Analysis of dupilumab for severe atopic dermatitis

Drug utilisation sub-committee (DUSC)

September 2023

Abstract

Purpose

To review the utilisation of dupilumab for severe atopic dermatitis, as requested by DUSC at its June 2023 meeting.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Dupilumab was PBS listed for severe atopic dermatitis 1 March 2021.

Data Source / methodology

Data extracted from the PBS database maintained by Department of Health and Aged Care, processed by Services Australia were used for the analyses.

Key Findings

- A total of 222,778 prescriptions of dupilumab for atopic dermatitis have been supplied to 16,995 patients since listing. In 2022, 104,967 prescriptions were supplied to 12,523 patients.
- Prescriptions supplied for the treatment of the whole body accounted for 82% of the 104,967 supplied prescriptions in 2022.
- The age group with the highest proportion of initiating patients was the 20 to 24 year old group. The proportion of males was higher than females in every age group, except in the 45 – 54 year range.
- Dermatology specialist prescribers accounted for 79% of the supplied prescriptions, and Immunology and Allergy specialist prescribers accounted for 8% of the supplied prescriptions.
- Of the 16,995 patients supplied dupilumab under a PBS item code for atopic dermatitis, 92% were previously supplied topical therapy through the PBS.

Purpose of analysis

To review the utilisation of dupilumab for severe atopic dermatitis, as requested by DUSC at its June 2023 meeting.

Background

Clinical situation

Atopic dermatitis, also called eczema, is a chronic health condition that affects the skin, causing redness, dryness itching and sometimes infections. Atopic dermatitis is most common in infants and children, and tends to improve in midlife, however it can occur at any age. Food allergy can trigger or worsen symptoms of atopic dermatitis in some people, however food allergy is rarely the cause of atopic dermatitis.[1]

Pharmacology

Dupilumab is a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor α subunit (IL-4Rα) of IL-4 heterodimeric type I and type II receptors that mediate IL-4/IL-13 signalling through this pathway. Blockade of these receptors broadly suppresses type 2 inflammation associated with atopic/allergic diseases, including atopic dermatitis and asthma.[2]

Therapeutic Goods Administration (TGA) approved indications

Atopic dermatitis

- Dupilumab is TGA approved for the treatment of moderate to severe atopic dermatitis in patients aged 6 months and older who are candidates for chronic systemic therapy.

Asthma

- Dupilumab is indicated as add on maintenance treatment in patients aged 6 years and older with moderate to severe asthma with type 2 inflammation that is inadequately controlled despite therapy with other medicinal products for maintenance treatment.

[1] Australasian Society of Clinical Immunology and Allergy . Eczema (Atopic Dermatitis). (Accessed 27 July 2023); Available from https://www.allergy.org.au/patients/skin-allergy/eczema

[2] Li Z, Radin A, Li M, Hamilton JD, Kajiwara M, Davis JD, et al. Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Dupilumab in Healthy Adult Subjects. Clin Pharmacol Drug Dev. 2020 Aug;9(6):742-755. doi: 10.1002/cpdd.798. Epub 2020 Apr 29. PMID: 32348036; PMCID: PMC7496261.

Chronic rhinosinusitis with nasal polyposis

- Dupilumab is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

Prurigo nodularis

- Dupilumab is indicated for the treatment of moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy. [3]

Dosage and administration

Dupilumab can be used with or without topical therapy, including corticosteroids and/or calcineurin inhibitors as appropriate. Adult patients should receive an initial dose of dupilumab of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites), followed by 300 mg given every other week. The recommended dosing of paediatric and adolescent patients (6 to 17 years of age) for atopic dermatitis depends on the body weight of the patient and is summarised in Table 1. The pre-filled pen is not intended for use in children below 12 years of age. For children 6 to 11 years of age with atopic dermatitis, the pre-filled syringe is the presentation appropriate for this population.[3]

Dupilumab is subject to additional monitoring in Australia under the Black Triangle Scheme.[3]

Table 1: Dosage of dupilumab for paediatric and adolescent patients

Body Weight of Patient	Initial Dose	Subsequent Doses
15 kg - <30 kg	600 mg (two 300 mg injections)	300 mg every 4 weeks (q4w)
30kg - < 60 kg	400 mg (two 200 mg injections)	200mg every other week (q2w)
≥ 60 kg	600 mg (two 300 mg injections)	300mg every other week (q2w)

Note: q2W, once every two weeks; q4w, once every four weeks.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at July 2023)

Dupilumab was PBS listed for atopic dermatitis 1 March 2021 in patients aged 12 years and older, and for asthma 1 April 2021. Details of the PBS listing of dupilumab for atopic dermatitis are summarised in Table b. Upadacitinib was PBS listed for atopic dermatitis 1 February 2022.

[3] Dupixent (dupilumab). Australian Approved Product Information. Macquarie Park NSW: Sanofi Aventis. Approved 24 January 2018, updated 29 June 2022. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01199-1

Table 2: PBS listing of dupilumab for atopic dermatitis

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
12291X	dupilumab 200 mg/1.14 mL injection, 2 x 1.14 mL syringes	2	5	$1755.19	Dupixent, sanofi-aventis Australia Pty Ltd
12292Y	dupilumab 300 mg/2 mL injection, 2 x 2 mL syringes	2	5	$1755.19	

Source: the PBS website. A Special Pricing Arrangement applies.

Restriction

Clinical criteria:

- Patient must have a Physicians Global Assessment (PGA) (5-point scale) baseline score of at least 4 as evidence of severe disease despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, AND
- Patient must have an Eczema Area and Severity Index (EASI) baseline score of at least 20 despite treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, AND
- Patient must have an age appropriate Dermatology Life Quality Index (DLQI) baseline score (of any value) measured following treatment with daily topical therapy (corticosteroid of medium to high potency/calcineurin inhibitor), for at least 28 days, AND
- The condition must have had lesions for at least 6 months from the time of the initial diagnosis of chronic severe atopic dermatitis affecting either of: (i) the whole body, (ii) face/hands, AND
- 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.

Treatment criteria:

- Must be treated by a dermatologist; OR
- Must be treated by a clinical immunologist.

For details of the current PBS listing refer to the PBS website.

Changes to listing

Dupilumab was PBS listed for atopic dermatitis on 1 March 2021 on the General Schedule. On 1 April 2021 the listing was altered to include a calcineurin inhibitor as daily topical therapy in addition to a corticosteroid of medium to high potency. The restrictions for transitioning patients from non-PBS to PBS-subsidised supply (Grandfather listings) were deleted 1 May 2022.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

Table 3: Summary of PBAC submissions for dupilumab

PBAC meeting	Submission purpose	Outcome
July 2018	Authority Required listing for dupilumab for treatment of atopic dermatitis.	Not recommended
July 2019	Authority Required listing for dupilumab for the treatment of atopic dermatitis (AD) in adult patients with moderate-to-severe disease who are inadequately controlled on topical therapies.	Not recommended
March 2020	Authority Required listing for dupilumab for the treatment of atopic dermatitis (AD) in adult patients with severe disease who are inadequately controlled on topical therapies	Recommended
November 2020	Following the PBAC's recommendation at its March 2020 meeting, a revised pricing proposal was submitted to the PBAC for atopic dermatitis for consideration. It included a revised dispensed price and an updated budget impact model.	Advised The PBAC considered that the sponsor's amended inputs to the economic model were acceptable overall in addressing the uncertainties previously outlined regarding phototherapy costs and maintenance of response. However, the PBAC maintained that a price reduction would be required to achieve the base case ICERs considered in March 2020: $45,000 to <$55,000/QALY for the cyclosporine A (CsA)-naïve population and $25,000 to <$35,000/QALY for the CsA-experienced population.
November 2020	Section 100, Authority Required listing for dupilumab for the treatment of uncontrolled, severe type 2 asthma, both with and without oral corticosteroid (OCS) dependence. Listing was requested on the basis of a cost-minimisation analysis versus three comparators: benralizumab, mepolizumab and omalizumab.	Recommended
March 2022	Authority Required listing for dupilumab for the treatment of children aged 6 to 11 years with severe atopic dermatitis (AD) who have had an inadequate response to topical therapies.	Recommended
July 2022	Requested an increase in the financial caps for the current risk share arrangement (RSA) to reflect the higher than estimated use of dupilumab for severe chronic atopic dermatitis (AD) since listing on 1 March 2021	Not recommended

PBAC meeting	Submission purpose	Outcome
November 2022	To list two new forms of dupilumab: 200 mg in 1.14 mL and 300 mg in 2 mL single dose autoinjector under the same circumstances as the currently listed dupilumab 200 mg in 1.14 mL and 300 mg in 2 mL single dose pre-filled syringe	Recommended
July 2023	To request the PBAC consider the previously estimated utilisation for chronic severe atopic dermatitis.	Advice provided

July 2018 submission

The first submission for dupilumab for atopic dermatitis was not recommended by the PBAC due to uncertainty regarding the appropriate place in therapy and uncertain cost effectiveness. The PBAC did not consider that the data presented in the submission supported restricting the use of dupilumab to only severe disease.

DUSC reviewed the submission and considered there was likely to be usage beyond the expectations because the uptake of dupilumab by atopic dermatitis patients was based on the uptake of the first biologics listed for psoriasis but the biologics market had evolved substantially since this time. Comparison with the submission's own market research on the percentage of atopic dermatitis patients that fulfil the restriction criteria suggested that the submission's approach may result in a substantial underestimate of dupilumab utilisation. The pre-PBAC response noted that several biologic medicines became available for psoriasis in the first years of listing, whereas dupilumab was the only biologic medicine available for atopic dermatitis. The sponsor argued that the evolution of the biologics market was likely to be largely offset by the difference in biologic medicine availability across the different indications.

DUSC considered there was likely to be use beyond the proposed restriction for patients with moderate atopic dermatitis and for continued use in patients with severe atopic dermatitis but who do not fulfil the response criteria. DUSC considered that the base case estimates for dupilumab should be consistent with the proposed PBS criteria, response rates from the clinical trials and modelled economic evaluation, with potential for use outside of the restriction managed through a risk sharing arrangement. The pre-PBAC response argued that the utilisation in the psoriasis market reflects real world use and would therefore capture leakage outside the approved indication.

For further details refer to the Public Summary Document from the July 2018 PBAC meeting.

July 2019 submission

The second submission for dupilumab for atopic dermatitis requested a Section 85 Authority Required listing for dupilumab for the treatment of atopic dermatitis in adult patients with moderate-to-severe disease who are inadequately controlled on topical therapies. It was not recommended by the PBAC.

The PBAC acknowledged the effectiveness of dupilumab in a therapeutic area of high clinical need, however considered that dupilumab was not cost-effective at the price proposed in the resubmission. The PBAC also considered that the criteria for defining the patient population for initial and continuing treatment did not appropriately consider the extent of disease in terms of the body surface area affected. The PBAC considered that the estimated financial implications were very high and uncertain, and that a risk sharing arrangement would be necessary to manage the uncertainty in patient estimates, likely treatment duration and the potential for use outside the proposed restriction.

This submission was considered by DUSC. The DUSC considered the financial cost presented in the resubmission to be underestimated.

Compared to the previous submission, the resubmission made the following changes to the financial estimates:

- Financial estimates for a broader population (moderate-to-severe AD inadequately controlled on topical therapies) were presented. As such, the financial estimations increased substantially from the previous submission.
- An epidemiological approach was taken whereby data on the size of the eligible population was derived largely from commissioned local market research data, and uptake and treatment discontinuation rates were derived from international market data. The previous submission utilised the psoriasis PBS biologic medicine market as a proxy to calculate the size of the eligible population and uptake rates. The PBAC considered that the reliance on the psoriasis market as a proxy for dupilumab uptake was not well supported and was likely to have underestimated the patient numbers (Dupilumab PSD, July 2018, paragraph 6.52).

Health budget cost-savings were incorporated into the financial estimates through annual health state costs applied in the economic model. The same method was used in the previous submission, however, because the annual non-responder health state costs increased substantially in the resubmission compared to the previous submission, the impacts on the estimated cost-savings to the health budget substantially increased. The resubmission estimated that at year 6, the estimated number of continuing patients was less than 10,000 and the net cost to the PBS would be more than $100 million based on the effective price and more than $100 million based on the published price.

For further details refer to the Public Summary Document from the July 2019 PBAC meeting.

March 2020 submission

The PBAC recommended the listing of dupilumab for the treatment of patients aged 12 years and older with severe atopic dermatitis (AD) who are inadequately controlled on topical therapies.

The resubmission requested a separate listing for patients with severe atopic dermatitis of the face or hands, which was not included in previous submissions. The evaluation noted that the estimates may be underestimated as the resubmission did not account for patients

with severe face or hand AD and some of the inputs relating to patient eligibility may be underestimated.

The financial estimates presented in the resubmission were substantially decreased compared to those presented in the July 2019 resubmission. This was primarily due to the narrower (severe AD) population proposed in the current resubmission. Compared to the July 2018 submission (also requesting use in a severe AD group, but defined differently), the financial estimates in this resubmission were substantially higher. This was primarily due to increases in input values such as prevalence of AD, proportion with severe disease and uptake rates. The uptake of dupilumab in the July 2018 submission was based on the observed uptake of biologic medicines when first listed on the PBS for psoriasis. DUSC considered that uptake of dupilumab was likely to be higher as: the biologics market had evolved compared to the uptake rates based on earlier listings; and the submission's estimate based on market research of the percentage of patients that would fulfil the restriction criteria was higher than the projected uptake of dupilumab. Compared to the July 2018 submission, the PBAC noted that the July 2019 and March 2020 submissions used a different, epidemiological approach to estimate the proportion of AD patients accessing dupilumab.

For further details refer to the Public Summary Document from the March 2020 PBAC meeting.

November 2020 submission

Dupilumab for the treatment of patients aged 12 years and older with severe atopic dermatitis (AD) who are inadequately controlled on topical therapies was recommended at the March 2020 PBAC meeting.

Following the recommendation, the sponsor submitted pricing proposals to the Department, which were not accepted, as they were not consistent with the PBAC advice. Primarily, after the sponsor's adjustment to the economic model, the resulting ICER was higher than the range considered by the PBAC.

The PBAC provided further advice in regard to its March 2020 recommendation for the listing of dupilumab for the treatment of patients aged 12 years and older with severe atopic dermatitis who are inadequately controlled on topical therapies, and the sponsor's subsequent listing proposal which included modifications to the economic model and the financial estimates model.

The PBAC noted the sponsor's revised approach to the uptake rates applied over time to the prevalent pool of eligible patients. While the PBAC noted that this was different to the method PBAC advised in March 2020, the PBAC acknowledged the proposal's claims that the proposed uptake rates were a better estimate of the pattern of uptake. Importantly, the PBAC considered that the uptake rates of patients from the prevalent pool proposed by the sponsor decreased over time and therefore were reasonable.

For further details refer to the Public Summary Document from the November 2020 PBAC meeting.

March 2022 submission

The PBAC recommended the listing of dupilumab for patients aged less than 12 years with severe atopic dermatitis. The PBAC noted the substantial clinical need for effective treatments for these patients and was satisfied that dupilumab provided, for some patients, a significant improvement in efficacy over standard care. The PBAC considered that the clinical evidence suggests the magnitude of benefit in patients aged 6-11 years is similar to that in the adult/adolescent population and the cost-effectiveness was acceptable at the same price per month as for the adult/adolescent population.

As at 1 August 2023 this recommendation had not been implemented.

For further details refer to the Public Summary Document from the March 2022 PBAC meeting.

July 2022 submission

The submission requested an increase in the financial caps for the current risk share arrangement (RSA) to reflect the higher than estimated use of dupilumab for severe chronic atopic dermatitis (AD) since listing on 1 March 2021.

The sponsor requested the PBAC to reconsider previously estimated utilisation of dupilumab in patients aged 12 years or older, with severe AD. The sponsor presented revised financial estimates to inform revised RSA caps with changes to assumptions regarding:

- the proportion of patients uncontrolled on topical corticosteroids (TCS) (from 68% to 100%)
- the proportion of patients engaged with a specialist (from 55-70% to 100%)

The PBAC previously considered there is potential for substantial use beyond the requested restriction to those with less severe atopic dermatitis, those with comorbid conditions such as asthma, and those with reduced QoL due to overly complex topical regimens. As noted by the submission, given the intent of the RSA it was necessary to determine whether the higher than predicted utilisation was the result of an underestimation of the size and/or uptake within the eligible population or due to use beyond the requested restriction.

The utilisation estimates did not account for patients with severe face and/or hand atopic dermatitis who would not otherwise meet the criteria for severe atopic dermatitis. Both the pre-PBAC response and communication from the sponsor for upadacitinib argued that exclusion of patients qualifying for treatment with advanced atopic dermatitis therapies due to severe atopic dermatitis of the hands and face was likely to be a significant contributor to the higher than expected observed utilisation of these treatments. The sponsor for upadacitinib estimated that up to one third of total services in atopic dermatitis would be for patients with severe atopic dermatitis of the face and hands who would not otherwise qualify for treatment.

The PBAC did not advise that its previous recommendation regarding the risk sharing arrangement (RSA) subsidisation caps for dupilumab for the treatment of severe atopic dermatitis in adult and adolescent patients be amended.

For further details refer to the Public Summary Document from the July 2022 PBAC meeting.

July 2023 submission

The PBAC advised that it would be reasonable for the current risk sharing arrangement (RSA) financial caps for dupilumab (and upadacitinib), for the treatment of severe atopic dermatitis in patients aged 12 years and older, to be increased for the remaining years of the arrangement, to account for patients with severe atopic dermatitis of the hands and/or face. In providing this advice, the PBAC noted that such use was not accounted for in the original RSA caps, however, given the apparent quality of life impacts of disease affecting the hands and/or face appear similar to that for the whole body, considered that use in these patients is likely to be cost-effective. The PBAC considered the submission's other proposed changes to the financial estimates (increasing the proportion of patients inadequately controlled on topical corticosteroids and increasing the uptake rates) to be overestimated and highly uncertain. The PBAC considered that the submission did not provide sufficient justification in relation to changing these assumptions and therefore did not support these amendments.[4]

Approach taken to estimate utilisation

The November 2020 resubmission used an epidemiological approach to estimate the number of treated patients. The model used a prevalence-based approach and applied the following assumptions:

- Prevalence rate of 9%
- Patients with severe disease of 5%
- Patients engaged with a specialist of 55% in year 1 and increasing to 70% in year 6
- Engaged patients who are uncontrolled on topical therapies of 100%
- Proportion of engaged patients meeting EASI requirement (EASI≥20) of 95%

The March 2020 submission had estimated the proportion of severe atopic dermatitis patients engaged with a specialist (55% to 70%) and the proportion of uncontrolled patients engaged with a specialist (68%). The PBAC noted that the proposed estimates changed the assumption regarding patients being adequately controlled on topical corticosteroids (from 68% to 100%) although the PBAC did not specify that this parameter be changed in the outcome of its March 2020 consideration. Table 4 shows the uptake rates that were applied to eligible patients.

[4] PBAC Outcomes from the July 2023 meeting https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2023-07/pbac-web-outcomes-07-2023.pdf

Table 4: Uptake applied to eligible patients

Estimated uptake in patients aged 18 to 100	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Initiating treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing treatment		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated uptake in patients aged 12-17						
Initiating treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The submission also included a grandfathered population. It assumed that prior to listing there would be [redacted] patients eligible for dupilumab and that [redacted] of these ([redacted]) would be supplied PBS treatment in the first year of listing, with an additional [redacted] ceasing treatment in each subsequent year.

Table 5: Estimates of all submissions

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
July 2018	Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
July 2019	Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
March 2020	Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
November 2020	Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final	Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Methods

Data extracted from the PBS claims database maintained by the Department of Health and Aged Care and processed by Services Australia were used for the analyses. Prescription data for dupilumab were extracted from 1 March 2021 up to and including 30 June 2023. Prescription data for other PBS medicines were extracted from 1 January 2017 up to and including 30 June 2023. These prescription data were used to analyse utilisation, the age and gender of patients, geographic location, time to resupply and prescriber type. These data were extracted on 17 August 2023.

Authorities data were extracted from the Authorities database, and matched to the prescription data to determine whether a prescription was supplied for atopic dermatitis or asthma. These matched data were used to analyse the consistency of utilisation by indication, and to analyse the data quality of PBS item codes the prescription was intended to treat.

Prescriptions for omalizumab, benralizumab and mepolizumab were extracted to compare dupilumab for asthma use to the market of biologics for asthma. Prescriptions for topical corticosteroids (creams, ointments and lotions) and pimecrolimus cream were extracted to investigate the prior supply of these medicines to patients who were supplied dupilumab for atopic dermatitis.

Treatment duration was analysed using the Kaplan-Meier method. A patient was censored if they were supplied a prescription within three times the median time to resupply prior to 30 June 2023 (i.e. 3×28 days). Three times the median time to resupply was used to test for breaks between supplies of dupilumab.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Services Australia Medicare date of processing data.[5]

Analyses were completed using SAS.

Results

Analysis of drug utilisation

Data quality

Table 6 and Figure 1 show prescriptions for dupilumab by the restriction determined from the PBS item code, and the restriction determined from the authority code. As dupilumab was listed for asthma one month after it was listed for atopic dermatitis, all prescriptions of dupilumab to the end of June 2023 are included.

[5] PBS statistics. Australian Government Services Australia. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

Table 6: Use of dupilumab by item code restriction and authority code restriction

Item code indication	Authority code indication	Prescriptions	Percent of subtotal	Percent of total
Asthma	Asthma	27,850	80%	11%
Asthma	Dermatitis	6,162	18%	2%
Asthma	Unknown	717	2%	0.3%
Asthma total		34,729		13%
Dermatitis	Dermatitis	218,022	98%	85%
Dermatitis	Asthma	3,634	2%	1%
Dermatitis	Unknown	1,142	1%	0.4%
Dermatitis total		222,798		87%
Total		257,527		

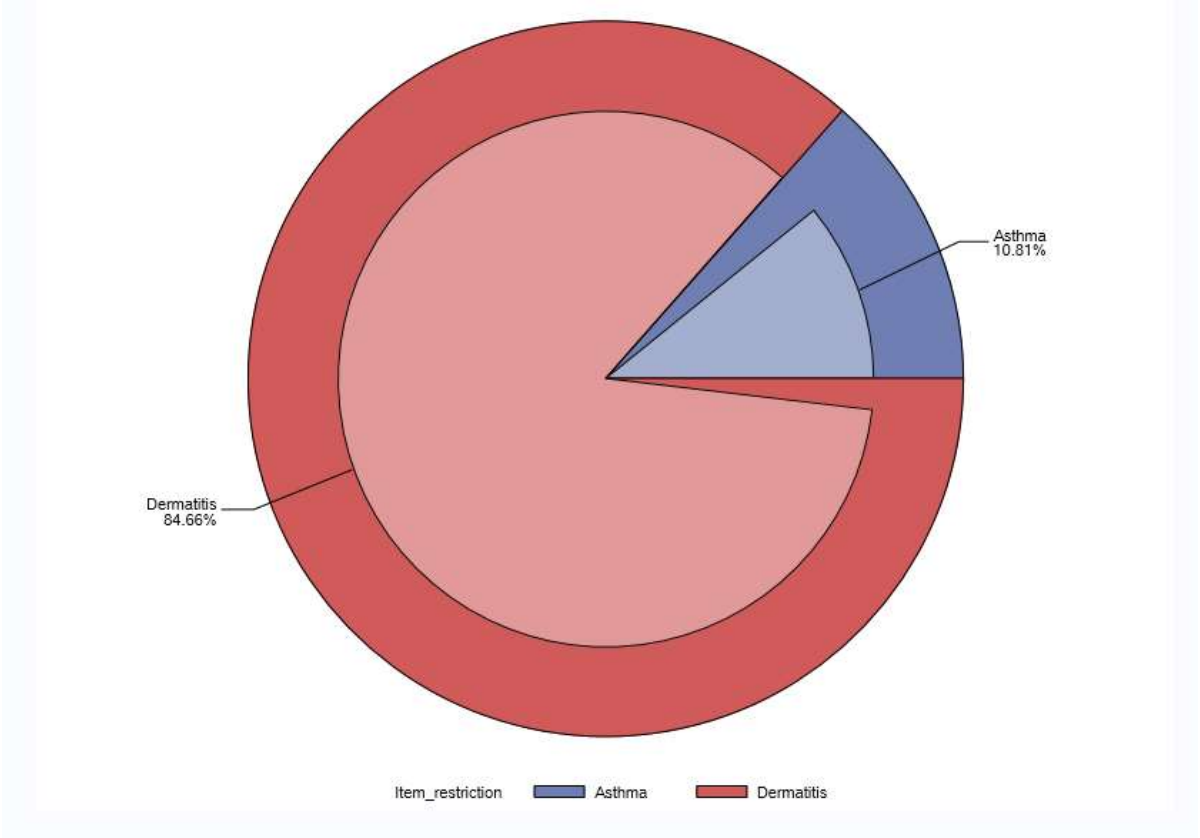

Figure 1: Use of dupilumab by item code restriction and authority code restriction

Figure 2 shows the use of dupilumab for severe asthma in the context of the monoclonal antibodies for severe asthma market, using authority code, since January 2017.

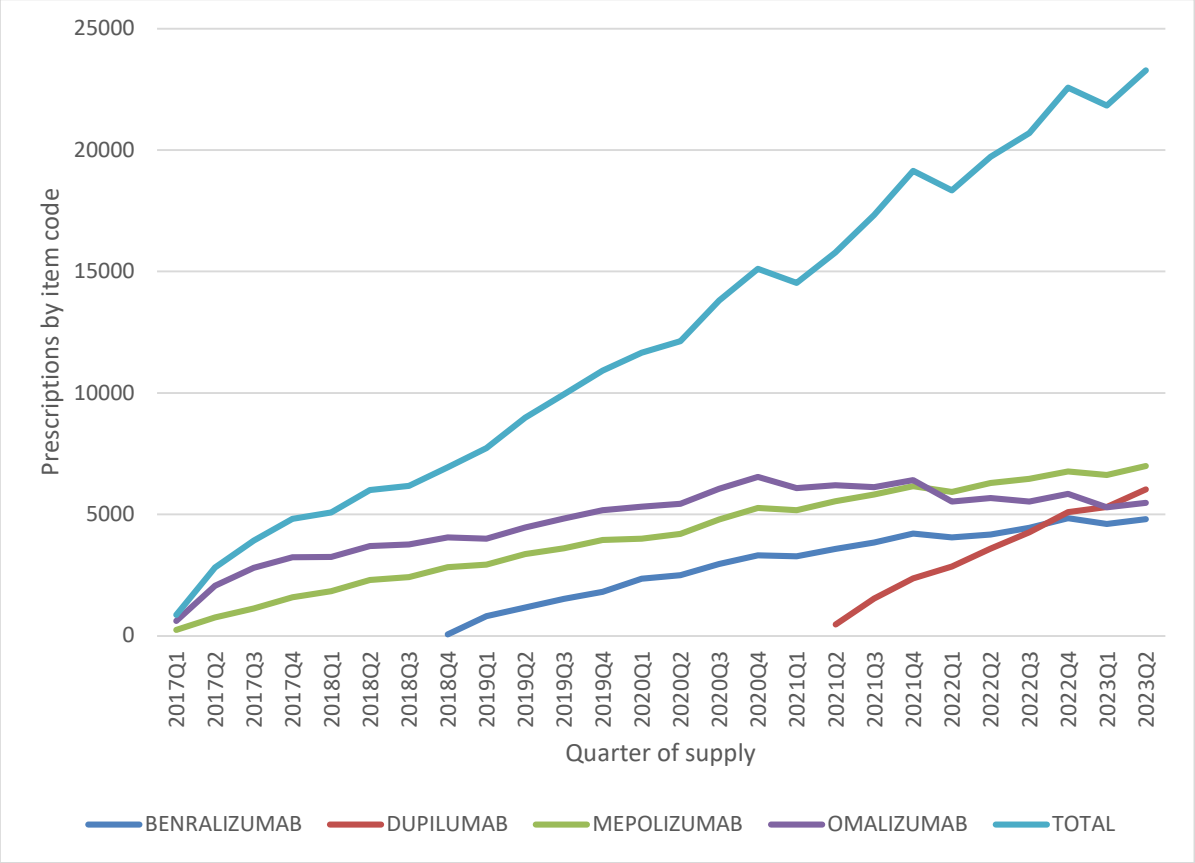

Figure 2: Use of monoclonal antibodies for severe asthma by authority code

Table 7 shows the number of patients who were supplied dupilumab for dermatitis by item code (16,995 patients) or authority code (16,373 patients), and whether they were supplied another monoclonal antibody (not dupilumab) for severe asthma by either item code, authority code, or both.

Table 7: Use of monoclonal antibodies for severe asthma in dermatitis patients

Restriction	Previous asthma supply by item code	Previous asthma supply by authority code	Patient count	Percent
Dermatitis by item code				
Dermatitis	False	False	16,526	97%
Dermatitis	True	False	98	1%
Dermatitis	True	True	371	2%
Dermatitis total (by item code)			16,995	
Dermatitis by authority code				
Chronic severe atopic dermatitis	False	False	16,253	99%
Chronic severe atopic dermatitis	True	False	57	0.3%
Chronic severe atopic dermatitis	True	True	63	0.4%
Dermatitis total (by authority code)			16,373	

It appears that the use of dupilumab is higher for dermatitis than for asthma, and that its use for asthma (by authority code) fits in the context of the asthma market. It is possible that there is more miscoding of asthma for dermatitis than dermatitis for asthma, possibly due to the relative market sizes. Overall it appears that the data quality by item code is good, as 98% of prescriptions supplied under a PBS item code for dermatitis had a matching authority code for dermatitis and 97% of patients who were supplied dupilumab under an item code for dermatitis had never been supplied a previous monoclonal antibody for asthma, noting that patients could have atopic dermatitis and asthma.

The subsequent analyses are of the use of dupilumab for atopic dermatitis using PBS item code, unless specified.

Overall utilisation

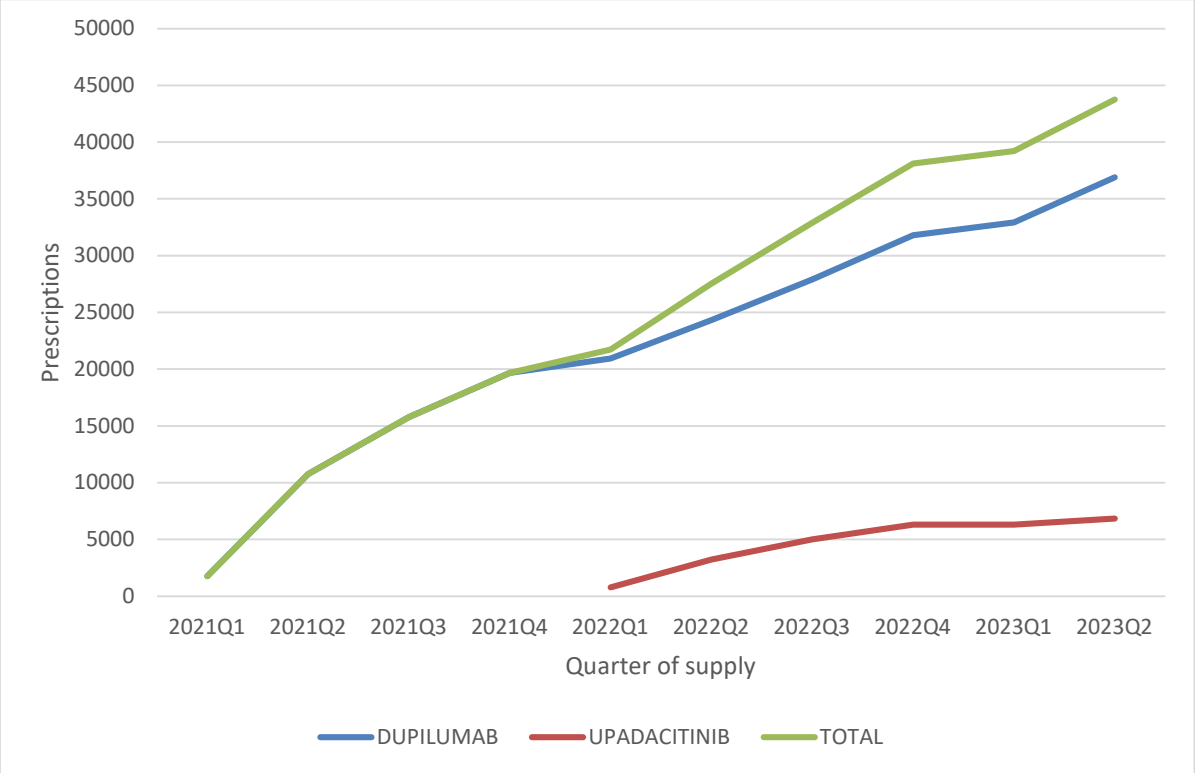

Figure 3: Prescriptions of dupilumab and upadacitinib for atopic dermatitis

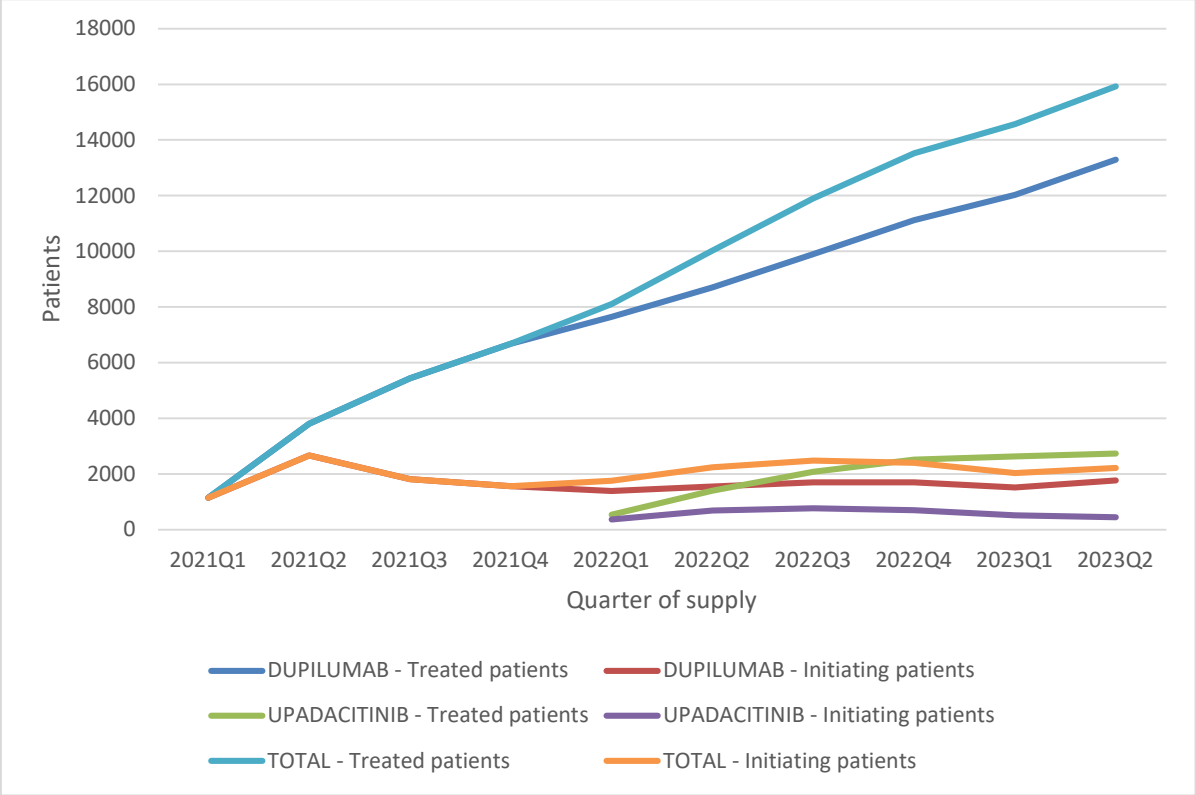

Figure 4: Patients supplied dupilumab and upadacitinib for atopic dermatitis

Figure 4 shows the market of dupilumab and upadacitinib prescriptions for atopic dermatitis by PBS item codes. Upadacitinib was listed February 2022 and dupilumab is the market leader, in the last 12 months of data there were more than five times as many prescriptions supplied for dupilumab than for upadacitinib. This report is mainly focused on the patients who were supplied dupilumab.

Table 8: Patient switching between dupilumab and upadacitinib

Sequence	Patient count	Percent of total
DUPILUMAB	15,886	78%
UPADACITINIB	3,339	16%
DUPILUMAB > UPADACITINIB	836	4%
UPADACITINIB > DUPILUMAB	125	0.6%
DUPILUMAB > UPADACITINIB > DUPILUMAB	77	0.4%
UPADACITINIB > DUPILUMAB > UPADACITINIB	19	0.1%
MORE THAN TWO SWITCHES	52	0.3%
TOTAL	20,334	

Table 8 shows the number of patients who have switched between dupilumab and upadacitinib, and that 95% of patients have not switched from their initial therapy. As dupilumab was listed 11 months before upadacitinib, it is more likely that patients will have switched from dupilumab to upadacitinib than from upadacitinib to dupilumab. However,

there are a small number of patients who initiated on upadacitinib and have switched to dupilumab.

Table 9: Patient and prescription counts between July 2022 and June 2023

	Dupilumab	Upadacitinib	Dupilumab/Upadacitinib
Prescriptions	129,527	24,478	5.3
Treated patients	46,344	9,968	4.6
Initiating patients (to therapy)	6,700	2,425	2.8

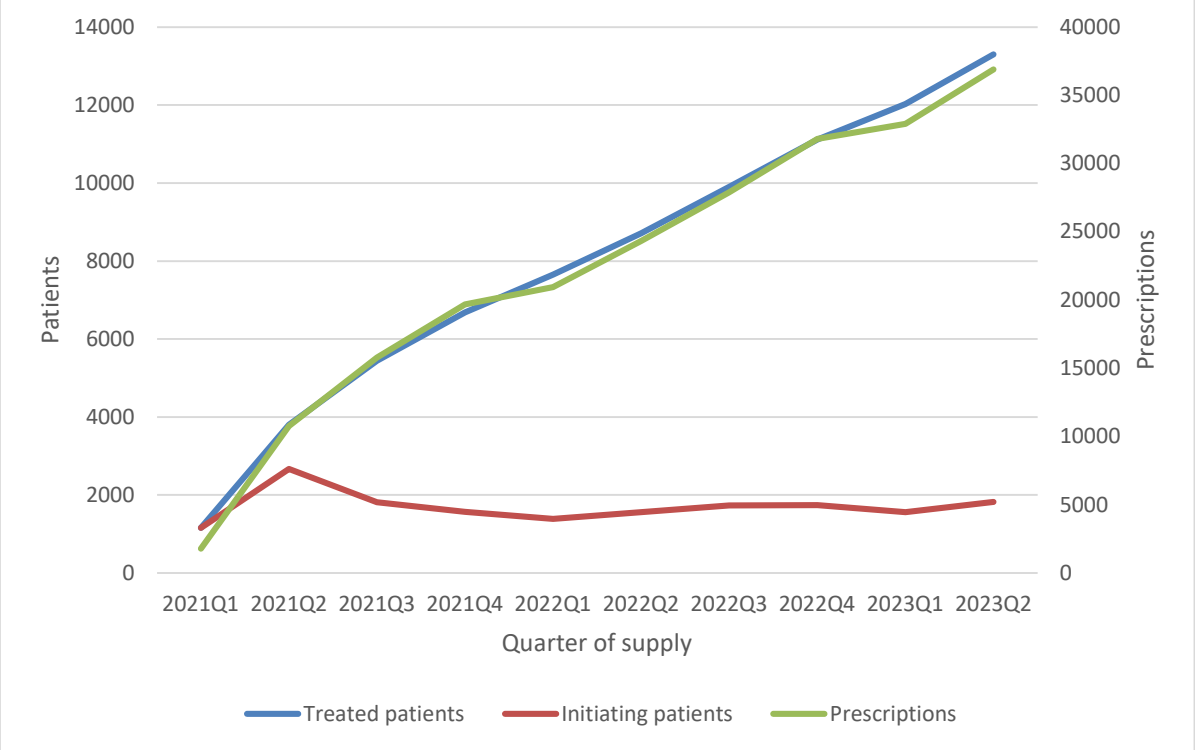

Figure 5: Patient and prescription counts for dupilumab for dermatitis

The number of initiating patients per quarter was highest in the second quarter of 2021, noting that the first quarter of 2021 only included one month of data as dupilumab was listed March 2021. The number of initiating patients per quarter has been fairly stable since the fourth quarter of 2021. The number of treated patients and supplied prescriptions have increased every quarter since listing, and the rate of growth does not appear to be decreasing.

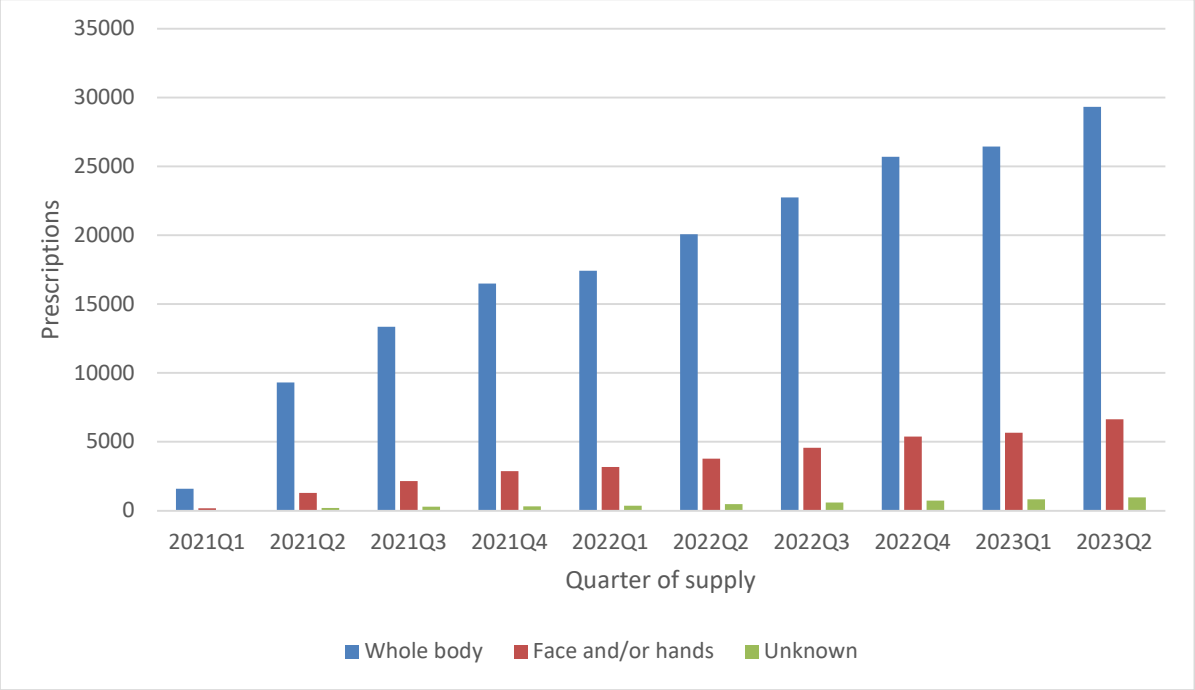

Figure 6: Prescriptions for whole body vs face and/or hands for dupilumab

The majority of use of dupilumab for atopic dermatitis has been supplied under authority codes for treatment of the whole body. In 2022, 82% of prescriptions were supplied under authority codes for treatment of the whole body, and 16% of prescriptions were supplied under authority codes for treatment of the face and/or hands. It appears the use for face and/or hands has increased, from January to June 2023 80% of prescriptions were supplied under authority codes for treatment of the whole body, and 18% of prescriptions were supplied under authority codes for treatment of the face and/or hands.

This is consistent with the prescription data presented to the July 2023 meeting. At the July 2023 meeting the PBAC noted the script data for dupilumab utilisation (March 2021 to August 2022) indicated that, of patients treated with dupilumab for severe AD, 17.6% were qualifying under the hands/face only criteria. The PBAC noted that in the most recent data available (March 2021 to March 2023) this proportion had increased to 19%.

Utilisation by relevant sub-populations/regions or patient level analysis

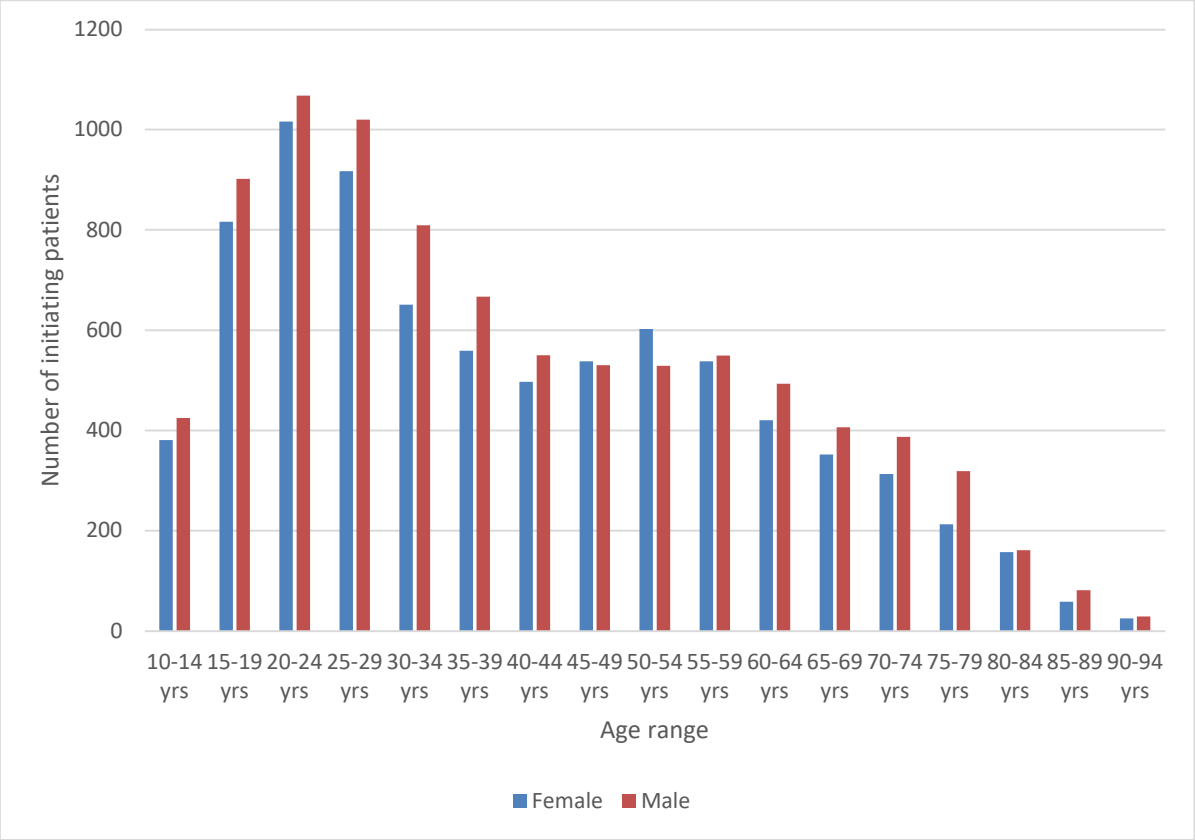

Figure 7: Age and gender of initiating patients for dupilumab

Figure 7 shows the age and gender of initiating patients of dupilumab for atopic dermatitis. The mean age at initiation was 40 years old, and the median was 36 years old. The group with the highest number of patients is those aged 20 to 24 years old. Patients aged 15 to 29 account for 34% of the 16,995 initiators. More males than female patients initiated in every age group, except in the 45 – 54 year range. Patients aged younger than 10 and older than 94 years old are not shown due to small numbers. Five patients initiated dupilumab for dermatitis aged younger than 12 years old.

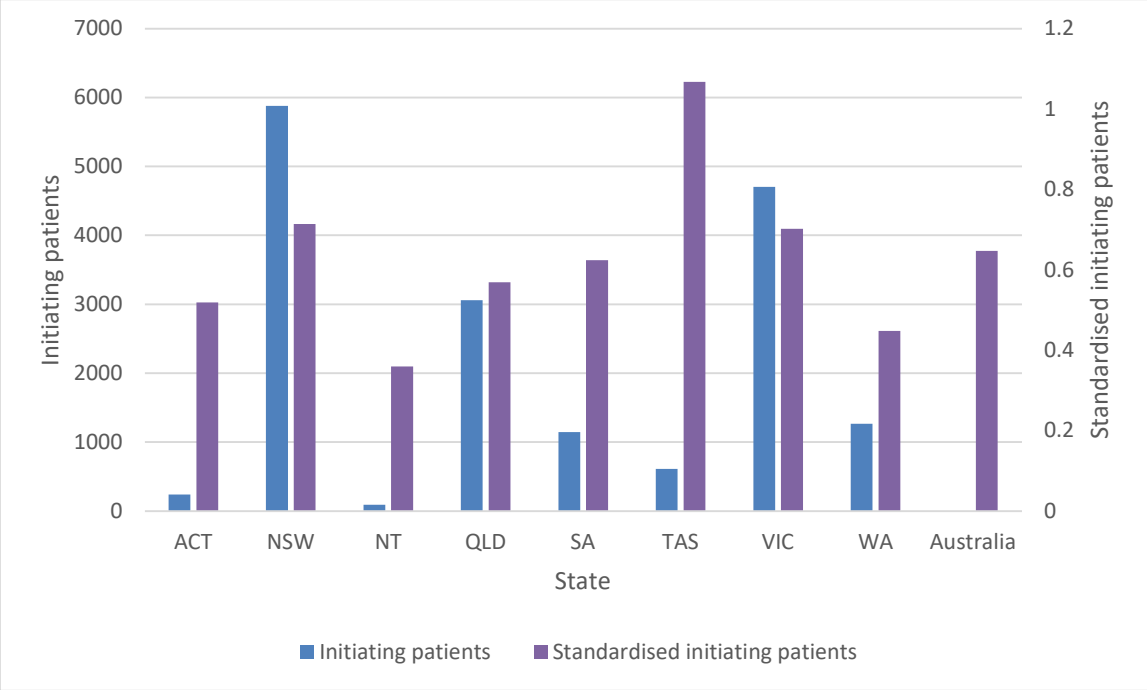

Figure 8: Number of initiating patients and standardised initiating patients by State

Note: Number of initiators for Australia (16,995) is not shown

Figure 8 counts every patient once for the State or Territory that the patient initiated in, using the patient's postcode. The State in Australia with the highest number of initiating patients was NSW, and the standardised data shows that the standardised number of initiating patients was highest in Tasmania. Northern Territory had the lowest number of initiating patients and the lowest standardised number of initiating patients.

Table 10: Prescriber type for initiating patients and prescriptions

Major Specialty Name	Initiating patients	Percent of total	Prescriptions	Percent of total
Dermatology	13,348	79%	176,765	79%
Immunology and Allergy	1,359	8%	17,542	8%
Unknown	558	3%	8,417	4%
GP	554	3%	8,375	4%
Respiratory and Sleep Medicine	532	3.1%	2,867	1.3%
Pathology	389	2.3%	5,861	3%
Paediatric Medicine	117	0.7%	1,558	0.7%
Internal Medicine	104	0.6%	1,110	0.5%
Other	34	0.2%	303	0.1%
Total	16,995		222,798	

Prescriber type is shown above for initiating patients and all supplied prescriptions. The proportions were similar across the two variables, with 87% of initiating patients and supplied prescriptions prescribed by dermatology or immunology and allergy specialists.

Table 11: Sequence of use of dupilumab and topical therapy

Sequence	Patients by item code	Percent by item code	Patients by authority code	Percent by authority code
CORTICOSTEROID > DUPILUMAB	15,702	92%	15,285	93%
DUPILUMAB	1,101	6.5%	728	4%
DUPILUMAB > CORTICOSTEROID	192	1.1%	168	1.3%
CORTICOSTEROID	-		140	0.9%
	16,995		16,367	

Note: Uses prescriptions from 2017 of topical corticosteroids (creams, ointments and lotions) and pimecrolimus cream.

Table 11 shows the sequence of use of topical therapies [topical corticosteroids (creams, ointments and lotions) and pimecrolimus cream] and dupilumab, using data from 1 January 2017. This analysis checks the sequence for patients supplied dupilumab under a PBS item code and under an authority code for atopic dermatitis. The proportion of patients who were supplied dupilumab without previously being supplied topical therapy was lower in patients when the authority code data is considered, 5.5% compared to 7.6%.

As this analysis uses supplies of dupilumab for dermatitis item codes only, the 140 patients who appear to have been supplied a topical corticosteroid or calcineurin inhibitor and not supplied dupilumab were supplied dupilumab under PBS item codes for asthma with authority codes for dermatitis.

Duration and number of treatments

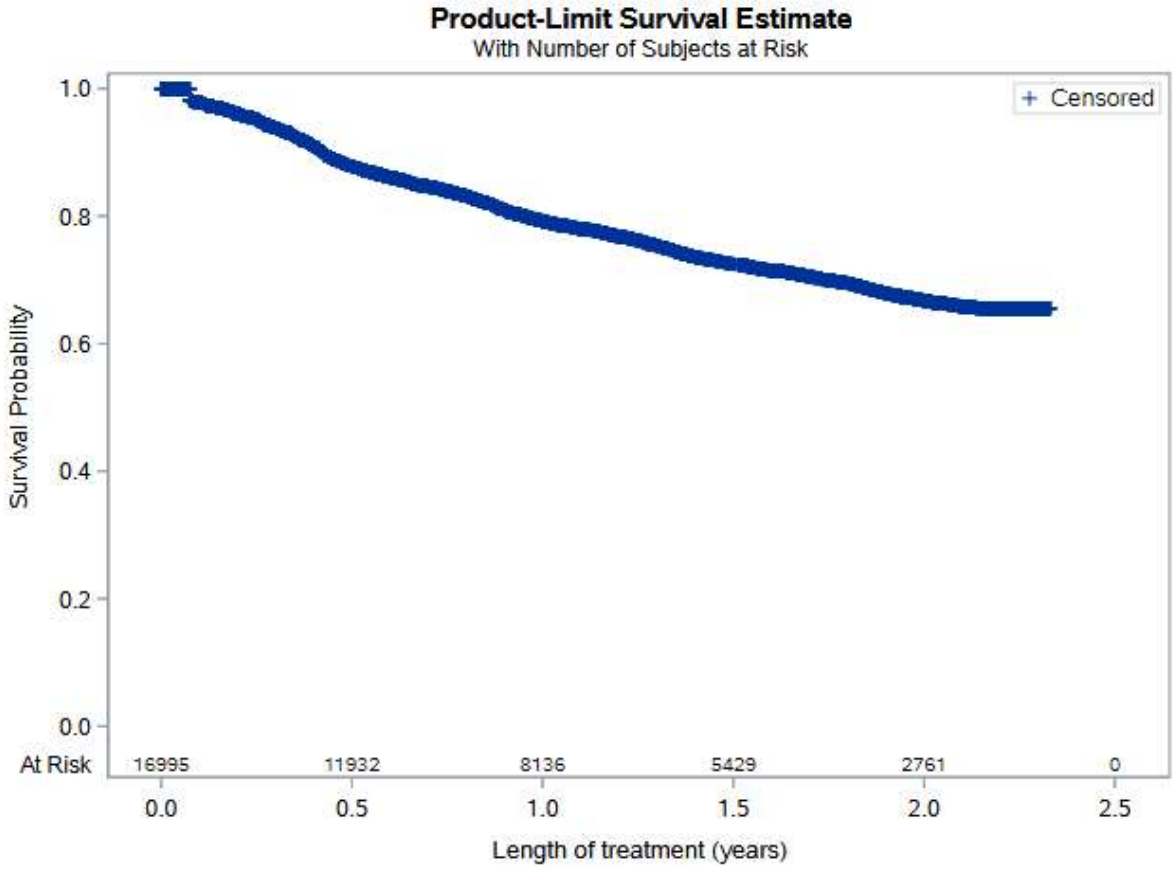

Figure 9: Length of treatment

Of the 16,995 patients who were supplied dupilumab under an item code for dermatitis, 78% (13,195) were supplied a prescription within 84 days (3 × median resupply of 28 days) of the last date of extracted data (30 June 2023) and were considered to be continuing treatment.

Of these 16,995 patients, 16% (2,788) were considered to have had a break in therapy as there was more than 84 days between supplies of dupilumab at least once during their course of treatment, and 84% (14,207) did not. There were 11,027 patients (65%) who did not have a break and were considered to be continuing treatment.

The data were too immature to assess the treatment duration with dupilumab, as the median time on therapy could not be estimated. Using data to the end of June 2023, the mean length of treatment was estimated to be 1.72909 years with a standard error of 0.00614 years.

Table 12: Number of treatments

Year of patient treatment	Number of patients	Mean	Median
Year 1	16,995	9.33	10
Year 2	7,742	7.57	8
Year 3	2,395	2.32	2

Table 12 shows the mean and median number of supplies patients received in each year of treatment, from the date the patient initiated. The data for year 3 is immature as the data extraction included two years and three months of dupilumab prescriptions.

Analysis of expenditure

Table 13: Expenditure by quarter and year of supply

Supply quarter	Benefit paid
2021Q1	$ 3,052,160.59
2021Q2	$ 18,528,742.88
2021Q3	$ 27,160,444.04
2021Q4	$ 33,897,033.17
2021 total	**$ 82,638,380.68**
2022Q1	$ 36,014,602.76
2022Q2	$ 41,850,590.02
2022Q3	$ 48,033,485.13
2022Q4	$ 54,794,744.55
2022 total	**$ 180,693,422.46**
2023Q1	$ 56,934,718.13
2023Q2	$ 63,865,613.43
2023 total	**$ 120,800,331.56**
Total since listing	**$ 384,132,134.70**

Note: 2023 includes January to June 2023
Benefits are based on the date of supply, there may be small differences between publicly available Medicare Australia date of processing data.

The total benefit paid for dupilumab for atopic dermatitis since PBS listing to the end of June 2023 is $384 million, based on published prices. A special pricing arrangement is in place.

Analysis of actual versus predicted utilisation

The submission used a prevalence-based approach to predict the use of dupilumab. The number of patients and prescriptions were underestimated, and the difference between predicted and actual values was higher in year 2 than year 1.

Table 14: Actual versus predicted utilisation of dupilumab

			Year 1	Year 2
Patients	Initiating	Predicted	[redacted]	[redacted]
	Continuing		[redacted]	[redacted]
	Grandfathered continuing		[redacted]	[redacted]
	Total		[redacted]	[redacted]
	Initiating	Predicted	[redacted]	[redacted]
		Actual	7,760	6,135
		Difference	[redacted]	[redacted]
	Total treated	Predicted	[redacted]	[redacted]
		Actual	8,011	13,628
		Difference	[redacted]	[redacted]
Prescriptions		Predicted	[redacted]	[redacted]
		Actual	61,113	112,753
		Difference	[redacted]	[redacted]

The submission estimated [redacted] patients would be eligible for treatment in year 1, and [redacted] would be eligible for treatment in year 2. It is unknown whether the epidemiological assumptions underestimated the number of eligible patients, whether the uptake assumptions were underestimated, or due to a combination of both. If the epidemiological assumptions were correct then the uptake rates would have been 16% in year 1 and 25% in year 2, including initiating, continuing and grandfathered patients.

As the submission estimated uptake of initial and continuing patients each year, it did not predict duration of treatment, except in grandfathered patients where it predicted there would be [redacted] patients eligible for dupilumab prior to listing and that 83.2% of these ([redacted]) would be supplied PBS treatment in the first year of listing, with an additional 3.2% ceasing treatment in each subsequent year.

Table 15: Actual versus predicted utilisation of dermatitis market

			Year 1	Year 2
Patients	Initiating	Predicted	[redacted]	[redacted]
	Continuing		[redacted]	[redacted]
	Grandfathered continuing		[redacted]	[redacted]
	Total		[redacted]	[redacted]
	Initiating	Predicted	[redacted]	[redacted]
		Actual	8,137	9,193
		Difference	[redacted]	[redacted]
	Total treated	Predicted	[redacted]	[redacted]
		Actual	8,137	16,691
		Difference	[redacted]	[redacted]
Prescriptions		Predicted	[redacted]	[redacted]
		Actual	61,320	131,909
		Difference	[redacted]	[redacted]

Table 15 compares the estimated use of dupilumab to the market for atopic dermatitis, including dupilumab and upadacitinib. When upadacitinib is included in the actual use, the utilisation beyond expectations in terms of the number of patients and prescriptions increases further.

Discussion

The use of dupilumab for atopic dermatitis has been higher than predicted. The number of treated patients and supplied prescriptions per quarter have increased every quarter since listing, and the rate of growth does not appear to be decreasing. The number of treated patients was within the estimate of eligible patients, however it is unknown whether the higher use is due to higher uptake than predicted or use outside the restriction in patients with mild to moderate disease.

It is often noted that medicines that require needles to be administered are likely to have lower uptake than oral medicines, however the method of administration does not appear to have affected the uptake of dupilumab. Upadacitinib is an oral alternative to dupilumab, listed February 2022. The uptake of upadacitinib has been reasonably small in the context of the market, with 2.8 times more patients initiating therapy to dupilumab than upadacitinib and more than five times as many prescriptions supplied for dupilumab than upadacitinib between July 2022 and June 2023.

The clinical criteria in the PBS restriction state that the patient must have a Physicians Global Assessment (PGA) (5-point scale) baseline score of at least 4, an Eczema Area and Severity Index (EASI) baseline score of at least 20, and an age appropriate Dermatology Life Quality Index (DLQI) baseline score despite treatment with daily topical therapy, for at least 28 days. The majority of patients supplied dupilumab (92%) were supplied prior topical therapy through the PBS, consistent with the restriction.

The treatment criteria in the PBS restriction state that the patient must be treated by a dermatologist or a clinical immunologist. It appears the majority of prescribers have met this criteria as 87% of initiating patients and supplied prescriptions were prescribed by dermatology or immunology and allergy specialists. The Northern Territory had the lowest number of initiating patients and the lowest standardised number of initiating patients which may reflect access issues to dermatologists and immunologists in rural and remote areas.

The July 2022 submission noted that the utilisation estimates did not account for patients with severe face and/or hand atopic dermatitis who would not otherwise meet the criteria for severe atopic dermatitis. The proportion of use to treat the face and/or hands appears to be increasing and accounted for 16% of prescriptions supplied in 2022 and 18% of prescriptions supplied in from January to June 2023.

DUSC consideration

DUSC noted the analyses of data quality between PBS item codes and authority codes showed that errors in coding are very small, and considered there was no issue with dermatitis and asthma markets overlapping, although patients could have both atopic dermatitis and asthma. DUSC considered that it was not necessary to be concerned about dupilumab being dispensed under the wrong item code.

DUSC noted that dupilumab has the majority of the market share over upadacitinib, and that dupilumab has more initiating patients in the recent time period since upadacitinib was PBS listed. DUSC noted only a small proportion (5%) of patients have switched between therapies, and commented that the black box warning on upadacitinib may have reduced its attractiveness as an oral therapy. DUSC suggested it is likely that dupilumab will continue to have the majority market share in the future. DUSC commented that the number of treated patients is increasing over time which suggests patients are staying on treatment and not ceasing. DUSC noted that the median length of treatment could not be estimated and commented that this confirms patients are remaining on treatment.

DUSC noted that the five year age group with the highest number of initiating patients was those aged 20 to 24 years old. DUSC considered this may impact the use of dupilumab in the future if younger patients are likely to remain on treatment for many years.

DUSC noted that the Northern Territory (NT) had the lowest number of initiating patients and the lowest standardised number of initiating patients. DUSC noted the response from Eczema Support Australia commented that for most people, dermatitis is generally made worse by cold dry climates. DUSC agreed with the response that the low use of dupilumab in the NT may reflect an access issue and that there may be lower prevalence in the NT due to the climate. DUSC noted that the standardised number of initiating patients was highest in Tasmania and noted the response from Eczema Support Australia commented that there was compassionate access available for dupilumab in Tasmania.

DUSC noted the sequence of use of dupilumab and topical therapy showed that 92% of patients were supplied prior use of topical corticosteroids or pimecrolimus cream under the

PBS. DUSC commented that topical treatment can be supplied over the counter, but considered patients with severe atopic dermatitis should be on high dose topical treatment which does require a prescription.

DUSC noted the analysis of predicted versus actual utilisation showed that the use of dupilumab was underestimated, and further underestimated when compared to the market use of dupilumab and upadacitinib. DUSC noted that there were more initiating patients than predicted, and that these patients were treated for longer than predicted. DUSC commented that topical treatments can be time consuming to apply for patients with severe disease and the injection appears to be well tolerated by patients. DUSC noted that it cannot be determined from the PBS supply data whether patients are being treated outside of the restriction, and considered that there may or may not be use of dupilumab in patients with mild to moderate disease.

DUSC commented that dermatitis can be a seasonal disease, and patients may use varying amounts of topical treatment through a year. However, patients may choose to stay on dupilumab rather than being treated seasonally. DUSC commented that patients do not rebound when dupilumab is stopped, but considered it may have taken time for patients to access a specialist prescriber and they may be concerned about getting back into a specialist if treatment is ceased. DUSC considered that given the young age of initiating patients and the potential for treatment to become lifelong, there may need to be consideration given to discontinuing patients from dupilumab during periods of less severe disease, without restricting future access.

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Sanofi welcomes the findings of the DUSC report which confirms that the use of dupilumab is higher than initially anticipated and that the majority of patients met the restriction criteria in terms of prior therapies.

AbbVie: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health and Aged Care has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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