08,0.16)</b>	<b>0.06 (0.02, 0.10)</b>
Drug-related AEs <sup>a</sup>	<b>310/990 (31.3)</b>	<b>390/997 (39.1)</b>	<b>196/992 (19.8)</b>	<b>0.10 (0.06, 0.15)</b>	<b>0.19 (0.14,0.24)</b>	<b>0.09 (0.03, 0.14)</b>
Severe AEs	45/990 (4.5)	46/997 (4.6)	42/992 (4.2)	0.01 (-0.01, 0.02)	0.00 (-0.02,0.03)	-0.00 (-0.02,0.02)
Serious AEs	20/990 (2.0)	20/997 (2.0)	27/992 (2.7)	-0.01 (-0.02,0.01)	-0.01 (-0.02,0.01)	-0.00 (-0.01,0.01)
Discontinuation from AEs	23/990 (2.3)	27/997 (2.7)	35/992 (3.5)	-0.01 (-0.02,0.00)	-0.01 (-0.02,0.01)	0.00 (-0.01, 0.02)
Deaths	0/990 (0)	0/997 (0)	0/992 (0)	-	-	-
TEAE of special interest						
Any serious infection	7/990 (0.7)	5/997 (0.5)	5/992 (0.5)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	-0.00 (-0.01,0.01)
Herpes zoster	14/990 (1.4)	18/997 (1.8)	5/992 (0.5)	0.01 (-0.00, 0.02)	0.01 (0.00, 0.02)	0.00 (-0.01, 0.02)
Hepatic disorder	12/990 (1.2)	16/997 (1.6)	12/992 (1.2)	-0.00 (-0.01,0.01)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)
Neutropenia	11/990 (1.1)	30/997 (3.0)	3/992 (0.3)	0.01 (-0.00, 0.01)	<b>0.03 (0.01, 0.04)</b>	0.02 (-0.00, 0.03)
Malignancy	3/990 (0.3)	6/997 (0.6)	0/992 (0)	0.00 (-0.00, 0.01)	0.01 (-0.00, 0.01)	0.00 (-0.00, 0.01)
CPK elevation	42/990 (4.2)	52/997 (5.2)	21/992 (2.1)	0.02 (0.00, 0.03)	<b>0.03 (0.01, 0.05)</b>	0.01 (-0.01, 0.03)
MACE	1/990 (0.1)	0/997 (0)	0/992 (0.3)	0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00,0.00)
VTE	0/990 (0)	0/997 (0)	1/992 (0.1)	-0.00 (-0.00,0.00)	-0.00 (-0.00,0.00)	0.00 (-0.00, 0.00)

Source: Table 2.25, p104 of the submission.

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; AE = adverse events; TEAE = treatment emergent adverse events; DUPI = dupilumab; UPA = upadacitinib

<sup>a</sup> Investigator assessed as having a reasonable possibility of being related to study drug.

- 6.38 In the PBO-controlled trials, a statistically higher proportion of patients experienced a TEAE with UPA 15 mg or UPA 30 mg compared to PBO. The majority of AEs were mild to moderate in severity, with less than 5% of patients on UPA experiencing a severe AE. Overall, a higher proportion of patients experienced a TEAE with UPA 30 mg (69%) compared to UPA 15 mg (63.1%). The most commonly reported adverse events for UPA (either dose) in the trials (acne, atopic dermatitis, upper respiratory tract infection, nasopharyngitis, headache, increased blood creatinine phosphokinase and oral herpes) were consistent with the known safety profile for UPA.
- 6.39 Table 10 summarises an indirect treatment comparison between UPA versus DUPI conducted during the evaluation for comparable safety outcomes, pooled across monotherapy and combination therapy trials. The indirect treatment comparisons show a lower proportion of patients experiencing any AEs with DUPI compared to UPA 30 mg, but similar rates of serious AEs and AEs leading to discontinuation.

Table 10 Summary of indirect treatment comparison between UPA and DUPI across safety outcomes at Week 16, safety population (adults & adolescents)

	RR# (95%CI)	RD# (95%CI)
<b>Monotherapy + Combination therapy</b>		
<b>Any AEs</b>		
UPA 15 mg ± TCS v DUPI 200/300 mg ± TCS	1.08 (0.99, 1.18)	0.05 (-0.01, 0.11)
UPA 30 mg ± TCS v DUPI 200/300 mg ± TCS	<b>1.19 (1.09, 1.30)</b>	<b>0.11 (0.05, 0.17)</b>
<b>Serious AEs</b>		
UPA 15 mg ± TCS v DUPI 200/300 mg ± TCS	1.48 (0.69, 3.17)	0.01 (-0.01, 0.03)
UPA 30 mg ± TCS v DUPI 200/300 mg ± TCS	1.50 (0.70, 3.23)	0.01 (-0.01, 0.03)
<b>Discontinuation due to AEs</b>		
UPA 15 mg ± TCS v DUPI 200/300 mg ± TCS	1.10 (0.44, 2.72)	0.00 (-0.02, 0.02)
UPA 30 mg ± TCS v DUPI 200/300 mg ± TCS	1.26 (0.52, 3.08)	0.00 (-0.03, 0.03)

Source: indirect comparisons performed during the evaluation based on data as presented in Attachment 2.5-6.

AE = adverse events; TEAE = treatment emergent adverse events; CI = confidence interval; RD = risk difference; RR = relative risk; DUPI = dupilumab; PBO = placebo; UPA = upadacitinib.

6.40 The ESC noted that AE data was only presented up to 24 weeks of follow-up (vs DUPI) and 16 weeks (vs PBO). The ESC noted that there is an increased risk of infection (including zoster) and malignancy associated with JAK inhibitors versus IL-4 inhibitors as a result of immunosuppression. These AEs may only be apparent with longer-term use. The ESC considered that longer-term data from other indications could be used to better understand the long-term UPA safety profile. The PBAC noted that the pre-PBAC response provided additional safety data up to week 52 for the AD trials and safety data in treatment of rheumatoid arthritis up to 4.5 years. No notable changes in the frequency of AEs were seen in this longer-term data.

### **Benefits/harms**

6.41 A summary of the comparative benefits and harms for UPA 30 mg versus DUPI is presented in Table 11.

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Table 11: Summary of comparative benefits and harms at Week 16 for UPA 30 mg and DUPI, based on direct evidence in HEADS UP and indirect evidence estimated from PBO-controlled trials

Benefits	UPA 30 mg n/N	DUPI n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				UPA 30mg	DUPI	
<b>Direct evidence in adults with moderate-to-severe AD (HEADS UP)</b>						
EASI 75	247/348	210/344	<b>1.16 (1.04,1.30)</b>	71.0	61.0	<b>0.10 (0.03, 0.17)</b>
<b>Indirect evidence in the PBS subgroup (pooled across PBO-controlled monotherapy/combination therapy trial)</b>						
PBS response, CsA-naive	214/265 (PBO: 61/246)	99/166 (PBO: 49/246)	1.11 (0.71,1.72)	80.8 (PBO: 24.8)	59.6 (PBO: 19.9)	<b>0.17 (0.05,0.29)</b>
PBS response, CsA-exp.	64/79 (PBO: 12/98)	91/152 (PBO: 91/152)	1.99 (0.41,9.56)	81.0 (PBO: 12.2)	59.9 (PBO: 14.0)	<b>0.24 (0.08, 0.40)</b>
<b>Indirect evidence in adults with moderate to severe AD (PBO-controlled trials)</b>						
EASI 50, monotherapy	447/532 (PBO: 145/524)	356/522 (PBO: 125/521)	1.07 (0.86,1.33)	84.0 (PBO: 27.7)	68.2 (PBO: 24.0)	<b>0.12 (0.05,0.19)</b>
EASI 50, combination	298/341 (PBO: 128/345)	371/445 (PBO: 236/547)	1.36 (0.93,1.98)	87.4 (PBO: 37.1)	83.4 (PBO: 43.1)	<b>0.14 (0.01, 0.27)</b>
DLQI ≥4, monotherapy	370/469 (PBO: 137/465)	297/432 (PBO: 127/431)	1.18 (0.90,1.54)	80.8 (PBO: 29.5)	68.8 (PBO: 29.5)	0.12 (-0.01,0.25)
DLQI ≥4, combination	215/254 (PBO: 106/256)	166/197 (PBO: 171/395)	1.07(0.87,1.31)	84.8 (PBO: 41.4)	84.3 (PBO: 43.3)	0.03 (-0.08, 0.14)
Harms	UPA 30 mg n/N	DUPI n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				UPA 30mg	DUPI	
<b>Direct evidence: HEADS UP</b>						
Any AEs	271/348	230/344	<b>1.16 (1.06,1.28)</b>	77.9	66.9	<b>0.11 (0.04, 0.18)</b>
Drug-related AEs <sup>a</sup>	170/348	129/344	<b>1.30 (1.09,1.55)</b>	48.9	37.5	<b>0.11 (0.04, 0.19)</b>
Severe AEs	31/348	15/344	<b>2.04 (1.12,3.72)</b>	8.9	4.4	<b>0.05 (0.01, 0.08)</b>

Source: constructed during the evaluation based on Table 14.2\_1 p614 of CSR M16046

HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; CsA = ciclosporin A; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; DUPI = dupilumab; UPA = upadacitinib.

\* Maximum duration of follow-up: 36 weeks or open-label extension (52 weeks).

<sup>a</sup> Investigator assessed as having a reasonable possibility of being related to study drug.

6.42 On the basis of indirect evidence presented by the submission in the PBS subgroup, for every 100 adult patients treated with UPA 30 mg in comparison with DUPI 300 mg:

- Approx. 17-24 additional patients would achieve PBS response (improvement of at least 50% from baseline in EASI score and an improvement in DLQI of ≥4 points from baseline) at Week 16.

There is uncertainty around this estimate. Based on other evidence presented in the submission, the number of additional patients who would respond to treatment with UPA 30 mg compared to DUPI 300 mg may be smaller (see Clinical claim).

6.43 On the basis of direct evidence presented by the submission, for every 100 patients treated with UPA 30 mg in comparison with DUPI 300 mg:

- Approx. 11 additional patients would have an adverse event.
- Approx. 11 additional patients would have drug-related adverse events.
- Approx. five additional patients would have severe adverse events.

### **Clinical claim**

- 6.44 The submission described:
- UPA 15 mg as non-inferior in terms of effectiveness and safety compared to DUPI, based on indirect evidence for the PBS response outcome in the PBS population supported by indirect evidence of other outcomes in a broader population.
  - UPA 30 mg as superior in terms of effectiveness and non-inferior in terms of safety compared to DUPI, based on indirect evidence for the PBS response outcome in the PBS population supported by direct and indirect evidence across other outcomes in a broader population.
- 6.45 The ESC agreed with the Commentary that the clinical claim for UPA 15 mg was reasonably supported by the indirect evidence presented in the submission.
- 6.46 The ESC considered that the clinical claim for UPA 30 mg at 16 weeks was generally supported by the direct and indirect evidence presented in the submission, however, the ESC considered that there was uncertainty regarding the magnitude of benefit for the following reasons:
- The response rates applied in the modelled economic evaluation correspond to a RD=0.21 (or an additional approx. 21 responders with UPA 30 mg compared to DUPI 300 mg for every 100 patients treated). This estimate was in-between the treatment effects for CsA-naïve (RD=0.17, 95%CI: 0.05, 0.29) and CsA-experienced (RD=0.24, 95%CI: 0.08, 0.40) based on indirect evidence for the composite PBS response criteria in the PBS-severe AD subgroup. There is uncertainty around these estimates given the post-hoc nature of the outcome and subgroup.
  - In the direct evidence presented in the submission, there was a much smaller treatment difference between UPA 30 mg and DUPI 300 mg for EASI 75 in both the ITT (RD=0.10, 95%CI: 0.03, 0.17) and pre-specified trial-based severe AD subgroups (IGA=4 subgroup, RD=0.11, 95%CI: 0.01, 0.21).
  - Supportive indirect evidence in the ITT population also found a smaller treatment difference for the individual components of the PBS response outcome, EASI 50 (monotherapy adults, RD=0.12, 95%CI: 0.05, 0.19; combination therapy adults, RD=0.14, 95%CI: 0.01, 0.27) and DLQI≥4 (monotherapy adults, RD=0.12, 95%CI: -0.01, 0.25; combination therapy adults, RD=0.03, 95%CI: -0.08, 0.14).
  - The ESC considered that in the PBS population TCS use may reduce differences between UPA and DUPI seen up to 16 weeks in the HEADS UP trial and the difference at 16 weeks may also be smaller.
  - The ESC considered that clinical data appeared to show that patients treated with UPA tended to respond to treatment faster than patients treated with DUPI, however beyond 16 weeks no significant difference in EASI 75 response between UPA and DUPI remained.

- 6.47 Direct evidence in HEADS UP found significantly more patients experienced AEs with UPA 30 mg compared to DUPI 300 mg (any TEAEs, drug-related AEs and severe AEs), and this was consistent with the available indirect evidence (any TEAEs). In addition, direct evidence also showed significantly more patients experienced AEs with UPA 30 mg compared to UPA 15 mg (any TEAEs, drug-related AEs), but the submission considered both doses as having non-inferior safety to DUPI. The ESC agreed with the Commentary that the evidence presented in the submission did not adequately support the claim of non-inferior safety between UPA 30 mg and DUPI 300 mg, and a claim of inferior safety may be more appropriate. Further, the ESC considered that there may be additional safety concerns for JAK inhibitors compared with IL-inhibitors that may become more apparent with longer term use.
- 6.48 The PBAC considered that the claim of non-inferiority for UPA 15 mg compared with DUPI 300 mg was reasonably supported by the indirect evidence presented in the submission. The PBAC considered that the claim of superior comparative effectiveness for UPA 30 mg compared with DUPI 300 mg was not sufficiently supported by the evidence presented in the submission, as the most reliable direct evidence indicated that the difference in response is likely to be less than that shown in the indirect evidence, and the difference may not be maintained beyond 16 weeks.
- 6.49 The PBAC considered that the claim of non-inferior comparative safety for UPA 15 mg was reasonable but the claim of non-inferior safety for UPA 30 mg was not adequately supported by the data.

### **Economic analysis**

- 6.50 The submission presented a cost-minimisation analysis for UPA 15 mg and a cost-effectiveness analysis for UPA 30 mg, corresponding to the different clinical claims of each dose. The modelled economic evaluation did not consider the potential dose titration between UPA 15 mg and UPA 30 mg.

#### **Cost-minimisation analysis: UPA 15 mg**

- 6.51 The submission presented a cost-minimisation analysis for UPA 15 mg versus DUPI, based on the nominated equi-effective doses (consistent with doses in the PIs):  
UPA 15 mg once daily = DUPI 600 mg as an initial dose then 300 mg every two weeks thereafter, or DUPI 400 mg as an initial dose then 200 mg every two weeks thereafter in adolescents with a body weight <60kg.
- 6.52 The analysis assumed equivalent drug costs over a two-year period based on a 'proxy' effective price for DUPI (DPMQ of \$ [REDACTED], AEMP of \$ [REDACTED]), because the true effective price was unknown to the sponsor. The submission estimated the proxy DPMQ for DUPI (\$ [REDACTED], AEMP of \$ [REDACTED]) from the modelled economic evaluation as the price corresponding to an ICER of \$75,000 to < \$95,000/QALY for DUPI versus best supportive care. Based on the proxy effective AEMP for DUPI, the analysis estimated the total drug cost over two years as \$ [REDACTED], corresponding to a proxy effective AEMP for UPA 15 mg of \$ [REDACTED] (or DPMQ of \$ [REDACTED]).

- 6.53 The analysis did not consider potential for additional monitoring costs associated with UPA 15 mg, given the draft PI for UPA recommends routine monitoring (for signs and symptoms of infection, lipids, ANC, ALC, Hb and hepatic transaminases) whereas the PI for DUPI does not recommend any monitoring. The analysis also did not consider potential administration cost-offsets, given a small proportion of patients treated with DUPI might require medical assistance to administer the SC injections.

**Cost-effectiveness analysis: UPA 30 mg**

- 6.54 The submission presented a stepped economic evaluation, based on results from the indirect treatment comparison at Week 16 and extrapolated to 5.3 years using a modelled cost-utility analysis. The model presented in the submission was similar to the model for DUPI, which the PBAC considered at the March 2020 and November 2020 PBAC meetings.
- 6.55 The model population was adults with severe AD, defined as IGA=4 and EASI  $\geq$ 20 at baseline in-line with the PBS eligibility criteria. The submission acknowledged that the proposed PBS listing also included adolescents, but the DUPI model only included adults and based on the draft PI, the 30 mg dose of UPA is not recommended for adolescents.

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**Table 12: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	UPA 30 mg versus DUPI
Time horizon	Approximately 5 years <sup>a</sup> in the model base case vs. 16-weeks double-blind, placebo-controlled phase in the key trials.
Outcomes	Life years, quality-adjusted life years
Methods used to generate results	Decision tree (to Week 42), Markov cohort model (after Week 42)
Health states	Four health states: <ul style="list-style-type: none"> <li>• Induction (first 16 weeks only)</li> <li>• Response (i.e. <math>\Delta</math> DLQI <math>\geq</math>4 and EASI 50)</li> <li>• Non-response</li> <li>• Death</li> </ul>
Cycle length	6 months
Transition probabilities or Allocation to health states (if partitioned survival model)	<p><u>Week 16 response</u> from trial data (DLQI <math>\Delta</math> <math>\geq</math>4 and EASI 50 at Week 16):</p> <ul style="list-style-type: none"> <li>• UPA: 80.8% (MEASURE UP 1, MEASURE UP 2, AD UP)</li> <li>• DUPI: 59.6% (1021, SOLO 1, SOLO 2, CHRONOS)</li> <li>• BSC: 20.4% (not reported)</li> </ul> <p><u>Maintenance of response after Week 16</u> from the March 2020 DUPI model:</p> <p>Maintenance of response   prior response:</p> <ul style="list-style-type: none"> <li>• Week 42: 95.7% for UPA and DUPI, 66.7% for BSC</li> <li>• Week 68, 94: 91.21%</li> <li>• Week 120, 146: 97.98%</li> <li>• Week 172, 198: 98.29%</li> <li>• Week 224, 250, 276: 98.43%.</li> </ul>
Health related quality of life	Values from the from the March 2020 DUPI model: <ul style="list-style-type: none"> <li>• Non-responder = 0.60;</li> <li>• Responder = 0.91;</li> <li>• Week 8-16 UPA 30 mg / DUPI = 0.847, BSC = 0.686.</li> </ul>
Health care resource use and costs	<p>Drug costs</p> <ul style="list-style-type: none"> <li>• UPA 30 mg: \$ [REDACTED] per box (28 tablets)</li> <li>• DUPI 300 mg: \$ [REDACTED] per pack (2 syringes)</li> </ul> <p>Health state costs from the March 2020 DUPI model:</p> <ul style="list-style-type: none"> <li>• Responder: \$984 per annum (appropriately excludes phototherapy)</li> <li>• Non-responder: \$5,493 per annum (appropriately excludes phototherapy)</li> </ul>

Source: Table 3-1, p124 of the submission.

DLQI = dermatology life quality index; EASI = eczema area and severity index; DUPI = dupilumab; UPA = upadacitinib; BSC = best supportive care.

<sup>a</sup> 42 weeks decision-tree model followed by a Markov model of 9 x 6-monthly cycles.

6.56 The model was comprised of two components: a 42-week decision tree followed by a Markov cohort model:

- The cohort enters the model in the ‘induction therapy’ health state of the decision tree, and initial response is assessed after 16 weeks of treatment. Patients with initial response enter the ‘responder’ health state, and patients who maintain response at 42 weeks remain in the same health state at the end of the decision tree. Patients without an initial response at Week 16 and those who do not maintain response at Week 42 transition to the ‘non-responder’ health state in the decision tree. The decision tree does not include the ‘dead’ health state.

- The cohort enters the Markov model at Week 42 in either the responder or non-responder health states, based on the health state at the end of the decision tree. Each cycle, all-cause mortality is applied to patients in both health states and maintenance of response is assessed for those in the responder health state. Responders who do not survive the cycle transition to dead, whereas responders who survive the cycle either remain in the responder health state or transition to the non-responder health state. Non-responders either transition to dead or remain in the non-responder health state.
  - Throughout the model, responders remain on active treatment whereas non-responders discontinue active treatment and commence BSC.
- 6.57 The main treatment effect included in the model was the proportion of patients who meet the PBS continuation criteria at Week 16.
- For DUPI, the submission assumed an initial response of 59.6%, corresponding to the proportion observed in the CsA-naïve subgroup of the DUPI trials.
  - For UPA 30 mg, the submission assumed an initial response of 80.8%, corresponding to the proportion observed in the CsA-naïve + experienced patients (the same proportion was observed in the CsA-naïve subgroup).
- 6.58 The model applied the rates observed in the UPA and DUPI treatment arms without adjusting for differences in the placebo response rates across the trials, resulting in an absolute treatment benefit of 21.2% with UPA 30mg compared to DUPI, which favours UPA 30 mg as it is larger than the absolute benefit of approx. 17% (16.98%) estimated using the indirect treatment comparison in the CsA-naïve subgroup. The PSCR acknowledged that estimation of the response rates in the model should be based on the adjusted (ITC) results for the combined CsA naïve + experienced patients. The PSCR and presented a revised approach, using response rates of 59.7% (190/318) and 17.5% (74/424) estimated for DUPI and PBO respectively; with application of the 0.18 risk difference, an UPA 30mg response rate of 77.7% was estimated from the ITC. The PSCR reported that the resulting ICER was approximately \$75,000 to < \$95,000/QALY. This value could not be verified and the ESC noted that the Commentary had estimated the ICER to be approximately \$75,000 to < \$95,000/QALY using this method (see highlighted cells in Table 15).
- 6.59 The ESC considered that for consistency with the DUPI consideration by the PBAC, it would be most appropriate to use the CsA naïve subgroup for both DUPI and UPA responders (para 6.49 dupilumab PSD, March 2020 PBAC meeting).
- 6.60 The ESC also noted that the estimation of the response rate for UPA varied depending on whether the RR or RD was used. The ESC noted that determining the most appropriate statistic depends on whether the treatment effect is likely to be more of a relative effect (i.e. benefit based on underlying risk), an absolute effect (constant benefit irrespective of underlying risk) or something in between. The submission and PSCR argued that it is an absolute effect, but there is very little subgroup data to

determine whether this is the case. However, the ESC noted that the direct (RR=1.11) and indirect (RR=1.11) evidence are consistent in terms of relative risk (despite differences in the absolute response rates for UPA and DUPI) suggesting that relative risk may be preferred. The pre-PBAC response argued that it was inappropriate to use the RR to calculate the response rate relative to DUPI from the indirect comparison “because RR across trials can be confounded by the specification of the baseline risk against which the RR is calculated”. Applying the odds ratio (OR) (OR=2.2, 95%CI: 1.1, 4.2 for the CsA naïve population) to the RR for DUPI (0.596) gives a response rate of 76.4% for UPA.

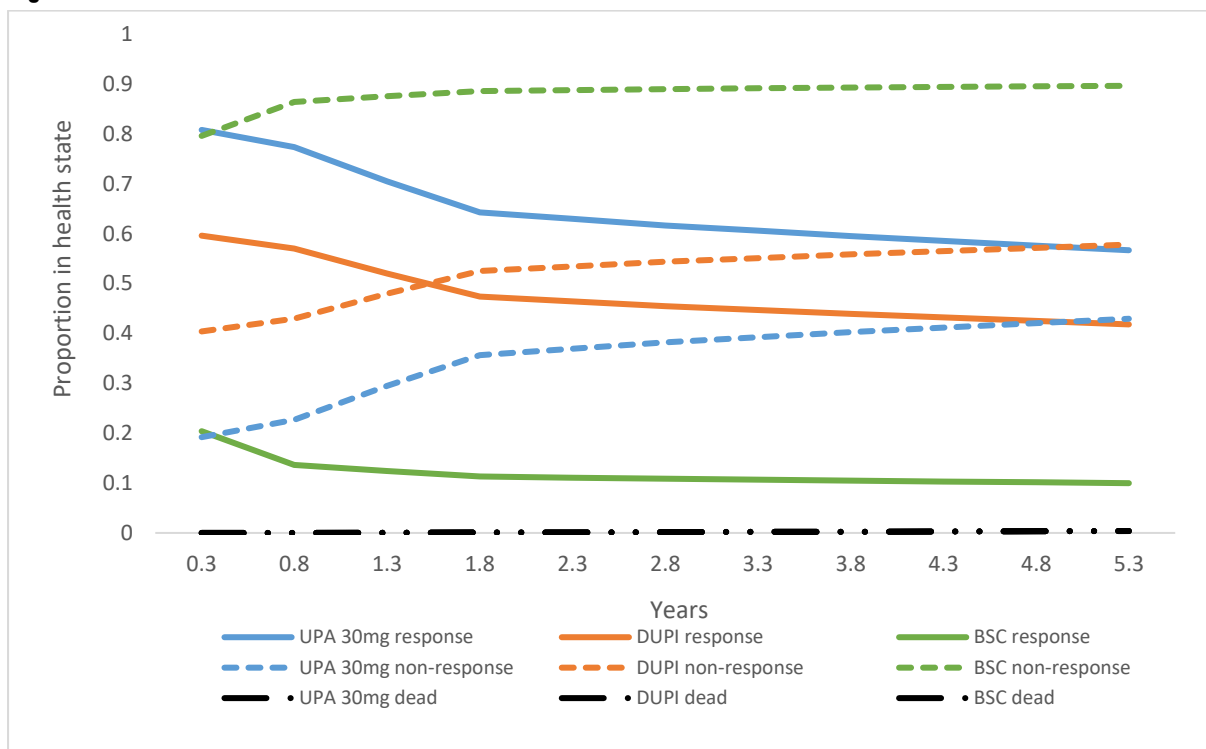
- 6.61 The ESC noted that the using the CsA naïve population, and adjusting the UPA week 16 response rate to 66.2% based on the RR from the indirect comparison of UPA vs DUPI (CsA-naïve populations) the ICER increased to \$115,000 to < \$135,000/QALY. The PBAC noted the direct evidence suggests for EASI 50 response there is an absolute benefit of 7.4% additional responders at Week 16 with UPA versus DUPI, which is similar to the 6.6% additional responders using the indirect RR compared with the 17.0% using the indirect RD.
- 6.62 In contrast to the DUPI model, which assumed a different utility for ‘short-term’ response (before Week 42: 0.91) and ‘long-term’ response (after Week 42: 0.79), the model presented in the submission assumed a constant utility value of 0.91 for responders. The ESC noted that the utility applied in the DUPI model for responders after week 42 was based on the week 44 EQ-5D Australian utility score for responders from the CHRONOS trial. The PSCR provided utility data from MEASURE UP 1, MEASURE UP 2 and AD UP at Week 52, indicating average utility weight of 0.92 at Week 52 in patients meeting the PBS response criteria in support of the assumption that there is no reduction in the utility of response over time. The model was sensitive to this assumption. The ESC considered that maintenance of this utility value for responders may be plausible but noted that the utility value was close to that of the population norm of EQ 5D 5L (0.92, in a population aged 35-44 years).<sup>3</sup>
- 6.63 Figure 3 presents a Markov trace generated during the evaluation. The figure illustrates that the relative difference between UPA 30 mg and DUPI 300 mg in terms of responders, which is established at Week 16 (or 0.31 years), is maintained over the course of the model. By 5.3 years, approximately 56.7% of patients on UPA 30 mg and 41.8% of patients on DUPI 300 mg are still on treatment. The submission did not present any clinical evidence to support this assumption. The ESC considered that maintenance of response in the model did not reflect HEADS UP data where difference in response was not significant at 24 weeks. Further, trial M16-047 (AD UP) showed faster decline in response for patients treated with UPA compared with the response estimated in the model. The ESC considered that as the head to head trial of UPA vs DUPI suggested that there was no difference in efficacy at 24 weeks, the model base

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<sup>3</sup> McCaffrey et al. Health and Quality of Life Outcomes (2016) 14:133

case should be more conservative in terms of maintenance of response. The ESC considered that convergence of responder curves at around 2.5 years (i.e. much sooner than 5.3 years as in the sensitivity analysis in Table 15) may be more clinically plausible. The pre-PBAC response argued that there is evidence that the quality of life of UPA responders is maintained over time (see paragraph 6.62) and that there is evidence that the quality of life of DUPI responders is not maintained over time based on the utility (0.79) applied in the dupilumab model post week 42 (Table 13 March 2020 dupilumab PSD). The pre-PBAC response also stated that the maintenance of difference in response was also supported by the statistically significant difference in EASI-100 in favour of UPA 30 mg in the HEADS UP trial, which was maintained to Week 24.

Figure 3. Markov trace of modelled health states



Source: constructed during the evaluation

Abbreviations: DUPI = dupilumab; UPA = upadacitinib; BSC=best supportive care.

6.64 Key drivers of the economic model are summarised in Table 13.

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Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ██████ <sup>1</sup> /QALY gained.
Week 16 response rates	The submission assumed naïve response rates observed in the UPA and DUPI treatment arms without adjusting for differences in the PBO response rates across the trials.	High, favours UPA. Assuming the DUPI and PBO response rate accepted in the DUPI and estimating the UPA 30 mg response using the relative risk or risk difference for UPA versus PBO, increases the ICER by up to 90% (depending on the method and population applied).
Maintenance of response after 16 weeks	The submission assumed the same relative loss of response each cycle for patients in the UPA 30 mg and DUPI arms after Week 16, based on data reported in the DUPI March 2020 model. The submission did not present any evidence to support this assumption.	Moderate, favours UPA. A linear decline in the relative treatment different over time from Week 42, such that the responder curves converge by 5.3 years, increases the ICER by 25%. The PBAC noted that ESC considered the curves should converge much sooner than 5.3 years as in the sensitivity analysis in Table 15), and therefore the impact of maintenance of response may be high.
Responder utilities	In contrast to the DUPI model, the model presented in the submission assumed a higher utility value for responders after Week 42 (0.91 vs 0.79).	Moderate, favours UPA. Assuming utility weight of 0.79 for long-term responders increases the ICER by 50%.

Source: constructed during the evaluation.

BSC = best supportive care; DUPI = dupilumab; PBO = placebo; UPA = upadacitinib

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

6.65 Table 14 presents the results of the stepped economic analysis.

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Table 14: Results of the stepped economic evaluation

Step and component	UPA 30 mg daily	DUPI 300 mg Q2W	Increment
<b>Step 1: Trial-based analysis at 16 weeks</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Responders	0.808	0.596	0.212
Incremental cost/responder gained at 16 weeks			
			\$ [REDACTED] <sup>1</sup>
<b>Step 2: extrapolated to include the first six months of maintenance treatment following the application of the requested continuation rule, taking the total period of this step to 42 weeks</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Responders	0.773	0.570	0.203
Incremental cost/responder gained at 42 weeks			
			\$ [REDACTED] <sup>2</sup>
<b>Step 3: utility values are applied</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.648	0.6150	0.329
Incremental cost/extra QALY			
			\$ [REDACTED] <sup>3</sup>
<b>Step 4: extrapolated to 5.3 years</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.8548	3.6154	0.2394
Incremental cost/extra QALY			
			\$ [REDACTED] <sup>3</sup>
<b>Step 5: include health care costs – BASE CASE presented in the submission</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.8548	3.6154	0.2394
Incremental cost/extra QALY			
			\$ [REDACTED] <sup>4</sup>
<b>Step 5*: Corrected health care costs<sup>a,b</sup> – BASE CASE, corrected during the evaluation</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.8548	3.6154	0.2394
Incremental cost/extra QALY			
			\$ [REDACTED] <sup>4</sup>

Source: Table3-19; 3-22, pp160-161 of the submission.

DUPI = dupilumab; UPA = upadacitinib

<sup>a</sup> The formula for pre-Markov 'other' costs (c\_HS\_preMarkov\_other) has been corrected to refer to i) 'other' costs instead of phototherapy costs for non-responders, and ii) annual costs rather than 6-monthly costs.

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$5,000

<sup>2</sup> \$5,000 to < \$15,000

<sup>3</sup> \$75,000 to < \$95,000

<sup>4</sup> \$55,000 to < \$75,000

6.66 Based on the 'proxy' effective DPMQ price for DUPI 300 mg of \$ [REDACTED], the submission estimated an ICER of approximately \$55,000 to < \$75,000 /QALY for UPA 30 mg. The incremental costs and QALYs were driven by more time spent in the responder health state (on treatment) compared to the non-responder health state with UPA 30 mg compared to DUPI. Two errors were identified during the evaluation in the calculation of health state costs in the decision-tree; once corrected they reduced the ICER to approximately \$55,000 to < \$75,000 /QALY in Step 5.

6.67 The results of key univariate sensitivity analyses and additional multivariate sensitivity analyses as suggested by the ESC are summarised in Table 15.

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Table 15: Sensitivity analyses conducted in the submission and additional sensitivity analyses conducted during the evaluation

Analyses	Incremental cost	Incremental QALY	ICER
<b>Base case</b>	\$ [redacted]	0.239	\$ [redacted] <sup>1</sup>
UPA 30 mg Week 16 response (base case 0.808)			
- 0.763 ('lower 95%CI')	\$ [redacted]	0.189	\$ [redacted] <sup>2</sup>
- 0.845 ('upper 95%CI')	\$ [redacted]	0.281	\$ [redacted] <sup>1</sup>
- 0.702 (halve absolute treatment difference)	\$ [redacted]	0.120	\$ [redacted] <sup>3</sup>
- 0.696 (RD = 0.10 for UPA vs DUPI in HEADS UP)	\$ [redacted]	0.113	\$ [redacted] <sup>3</sup>
Adjusted UPA 30 mg Week 16 response (base case 0.808), versus DUPI response of 0.596 (CsA naïve population)			
- 0.659 using pooled RR of UPA v PBO	\$ [redacted]	0.071	\$ [redacted] <sup>4</sup>
- 0.769 using pooled RD of UPA v PBO	\$ [redacted]	0.195	\$ [redacted] <sup>2</sup>
- 0.662 using RR from indirect comparison of UPA v DUPI	\$ [redacted]	0.075	\$ [redacted] <sup>4</sup>
- 0.766 using RD from indirect comparison of UPA v DUPI	\$ [redacted]	0.192	\$ [redacted] <sup>2</sup>
Adjusted UPA 30 mg Week 16 response (base case 0.808), versus DUPI response of 0.597 (ITT)			
- 0.707: using pooled RR of UPA v PBO	\$ [redacted]	0.124	\$ [redacted] <sup>3</sup>
- 0.775 using pooled RD of UPA v PBO	\$ [redacted]	0.201	\$ [redacted] <sup>2</sup>
- 0.705 using RR from indirect comparison of UPA v DUPI	\$ [redacted]	0.122	\$ [redacted] <sup>3</sup>
- 0.777 using RD from indirect comparison of UPA v DUPI	\$ [redacted]	0.203	\$ [redacted] <sup>2</sup>
Adjusted DUPI Week 16 response (base case 0.596), versus UPA 30 mg response of 0.808 (CsA naïve population)			
- 0.742 using pooled RR of DUPI v PBO	\$ [redacted]	0.075	\$ [redacted] <sup>5</sup>
- 0.648 using pooled RD of DUPI v PBO	\$ [redacted]	0.181	\$ [redacted] <sup>2</sup>
- 0.728 using RR from indirect comparison of UPA v DUPI	\$ [redacted]	0.090	\$ [redacted] <sup>4</sup>
- 0.638 using RD from indirect comparison of UPA v DUPI	\$ [redacted]	0.192	\$ [redacted] <sup>2</sup>
Assuming higher loss of response for UPA 30 mg from Week 42 (responder curves converge at 5.3 years)	\$ [redacted]	0.134	\$ [redacted] <sup>2</sup>
Costs of phototherapy included	\$ [redacted]	0.239	\$ [redacted] <sup>1</sup>
Utility values			
- 0.79 for long-term responder	\$ [redacted]	0.159	\$ [redacted] <sup>3</sup>
- 0.75 non-responder Week 16-42, and 0.62 ≥Week 42	\$ [redacted]	0.210	\$ [redacted] <sup>2</sup>
<b>Multivariate sensitivities</b>			
Assuming higher loss of response for UPA 30 mg from Week 42 (responder curves converge at 5.3 years) AND Adjusted UPA 30 mg Week 16 response (base case 0.808), versus DUPI response of 0.596 (CsA naïve population)			
- 0.662 using RR from indirect comparison of UPA v DUPI	\$ [redacted]	0.043	\$ [redacted] <sup>6</sup>
- 0.766 using RD from indirect comparison of UPA v DUPI	\$ [redacted]	0.108	\$ [redacted] <sup>3</sup>

Source: Table 3-23, p163 of the submission; constructed during the evaluation.

DUPI = dupilumab; UPA = upadacitinib.

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>4</sup> \$115,000 to < \$135,000

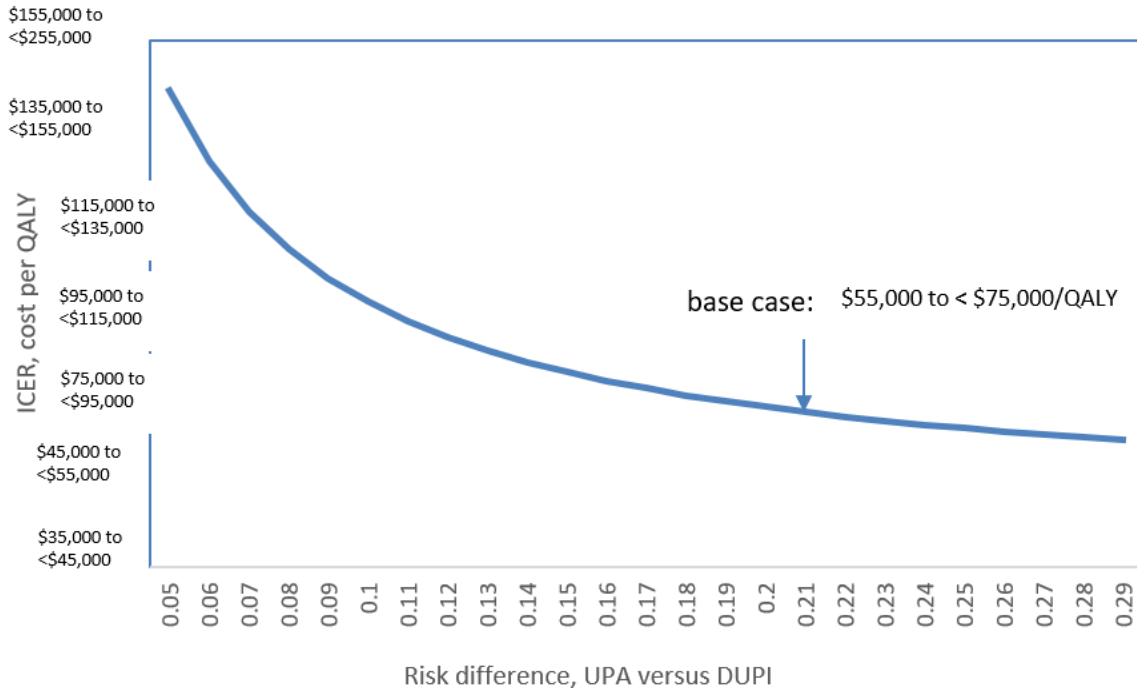
<sup>5</sup> \$135,000 to < \$155,000

<sup>6</sup> \$155,000 to < \$255,000

6.68 Aside from the assumed proxy drug costs, the model was sensitive to the assumed utility values and the difference in the treatment response at Week 16. As discussed above (see Clinical claim), the treatment effect in the model was approximately

double that observed in the direct evidence (for EASI 75 or EASI 50). Halving the assumed absolute treatment difference in the model increased the ICER by 30.3% to \$95,000 to < \$115,000 /QALY, illustrated in Figure 4.

Figure 4: Relationship between the ICER (cost per QALY) and UPA 30mg response at Week 16, expressed as a risk difference versus DUPI 300mg (with 16 week response of 0.596)



Source: constructed during the evaluation.  
DUPI = dupilumab; UPA = upadacitinib.

6.69 The PBAC noted that 1) adjusting UPA week 16 response (0.662, based on RR from the indirect comparison of UPA and DUPI, in the CsA naïve subgroup); and 2) assuming higher loss of response for UPA 30 mg from Week 42 (responder curves converge at 5.3 years) resulted in an ICER of \$155,000 to < \$255,000/QALY. The PBAC considered that this ICER may still be underestimated due to uncertainty in the magnitude of benefit for UPA as described in paragraph 6.46 and because convergence of the responder curves over a shorter period would be more appropriate as described in paragraph 6.63.

**Drug cost/patient/year**

6.70 The annual drug cost is \$ [redacted] for UPA 15 mg and \$ [redacted] for UPA 30 mg, assuming 13 scripts per year at the proxy effective DPMQs (\$ [redacted] and \$ [redacted], respectively). The annual drug cost is \$ [redacted] for DUPI 300 mg, assuming 13 scripts per year at the proxy effective DPMQ of \$ [redacted].

**Estimated PBS usage & financial implications**

- 6.71 This submission was not considered by DUSC. The submission estimated the financial implications of the proposed listing using an epidemiological approach, including treatment of approximately < 500 grandfathered patients. The analysis presented in the submission used proxy effective prices, consistent with the cost-minimisation analysis and modelled economic evaluation.
- 6.72 The epidemiological approach was based on the following assumptions:
- The model estimated the number of patients each year who initiate any treatment (DUPI or UPA) by multiplying the assumed uptake rates to the prevalent pool of eligible patients.
  - Patients initiated treatment with either DUPI or UPA based on the assumed market shares. Patients could only initiate one treatment (in the main analysis) in a lifetime and patients initiating UPA in Year 1 included the < 500-grandfathered patients.
  - The model estimated the number of patients continuing treatment each year based on the assumed continuation rates. The assumed difference in response rates at Week 16 drives the difference in continuation rates between the agents, where more patients remain on UPA compared to DUPI.
  - The model estimated the corresponding number of scripts each year, based on the number of patients on initial and continuing treatment.
- 6.73 Table 16 summarises the key inputs in the financial estimates.

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Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment																		
Australian population aged ≥12 years	Yr 1: 22,320,412 Yr 2: 22,696,040 Yr 3: 23,062,732 Yr 4: 23,423,761 Yr 5: 23,780,244 Yr 6: 24,125,467 Source: ABS 3222.0 Population Projection	Reasonable.																		
Prevalence of severe AD	45 per 10,000 Source: Table 19, Dupilumab PSD March 2020 PBAC meeting. Assumed 9% of Australian adults have AD and 5% have severe AD	Consistent with estimate used for dupilumab PBAC submission.																		
Proportion of severe AD patients with EASI ≥20	95% Source: Table 19, Dupilumab PSD March 2020 PBAC meeting	Consistent with estimate used for dupilumab PBAC submission. The eligible PBS population initiating treatment must have severe disease defined by PGA=4 and EASI ≥20.																		
Proportion of patients on TCS therapy with uncontrolled AD	68% Source: Table 19, Dupilumab PSD March 2020 PBAC meeting	Consistent with estimate used for dupilumab PBAC submission.																		
DUPI/UPA annual uptake (initiation) rate	Yr 1: 5% Yr 2 to Yr 6: 9% Source: Assumption, applied to pool of prevalent patients. Calculated based on assumed cumulative uptake rate: 5% in Yr 1, up to 50% in Yr 6. Assumed patients only receive up to one treatment per lifetime.	The submission did not provide any data to support this assumption. The assumed uptake rate, applied to the pool of prevalent patients, was higher than DUPI November 2020 estimates (cumulative 24% by Year 6) or those recommended by the PBAC (cumulative 19.7% by Year 6) (Table 1, Dupilumab PSD November 2020 PBAC meeting). The submission argued (p171) that the sponsor expected a sizeable proportion of patients would be treated over time, and therefore a cumulative uptake rate of 50% by Year 6 was assumed. SA conducted during the evaluation showed the net financial estimates are sensitive to the assumed uptake rate.																		
DUPI/UPA market share	<table border="1"> <thead> <tr> <th></th> <th>DUPI</th> <th>UPA</th> </tr> </thead> <tbody> <tr> <td>Yr 1</td> <td>%</td> <td>%</td> </tr> <tr> <td>Yr 2</td> <td>%</td> <td>%</td> </tr> <tr> <td>Yr 3</td> <td>%</td> <td>%</td> </tr> <tr> <td>Yr 4</td> <td>%</td> <td>%</td> </tr> <tr> <td>Yr 5 / Yr 6</td> <td>%</td> <td>%</td> </tr> </tbody> </table> <p>Source: Assumption</p>		DUPI	UPA	Yr 1	%	%	Yr 2	%	%	Yr 3	%	%	Yr 4	%	%	Yr 5 / Yr 6	%	%	The submission did not provide any data to support this assumption. Overall, the market share of UPA was likely an underestimate, given the claimed superiority of UPA 30 mg versus DUPI, and convenience of oral administration versus SC injection. The ESC considered that UPA 30 mg would be expected to have a higher uptake and a higher proportion of the market than DUPI due to the perceived superior efficacy and as an oral formulation. The PBAC considered that safety was also a factor that would moderate uptake of UPA.
	DUPI	UPA																		
Yr 1	%	%																		
Yr 2	%	%																		
Yr 3	%	%																		
Yr 4	%	%																		
Yr 5 / Yr 6	%	%																		
Initial response to treatment (DUPI, UPA 15 mg, UPA 30 mg)	<table border="1"> <thead> <tr> <th>Drug</th> <th>% Wk 16</th> </tr> </thead> <tbody> <tr> <td>DUPI</td> <td>59.6%</td> </tr> <tr> <td>UPA 15 mg</td> <td>69.6%</td> </tr> <tr> <td>UPA 30 mg</td> <td>80.8%</td> </tr> </tbody> </table> <p>Source: Clinical trial data, corresponding to response at Week 16 (unadjusted).</p>	Drug	% Wk 16	DUPI	59.6%	UPA 15 mg	69.6%	UPA 30 mg	80.8%	The submission applied the naïve proportions observed in the DUPI and UPA trials, without adjusting for differences in the placebo response rates across the two sets of trials. It would be more appropriate to use the RR or RD statistics to derive the response rates for DUPI relative to UPA or UPA relative to DUPI as discussed in paragraph 6.58 and 6.59. SA conducted during the evaluation showed that the net financial estimates are sensitive to the adjusted response rate for DUPI. However, the PBAC did not accept that assuming a difference in response was reasonable.										
Drug	% Wk 16																			
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Parameter	Value applied and source	Comment																																										
Long term response rates (DUPI, UPA 15 mg, UPA 30 mg)	<p><b>Maintain response given response at Week 16</b></p> <table border="1"> <thead> <tr> <th>Time point</th> <th>% respond</th> </tr> </thead> <tbody> <tr> <td>Week 42/44</td> <td>95.7%</td> </tr> </tbody> </table> <p><b>Maintain response given response at Year 1</b></p> <table border="1"> <thead> <tr> <th></th> <th>% respond</th> </tr> </thead> <tbody> <tr> <td>Year 2</td> <td>83.2%</td> </tr> <tr> <td>Year 3</td> <td>79.87%</td> </tr> <tr> <td>Year 4</td> <td>77.16%</td> </tr> <tr> <td>Year 5</td> <td>74.76%</td> </tr> </tbody> </table> <p>Source: Table 19, Dupilumab PSD March 2020 PBAC meeting. Assumed equal relative maintenance of response for all active therapies, consistent with the modelled economic evaluation.</p>	Time point	% respond	Week 42/44	95.7%		% respond	Year 2	83.2%	Year 3	79.87%	Year 4	77.16%	Year 5	74.76%	<p>The submission applied the same persistence estimates as assumed by the DUPI submission. CHRONOS data informed the maintenance of response at Week 44 given response at Week 16; assumed to apply to Week 52 in the financial estimates. A time-to-event analysis of CHRONOS data (Week 16 to Week 52) informed the maintenance of response beyond CHRONOS (i.e. Week 52). The details of this analysis were not available, but the PBAC considered this extrapolation increased uncertainty in the modelled outcomes (paragraph 7.15, Dupilumab PSD July 2019 PBAC meeting).</p> <p>The table below summarises the proportion of initial patients maintaining response over the 6 years of the financial model. The Week 42/44 CHRONOS data informed Week 52.</p> <p><b>% initial patients maintaining response</b></p> <table border="1"> <thead> <tr> <th></th> <th>DUPI</th> <th>UPA 15 mg</th> <th>UPA 30 mg</th> </tr> </thead> <tbody> <tr> <td>Week 16 to 52</td> <td>59.6%</td> <td>69.7%</td> <td>80.8%</td> </tr> <tr> <td>In Year 2</td> <td>57.0%</td> <td>66.7%</td> <td>77.3%</td> </tr> <tr> <td>In Year 3</td> <td>47.5%</td> <td>55.5%</td> <td>64.3%</td> </tr> <tr> <td>In Year 4</td> <td>45.6%</td> <td>53.3%</td> <td>61.8%</td> </tr> <tr> <td>In Year 5</td> <td>44.0%</td> <td>51.5%</td> <td>59.7%</td> </tr> <tr> <td>In Year 6</td> <td>42.6%</td> <td>49.9%</td> <td>57.8%</td> </tr> </tbody> </table>		DUPI	UPA 15 mg	UPA 30 mg	Week 16 to 52	59.6%	69.7%	80.8%	In Year 2	57.0%	66.7%	77.3%	In Year 3	47.5%	55.5%	64.3%	In Year 4	45.6%	53.3%	61.8%	In Year 5	44.0%	51.5%	59.7%	In Year 6	42.6%	49.9%	57.8%
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UPA scripts by strength	<p>15 mg: █ % 30 mg: █ % Source: Assumption.</p>	<p>The submission did not provide any data to support this assumption. The draft PI recommended 15 mg or 30 mg in adults, and 15 mg for adolescents (weighing ≥40 kg; no studies in &lt;40 kg), although in the UPA trials that included adolescents both 15 mg and 30 mg were used in adolescents. Based on the ABS population 2021-2026 data, approximately 9% of the prevalent population are adolescents aged 12-17 years who would receive UPA 15 mg as recommended by the draft PI. The financial estimates were sensitive to the script proportions by strength. The PBAC considered that the relative proportions of doses would be impacted by the dosing approach recommended by the TGA and adopted by clinicians.</p>																																										
UPA cost	<p>Proxy effective price UPA 30 mg \$ █ UPA 15 mg \$ █ Published DPMQ UPA 30 mg \$ █ UPA 15 mg \$ █ Source: Requested price</p>	<p>The submission presented estimates using the published DPMQs, and the 'proxy' effective DPMQs used in the cost-minimisation analysis and cost-effectiveness analysis.</p>																																										

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Parameter	Value applied and source	Comment
DUPI cost	Proxy effective price DUPI 200 mg \$ [REDACTED] DUPI 300 mg \$ [REDACTED] Published DPMQ DUPI 200 mg \$ [REDACTED] DUPI 300 mg \$ [REDACTED] Source: PBS item 12292Y	

Source: Tables 4.1, 4.5 to 4.10, pp168-177 of the submission.

AD = atopic dermatitis; BSC = best supportive care; DUPI = dupilumab; EASI = Eczema Area and Severity Index; TCS = topical corticosteroids; PGA = Physician's Global Assessment; SA = sensitivity analysis; UPA = upadacitinib; Yr = year

6.74 Table 17 summarises the estimated net financial implications for the proposed listing of UPA on the PBS/RPBS for AD. As noted below, the sponsor proposed that any RSA caps in place should increase for each additional therapy added to the PBS to allow for sequential treatment. The submission presented increased caps assuming [REDACTED]% of newly initiating patients would re-initiate a second alternative therapy in the same year assuming the same cost and treatment response as UPA 15 mg.

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Table 17: Estimated use and financial implications to the PBS/RPBS for the proposed listing of UPA using the proxy effective prices<sup>^</sup>

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated number of prevalent patients</b>						
Prevalent patients, severe AD	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Eligible population	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Patients initiating DUPI/UPA	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Estimated use of UPA</b>						
<b>Patients treated with UPA</b>						
Initiating patients	█ <sup>5</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Continuing patients	█ <sup>5</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>UPA scripts</b>						
UPA 15 mg initial	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
UPA 15 mg continuing	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>6</sup>	█ <sup>10</sup>	█ <sup>7</sup>	█ <sup>11</sup>
UPA 30 mg initial	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
UPA 30 mg continuing	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>6</sup>	█ <sup>10</sup>	█ <sup>7</sup>	█ <sup>11</sup>
UPA PBS/RPBS cost#	\$█ <sup>12</sup>	\$█ <sup>13</sup>	\$█ <sup>14</sup>	\$█ <sup>15</sup>	\$█ <sup>16</sup>	\$█ <sup>16</sup>
UPA net PBS/RPBS cost#	\$█ <sup>12</sup>	\$█ <sup>13</sup>	\$█ <sup>17</sup>	\$█ <sup>15</sup>	\$█ <sup>16</sup>	\$█ <sup>16</sup>
<b>Estimated changes of use of the proposed listing</b>						
<b>Patients treated with DUPI</b>						
Initiating patients	█ <sup>5</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Continuing patients	█ <sup>5</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>
<b>DUPI scripts</b>						
DUPI 200/300 mg initial	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
DUPI 200/300 mg continuing	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>6</sup>	█ <sup>7</sup>	█ <sup>8</sup>	█ <sup>18</sup>
DUPI PBS/RPBS cost	-\$█ <sup>12</sup>	-\$█ <sup>13</sup>	-\$█ <sup>17</sup>	-\$█ <sup>20</sup>	-\$█ <sup>22</sup>	-\$█ <sup>16</sup>
DUPI net PBS/RPBS cost	-\$█ <sup>12</sup>	-\$█ <sup>13</sup>	-\$█ <sup>19</sup>	-\$█ <sup>20</sup>	-\$█ <sup>22</sup>	-\$█ <sup>16</sup>
<b>Net financial implications to the government</b>						
Net cost to PBS/RPBS	\$█ <sup>12</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>	\$█ <sup>21</sup>	\$█ <sup>13</sup>	\$█ <sup>19</sup>
<b>Estimated increase in net PBS/RPBS cost for the proposed listing of UPA, allowing for a second treatment if the first treatment was unsuccessful or not tolerated (two drug market scenario), using UPA 15mg price as proxy for second alternative therapy</b>						
Net PBS/RPBS cost	\$█ <sup>12</sup>	\$█ <sup>13</sup>	\$█ <sup>19</sup>	\$█ <sup>14</sup>	\$█ <sup>20</sup>	\$█ <sup>23</sup>

Source: Tables 4.11 to 4.19, pp178-183 of the submission. Table 4.20, pp184-185 of the submission.

AD = atopic dermatitis; DUPI = dupilumab; UPA = upadacitinib

<sup>^</sup> %PBS/RPBS and patient co-pay were corrected during the evaluation to include PBS/RPBS utilisation data for PBS item 9304Q (initial treatment with ustekinumab 45 mg for severe chronic plaque psoriasis) as initial services and 9305R (continuing treatment with ustekinumab 45 mg for severe chronic plaque psoriasis) as continuing services.

# number of PBS/RPBS initial scripts were corrected during the evaluation for rounding errors in the number of patients treated by % UPA scripts by strength i.e. '3a. Scripts – proposed' cells H16:M16 to reference 'AbbVie BIM' cells K198:P198, '3a. Scripts – proposed' cells O16:T16 to reference 'AbbVie BIM' cells Q198:V198, and '3a. Scripts – proposed' cells H17:M17 to reference 'AbbVie BIM' cells K201:P201, '3a. Scripts – proposed' cells O17:T17 to reference 'AbbVie BIM' cells Q201:V201.

The redacted values correspond to the following ranges:

<sup>1</sup> 100,000 to < 200,000

<sup>2</sup> 60,000 to < 70,000

<sup>3</sup> 500 to < 5,000

<sup>4</sup> 5,000 to < 10,000

<sup>5</sup> < 500

<sup>6</sup> 10,000 to < 20,000

<sup>7</sup> 30,000 to < 40,000

<sup>8</sup> 50,000 to < 60,000

<sup>9</sup> 80,000 to < 90,000

<sup>10</sup> 20,000 to < 30,000

<sup>11</sup> 40,000 to < 50,000

<sup>12</sup> \$0 to < \$10 million

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<sup>13</sup> \$20 million to < \$30 million

<sup>14</sup> \$50 million to < \$60 million

<sup>15</sup> \$80 million to < \$90 million

<sup>16</sup> \$100 million to < \$200 million

<sup>17</sup> \$40 million to < \$50 million

<sup>18</sup> 70,000 to < 80,000

<sup>19</sup> \$30 million to < \$40 million

<sup>20</sup> \$60 million to < \$70 million

<sup>21</sup> \$10 million to < \$20 million

<sup>22</sup> \$90 million to < \$100 million

<sup>23</sup> \$70 million to < \$80 million

6.75 Assuming the proxy effective prices, the submission estimated the proposed listing of UPA would result in a net cost of \$90 million to < \$100 million to the health budget over the first 6 years. The net cost to the government is uncertain given:

- The assumed uptake rate, applied to the pool of prevalent patients (a cumulative uptake rate of 50% by Year 6), was higher than DUPI November 2020 estimates (cumulative 24% by Year 6) or those recommended by the PBAC (cumulative 19.7% by Year 6) (Table 1, Dupilumab PSD November 2020 PBAC meeting). The ESC considered that there may be higher uptake of UPA than DUPI given the perceived benefit and oral formulation, however the uptake assumed in the financial estimates appears overestimated. The PBAC considered that uptake of UPA would also be moderated by safety concerns for JAK inhibitors. The pre-PBAC response argued that uptake rates are likely to be higher than assumed in the dupilumab submission, because demand for treatment appears to have been underestimated based on PBS scripts of dupilumab to date and the availability of an oral treatment may increase uptake further.
- There is uncertainty around the response parameters. Consistent with the modelled economic evaluation, the financial estimates did not adjust the response rate at Week 16 assumed for UPA and DUPI for differences in the placebo response rates across the two sets of trials. The PBAC noted that the financial estimates also assumed a higher treatment response after initiation for the UPA 15 mg dose compared with DUPI, despite the claim of non-inferiority. The financial model also used the same long-term maintenance of response assumed in the DUPI submission, but the PBAC considered this extrapolation was uncertain (para 7.15, Dupilumab PSD July 2019 PBAC meeting).
- The ESC noted there is uncertainty around the proportional use of UPA 15 mg and 30 mg tablets. The submission assumed ■■■:■■■ split between the two strengths of UPA, but more patients may use UPA 30 mg as a more efficacious treatment (if tolerated) and patients may be titrated to the 30 mg dose to achieve a better response. The ESC considered that it is likely that more patients would be treated with the 30 mg dose and therefore the assumption of a ■■■:■■■ split may underestimate the costs of listing UPA. This was consistent with clinician comments in the sponsor hearing, which indicated a preference for initiating patients on the 30 mg dose and titrating down if response is adequate. The PBAC noted the split would be impacted by the dosing approach recommended by the

TGA and adopted by clinicians. The PBAC also noted that the split would not have a substantial effect on the overall financial impact of listing UPA if both doses are listed on a cost-minimisation basis compared with DUPI.

- 6.76 The PBAC considered there was a moderate level of confidence in the modelled costs as calculation of drug costs appeared reasonable but the estimates did not include additional MBS costs of monitoring infection, lipids, ANC, ALC, Hb and LFT.

### **Financial Management – Risk Sharing Arrangements**

- 6.77 The sponsor requested that any RSA in place should reflect the superior response of UPA 30 mg (and the higher proportion of patients who remain on treatment). The PBAC agreed with the ESC that the HEADS UP trial suggested there was no difference in the number of responders at 24 weeks and the assumption of an ongoing difference in the proportion of responders beyond 16 weeks may not be reasonable. Therefore, PBAC considered that increasing the caps in this way was not justified.
- 6.78 The submission also argued that the financial caps should increase for each additional therapy added to the PBS to allow for sequential treatment. The ESC considered that this may be reasonable, however the extent of additional use due to sequential treatments is uncertain. The submission presented increased caps assuming █% of newly initiating patients would re-initiate a second alternative therapy in the same year.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred making a recommendation to list upadacitinib (UPA) for severe atopic dermatitis (AD) as a TGA Delegate's Overview was not available at the time of PBAC consideration. The PBAC was of a mind to recommend 15 mg and 30 mg UPA on a cost minimisation basis compared to DUPI, pending receipt of a positive TGA Delegate's Overview. The PBAC acknowledged the clinical need for additional systemic treatments for severe AD and considered that UPA provides an overall clinical benefit similar to the comparator, dupilumab (DUPI). The PBAC did not accept the submission's claim that UPA 30 mg is superior to DUPI in terms of response, based on the direct head to head evidence presented, although acknowledged that the response to treatment may be faster with UPA. The PBAC considered that safety for UPA 30 mg may be inferior to DUPI.
- 7.2 The PBAC noted that UPA is a novel medicine, as no other Janus Kinase (JAK) inhibitor is available on the PBS for AD. The PBAC acknowledged the clinical need for additional alternative systemic treatments for severe AD, but considered that the additional need was limited in the context of the availability of DUPI for patients with severe AD. The PBAC noted that the clinical need remained high for patients with moderate AD, who also experience a high level of disease burden, as outlined in the consumer comments.

- 7.3 The PBAC considered that it was appropriate for the listing for UPA be similar to the listing for DUPI in terms of the clinical criteria and response criteria. The PBAC considered that the restriction wording should limit prescription of UPA 30 mg tablets to patients aged  $\geq 18$  years and  $< 65$  years, consistent with the Product Information (PI). The PBAC considered that it may be useful for the restriction to provide advice regarding dose titration and how this would be managed in the context of assessing whether patients have met response criteria to qualify for ongoing treatment on the PBS. The pre-PBAC response stated that the restriction should have sufficient flexibility to allow clinicians to titrate the dose up or down dependent on the clinical characteristics of each patient. The PBAC considered that further clinical input from dermatologists and clinical immunologists may be required regarding restrictions concerning the starting dose and approach to titration, and the approach would need to be consistent with the Australian PI recommendations.
- 7.4 The submission presented DUPI as the comparator as it is the treatment most likely to be replaced by UPA. The submission also presented baricitinib, abrocitinib and tralokinumab as secondary near market comparators. The PBAC considered these were the appropriate comparators/near market comparators.
- 7.5 The submission was based on one head-to-head randomised trial comparing 30 mg UPA to 300 mg DUPI (HEADS UP), five randomised trials comparing UPA (15 mg or 30 mg) to placebo (PBO), and seven randomised trials comparing DUPI (300 mg and 200 mg) to PBO. The PBAC noted that an indirect treatment comparison (using PBO as a common reference) was presented because the HEADS UP trial did not include the UPA 15 mg dosing regimen or capture the Dermatology Life Quality Index (DLQI), which is a patient relevant outcome used to assess response for continuing treatment on the PBS. The PBAC noted that the submission relied on the indirect treatment comparison to inform the clinical claim, economic model and financial estimates. The PBAC considered that the indirect comparison was a reasonable basis for establishing the non-inferiority of the 15 mg UPA dose compared with DUPI, however the direct head-to-head trial was the most reliable source of data for the comparison of UPA 30 mg and DUPI.
- 7.6 The PBAC noted that the indirect comparisons found no statistically significant difference between UPA 15 mg versus DUPI (RR=0.93, 95%CI: 0.64, 1.37 in CsA naïve patients and RR=1.67, 95%CI: 0.36, 7.69 in the CsA experienced patients) for PBS response (EASI 50 and DLQI  $\geq 4$ ) in the PBS adult population (i.e. severe AD defined as IGA=4 and EASI  $\geq 20$  at baseline). The PBAC noted that results in the ITT population were generally consistent with the PBS subgroup. The PBAC noted that interpretation of the indirect comparisons for adolescents was problematic, given the small patient numbers and differences in the PBO response rates across the trials (particularly for EASI 50) however, the PBAC considered that the benefit in adolescents is likely to be similar between UPA 15 mg and DUPI 200 mg (or 300 mg for adolescents weighing  $> 60$  kg). Overall, the PBAC considered that the clinical claim of non-inferiority for UPA 15

mg compared with DUPI 300 mg was reasonably supported by the indirect evidence presented in the submission.

- 7.7 In the head-to-head comparison of UPA 30 mg and DUPI 300 mg a significantly larger proportion of patients achieved EASI 75 at Week 16 with UPA 30 mg compared to DUPI, and secondary endpoints showed similar effects. However, the statistically significant treatment difference observed at Week 16 was no longer observed at Week 24 (see figure 1). The PBAC considered that these results appeared to show that patients treated with UPA tended to respond to treatment faster than patients treated with DUPI, however beyond 16 weeks the difference in EASI 75 response between UPA and DUPI may not be maintained. The PBAC also noted that in the post hoc PBS subgroup (EASI score  $\geq 20$  and IGA score = 4) the outcome of EASI 50 was numerically but not statistically significantly different between UPA 30 mg and DUPI 300 mg at 16 weeks (76.3% vs 68.9% respectively, RR=1.11 95%CI: 0.97, 1.27).
- 7.8 Based on indirect evidence for the PBS response criteria in the PBS population ('severe' AD), the submission estimated a relatively large effect for UPA 30 mg compared with DUPI (RD=0.17-0.24, depending on prior CsA). The PBAC considered there was uncertainty around these estimates given the post-hoc nature of the outcome and subgroup, and as the analyses do not control for monotherapy versus combination therapy (a prognostic factor). The PBAC noted indirect evidence in the ITT population also found a smaller treatment difference for the individual components of the PBS response outcome, EASI 50 (monotherapy adults, RD=0.12, 95%CI: 0.05, 0.19; combination therapy adults, RD=0.14, 95%CI: 0.01, 0.27) and DLQI $\geq 4$  (monotherapy adults, RD=0.12, 95%CI: -0.01, 0.25; combination therapy adults, RD=0.03, 95%CI: -0.08, 0.14).
- 7.9 For the outcome of EASI 75 the difference between DUPI and the JAK inhibitors (UPA, baricitinib, abrocitinib and tralokinumab) appeared to be somewhat attenuated in the trials that allowed concomitant TCS (see figure 2). The PBAC considered that in the PBS population TCS use may reduce differences between UPI and DUPA seen up to 16 weeks in the HEADS UP trial and the difference at 16 weeks may also be smaller.
- 7.10 The PBAC noted that direct evidence in HEADS UP found significantly more patients experienced adverse reactions with UPA 30 mg compared to DUPI 300 mg (any AEs, drug-related AEs and severe AEs), and this was consistent with the available indirect evidence (any AEs). In addition, significantly more patients experienced AEs with UPA 30 mg compared to UPA 15 mg (any TEAEs, drug-related AEs). The ESC noted that there is an increased risk of infection (including zoster) and malignancy associated with JAK inhibitors versus IL-4 inhibitors as a result of immunosuppression. These AEs may only be apparent with longer-term use. The PBAC noted that the pre-PBAC response provided additional safety data up to week 52 for the AD trials and safety data in the treatment of rheumatoid arthritis for up to 4.5 years. No notable changes to the safety profile were seen in this longer term data. The PBAC considered the claim of non-inferior safety for UPA 15 mg relative to DUPI was reasonable, though long term effects remain somewhat uncertain. The PBAC considered that the evidence

presented in the submission did not adequately support the claim of non-inferior safety between UPA 30 mg and DUPI 300 mg, and considered that UPA 30 mg appears to have inferior safety to DUPI.

- 7.11 Overall the PBAC considered that the clinical claim of superior comparative effectiveness for UPA 30 mg compared with DUPI 300 mg was not adequately supported by the evidence presented in the submission, as the most reliable direct evidence indicated that the difference in response is likely to be less than that shown in the indirect evidence and may not be maintained beyond 16 weeks. The PBAC considered that there was no added benefit for disease activity or quality of life for UPA 15 mg compared with DUPI 300 mg. The PBAC considered there was a possible minor added benefit for UPA 30 mg compared with DUPI 300 mg in terms of disease activity and quality of life due to faster onset of response. The PBAC considered that this benefit was offset by an increase in treatment related adverse events.
- 7.12 The submission presented a cost-minimisation analysis for UPA 15 mg versus DUPI, based on the nominated equi-effective doses of UPA 15 mg once daily and DUPI 600 mg as an initial dose then 300 mg every two weeks thereafter, or DUPI 400 mg as an initial dose then 200 mg every two weeks thereafter in adolescents with a body weight <60kg, assuming equivalent drug costs over a two-year period. No costs for monitoring or drug administration were included. The PBAC considered this approach was reasonable.
- 7.13 Based on the claim of superior efficacy the submission presented a stepped economic evaluation, using results from the indirect treatment comparison at Week 16 and extrapolated to 5.3 years using a modelled cost-utility analysis. As the claim of superiority was not supported by the evidence presented in the submission the PBAC considered that the cost-effectiveness analysis for UPA 30 mg was not appropriate and a cost-minimisation approach compared with DUPI would be a more appropriate. The PBAC considered that the equi-effective doses are UPA 30 mg once daily and DUPI 600 mg as an initial dose then 300 mg every two weeks thereafter. The PBAC considered it would be appropriate to assume equivalent drug costs over a two-year period and no costs for monitoring or drug administration as per the cost-minimisation analysis for UPA 15 mg.
- 7.14 The PBAC considered that there was a low level of confidence in the size of the estimated patient population which relied on a difference in response rates for UPA 15 mg, UPA 30 mg and DUPI and ongoing maintenance of this difference. In addition, the uptake estimates were considerably higher than the PBAC's accepted uptake estimates for DUPI. The PBAC considered that the financial estimates appeared overestimated based on these two factors. The PBAC noted the proportion of 15 mg and 30 mg UPA scripts would be impacted by the dosing approach recommended by the TGA and adopted by clinicians. The PBAC also noted that the split would not have a substantial effect on the financial impact of listing UPA if both are listed on a cost-minimisation basis compared with DUPI. The PBAC noted that the listing would result in increased costs due to sequential use (as per paragraph 7.16).

- 7.15 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). As noted in paragraph 7.11, 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.
- 7.16 The PBAC noted the submission did not present any data to assess the effectiveness or cost-effectiveness of UPA in patients not responding to DUPI or vice versa. However, the PBAC considered 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 noted the submission estimated █% of initiating patients would re-initiate with the second treatment. The PBAC considered that an increase to initiating patients of █% was reasonable, noting advice from the Department that an increase of █% in initiating patients from DUPI estimates equates to an approximate █% increase in the DUPI financial estimates and caps over a period of 6 years. The PBAC advised that an increase in the DUPI financial caps of █% or less to account for sequential use of UPA and DUPI is reasonable. 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.
- 7.17 The PBAC noted that the sponsor indicated that < 500 patients are expected to be included in a Patient Familiarisation Program and would require transitioning onto the PBS if UPA is listed. The PBAC considered that these patients should be captured within the estimated financial implications, which used an epidemiological approach. These patients should also be captured within the proposed caps and no further increase in caps would be needed to account for 'grandfather' patients.
- 7.18 The PBAC noted that its foreshadowed recommendation was on a cost-minimisation basis for both the 15mg and 30mg doses, and advised that, because UPA 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 2009* for Pricing Pathway A were not met.

**Outcome:**

Deferred

## Addendum to the July 2021 PBAC PSD:

### 8 Purpose of application

8.1 At its July 2021 meeting, the PBAC deferred making a recommendation for the listing of upadacitinib for the treatment of severe atopic dermatitis pending receipt of a positive TGA Delegate's Overview.

8.2 A positive TGA delegate's overview and ACM minutes were provided following the July 2021 PBAC meeting and TGA registration was approved in September 2021. The final PI includes the following indication:

*"RINVOQ is indicated for use in adults and adolescents aged 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated."*

8.3 The PI also includes the following dose recommendations in atopic dermatitis:

*"The recommended starting dose of RINVOQ is 15 mg once daily for adults. In adults aged less than 65 years, the dose may be increased to 30 mg once daily from 4 weeks after initiation of treatment, if clinically warranted and based on benefit-risk assessment. The lowest effective dose for maintenance should be considered."*

*The recommended dose of RINVOQ is 15 mg once daily for adolescents weighing at least 40 kg. RINVOQ has not been studied in adolescents weighing less than 40 kg."*

### 9 PBAC outcome

9.1 The PBAC recommended the listing of upadacitinib for severe atopic dermatitis. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of upadacitinib would be acceptable if it were cost-minimised against dupilumab. The PBAC advised that the equi-effective doses are UPA 15 mg or 30 mg once daily and DUPI 600 mg as an initial dose then 300 mg every two weeks thereafter, or DUPI 400 mg as an initial dose then 200 mg every two weeks thereafter in adolescents with a body weight <60kg, assuming equivalent drug costs over a two-year period.

9.2 As noted in paragraph 7.3 the PBAC considered that the restriction should reflect dosing requirements as outlined in the PI (paragraph 8.3) where all patients are initiated on the 15 mg dose and adult patients aged less than 65 years may increase to the 30 mg dose after 4 weeks, if clinically warranted. The PBAC considered that where patients increase their dose after 4 weeks of treatment at the 15 mg dose, 16 weeks would still allow sufficient time for assessment of response following a dose increase. However, the PBAC considered that the restriction should have sufficient

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flexibility to allow clinicians to titrate the dose up or down such that prescribers can use the lowest effective dose.

- 9.3 The PBAC noted the flow-on restriction changes to DUPI are required to allow switching between treatments (UPA, DUPI or other biological/immunomodulatory treatments for AD if listed in the future) and use of baseline scores measured prior to the first medicine used for this indication. Finalisation of the details of the restrictions will be required, including provision of practical administrative advice on how clinicians are to access the various disease measurement indices referenced in the restriction (e.g. EASI, DLQI and PGA scales).
- 9.4 The PBAC recalled its advice that UPA should be subject to the same RSA as DUPI, with a modest increase to the caps to account for sequential use as noted in paragraph 7.16 above.
- 9.5 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

**Outcome:**

Recommended

## 10 Recommended listing

Add new items:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
UPADACITINIB					
upadacitinib 15 mg modified release tablet, 28	New	1	30	4	Rinvoq
upadacitinib 30 mg modified release tablet, 28	New	1	30	4	Rinvoq
		Max.qty (packs) multiplier = 1 Repeat increases: nil			
<b>Restriction Summary [New; based on 11424] / ToC: [New; based on 11443 attached to dupilumab as of 1 April 2021]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia					
<b>Administrative Advice:</b> Instructions on the use of the Eczema Area and Severity Index and copyright details can be found here: [insert sponsor-neutral location here or AbbVie contact details]					
<b>Administrative Advice:</b> Instructions on the use of the Dermatology Life Quality Index and copyright details can be found here: <a href="https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index">https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index</a>					
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					

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<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Indication:</b> Chronic severe atopic dermatitis
<b>Treatment Phase:</b> Initial treatment of the whole body
<b>Clinical criteria:</b>
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
<b>AND</b>
<b>Clinical criteria:</b>
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
<b>AND</b>
<b>Clinical criteria:</b>
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
<b>AND</b>
<b>Clinical criteria:</b>
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
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised biological medicine for this PBS indication.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have experienced an inadequate response to this biological medicine in this PBS indication
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a dermatologist; or
Must be treated by a clinical immunologist
<b>AND</b>
<b>Population criteria:</b>
Patient must be 12 years of age or older
<b>Prescribing Instructions:</b>
Patients must be initiated on a dose of 15 mg per day and adult patients aged less than 65 years may increase to 30 mg per day after 4 weeks, if clinically warranted.
<b>Prescribing Instructions:</b>
State each of the qualifying PGA, EASI and DLQI scores in the authority application if this is the first time the patient is being treated with a biological/immunomodulatory medicine for this PBS indication. Past baseline measurements need not be repeated. Baseline scores must have been measured within the 4 weeks immediately prior to the first biological/immunomodulatory medicine prescribed for this PBS indication for this patient. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine is/are to be documented in the patient's medical records. The EASI and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction.
<b>Administrative Advice:</b>
Instructions on the use of the Physician's Global Assessment (5-point scale) can be obtained from [insert sponsor-neutral location here or AbbVie contact details]

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<p><b>Administrative Advice:</b> Where the full number of stated repeat prescriptions was not sought in the original prescription, the balance of the repeats can be sought under this treatment phase listing.</p>
<p><b>Restriction Summary: New</b> (based on 11490) / <b>ToC: New</b> (based on 11480 attached to dupilumab as at 1 April 2021)</p>
<p><b>Indication:</b> Chronic severe atopic dermatitis</p>
<p><b>Treatment Phase:</b> Initial treatment of the face and/or hands</p>
<p><b>Clinical criteria:</b> 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><b>AND</b></p>
<p><b>Clinical criteria:</b> 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><b>AND</b></p>
<p><b>Clinical criteria:</b> 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><b>AND</b></p>
<p><b>Clinical criteria:</b> The treatment must be the sole PBS-subsidised biological medicine for this PBS indication</p>
<p><b>AND</b></p>
<p><b>Clinical criteria:</b> Patient must not have experienced an inadequate response to this biological medicine in this PBS indication</p>
<p><b>AND</b></p>
<p><b>Treatment criteria:</b> Must be treated by a dermatologist; or Must be treated by a clinical immunologist</p>
<p><b>AND</b></p>
<p><b>Population criteria:</b> Patient must be 12 years of age or older</p>
<p><b>Prescribing Instructions:</b> Patients must be initiated on a dose of 15 mg per day and adult patients aged less than 65 years may increase to 30 mg per day after 4 weeks, if clinically warranted.</p>
<p><b>Prescribing Instructions:</b> State each of the 4 Eczema Area and Severity Index (EASI) symptom sub-score ratings for erythema, oedema/papulation, excoriation, lichenification, in the authority application. Past baseline measurements need not be repeated. Baseline scores must have been measured within the 4 weeks immediately prior to the first biological/immunomodulatory medicine prescribed for this PBS indication for this patient. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine is/are to be documented in the patient's medical records.</p>
<p><b>Restriction Summary: New</b> (based on 11504) / <b>ToC: New</b> (based on 11425 attached to dupilumab as at 1 April 2021)</p>
<p><b>Indication:</b> Chronic severe atopic dermatitis</p>
<p><b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsidised supply - treatment of the whole body (Grandfather listing)</p>

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<b>Clinical criteria:</b>
Patient must have been receiving treatment with this drug for this PBS indication prior to [1 Month 20XX – insert listing date here]
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have had a Physicians Global Assessment (PGA) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have had an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days prior to commencing non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; or
Patient must have, where the above baseline DLQI was not recorded in the patient’s medical records, a current age-appropriate DLQI score (of any value) measured
<b>AND</b>
<b>Clinical criteria:</b>
The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, prior to commencing non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a dermatologist; or
Must be treated by a clinical immunologist
<b>AND</b>
<b>Population criteria:</b>
Patient must be 12 years of age or older
<b>Prescribing Instructions:</b>
State each of the qualifying PGA, EASI and DLQI scores in the authority application. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine must be documented in the patient’s medical records.
The EASI and DLQI baseline measurements are to form the basis of determining if an adequate response to treatment has been achieved under the Continuing treatment restriction.

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<b>Prescribing Instructions:</b> A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only.
<b>Prescribing Instructions:</b> For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
<b>Administrative Advice:</b> This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
<b>Administrative Advice:</b> Instructions on the use of the Physician's Global Assessment (5-point scale) can be obtained from [insert sponsor-neutral location here or AbbVie contact details]
<b>Restriction Summary: New</b> (based on 11491) / <b>ToC: New</b> (based on 11479 attached to dupilumab as at 1 April 2021)
<b>Indication:</b> Chronic severe atopic dermatitis
<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsidised supply - treatment of the face and/or hands (Grandfather listing)
<b>Clinical criteria:</b> Patient must have been receiving treatment with this biological medicine for this PBS indication prior to [1 Month 20XX – insert PBS listing date here]
<b>AND</b>
<b>Clinical criteria:</b> The condition must have had at least 2 of the following Eczema Area and Severity Index (EASI) symptom sub-scores for erythema, oedema/papulation, excoriation, lichenification rated as severe despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to commencing non-PBS-subsidised therapy with this biological medicine; or The condition must have affected at least 30% of the face/hands surface area despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to commencing non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Clinical criteria:</b> Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, prior to having commenced non-PBS-subsidised therapy with this biological medicine; or Patient must have, where the above baseline DLQI was not recorded in the patient's medical records, a current age-appropriate DLQI score (of any value) measured
<b>AND</b>
<b>Clinical criteria:</b> The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, prior to commencing non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Clinical criteria:</b> Patient must not be experiencing an inadequate response to current non-PBS-subsidised therapy with this biological medicine
<b>AND</b>
<b>Clinical criteria:</b> The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
<b>AND</b>
<b>Clinical criteria:</b> Patient must not have experienced an inadequate response to this biological medicine in this indication, prior to commencing non-PBS-subsidised therapy with this biological medicine
<b>AND</b>

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<b>Treatment criteria:</b>
Must be treated by a dermatologist; or
Must be treated by a clinical immunologist
<b>AND</b>
<b>Population criteria:</b>
Patient must be 12 years of age or older
<b>Prescribing Instructions:</b>
State each of the 4 Eczema Area and Severity Index (EASI) symptom sub-score ratings for erythema, oedema/papulation, excoriation, lichenification that were present prior to having commenced non-PBS-subsidised therapy, in the authority application. The name/s of the medium to high potency topical corticosteroids trialled prior to commencing treatment with this biological medicine is/are to be documented in the patient's medical records.
<b>Prescribing Instructions:</b>
A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only.
<b>Prescribing Instructions:</b>
For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
<b>Administrative Advice:</b>
This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB					
upadacitinib 15 mg modified release tablet, 28	11979L	1	30	5	Rinvoq
upadacitinib 30 mg modified release tablet, 28	New	1	30	5	Rinvoq
		Max.qty (packs) multiplier = 1			
		Repeat increases: nil			

<b>Restriction Summary:</b> New (based on 11374) / <b>ToC:</b> New (based on 11374 attached to dupilumab as at 1 April 2021)
<b>Indication:</b> Chronic severe atopic dermatitis
<b>Treatment Phase:</b> Continuing or resuming treatment of the whole body
<b>Clinical criteria:</b>
Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the whole body
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have achieved an adequate response within the first 16 weeks of treatment; or
Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; or
Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. family planning, vaccination with live vaccines, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a dermatologist; or

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Must be treated by a clinical immunologist
<p><b>Prescribing Instructions:</b>          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</p> <p>Where an initial baseline (post-topical corticosteroid, pre-biological medicine) DLQI score was not measured for a patient who had commenced treatment through a clinical trial, early access program or through private, non-PBS-subsidised supply, an absence of worsening in the current DLQI score compared to that measured at the time of the 'Grandfather listing' authority application will suffice as an adequate response for requirement (b) above.          State each of the current EASI and DLQI scores for this authority application.</p>
<b>Restriction Summary: New</b> (based on 11377) / <b>ToC: New</b> (based on 11377 attached to dupilumab as at 1 April 2021)
<b>Indication:</b> Chronic severe atopic dermatitis
<b>Treatment Phase:</b> Continuing or resuming treatment of the face and/or hands
<b>Clinical criteria:</b>
Patient must have received PBS-subsidised treatment with this biological medicine for the treatment of chronic severe atopic dermatitis affecting the face/hands
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have achieved an adequate response within the first 16 weeks of treatment; or
Patient must have maintained an adequate response to their most recent course of PBS-subsidised treatment with this biological medicine for this PBS indication if this is the second or subsequent Continuing treatment authority application; or
Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. family planning, vaccination with live vaccines, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised biological medicine for this PBS indication
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a dermatologist; or
Must be treated by a clinical immunologist
<p><b>Prescribing Instructions:</b>          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</p> <p>Where an initial baseline (post-topical corticosteroid, pre-biological medicine) DLQI score was not measured for a patient who had commenced treatment through a clinical trial, early access program or through private, non-PBS-subsidised supply, an absence of worsening in the current DLQI score compared to that measured at the time of the 'Grandfather listing' authority application will suffice as an adequate response for requirement (b) above.          Document each qualifying response measure in the patient's medical records for PBS compliance auditing purposes</p>

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

## **11 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.

## **12 Sponsor's Comment**

AbbVie welcomes the PBAC's recommendation for 15mg and 30mg upadacitinib for severe AD patients and their advice that an increase in existing financial caps for AD may be reasonable. AbbVie maintains that upadacitinib 30 mg is superior to dupilumab in patients with moderate to severe AD, based on the results of a randomised controlled head-to-head trial with dupilimab 300mg (HEADS UP), which demonstrated superiority of upadacitinib on the primary endpoint of 75% improvement in EASI (EASI75) at Week 16.