Biologics for uncontrolled severe allergic and eosinophilic asthma

Drug utilisation sub-committee (DUSC)

October 2019

Abstract

Purpose

DUSC requested a review of biologics for uncontrolled severe asthma when 24 months of data were available since the listing of mepolizumab. When DUSC last considered omalizumab for review (September 2017), it decided to delay further review of omalizumab until sufficient mepolizumab data were available.

Following publication of the outcomes from the severe asthma stakeholder meeting, DUSC considered it timely to consider the use of biologics for the treatment of uncontrolled severe asthma.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

- Omalizumab: 1 July 2011
- Mepolizumab: 1 January 2017
- Benralizumab: 1 December 2018

Data Source / methodology

Data were extracted from the PBS supplied prescription database from the date of first listing of a severe asthma biologic (1 July 2011) to 30 June 2019. Analyses included prescription counts, new and prevalent patient counts, treatment sequence, switching, length of treatment and prescriber type. A predicted versus actual analysis of mepolizumab in the first 24 months of listing was also conducted.

Key Findings

- In 2018,
    - 1,250 patients were supplied omalizumab for the treatment of severe allergic asthma. Of these, 444 received their first PBS supply in that year.
    - 1,222 patients received PBS-subsidised treatment for severe eosinophilic asthma, of which 665 were new to treatment that year.
    - The number of prescriptions supplied for severe asthma biologics was over 24,000. There were 14,620 prescriptions dispensed for omalizumab and 9,415 prescriptions dispensed for mepolizumab. A small number of prescriptions were dispensed for benralizumab (listed December 2018).

    - expenditure for severe asthma biologics was $31.3 million based on the published prices (special pricing arrangements apply). This expenditure was mostly attributed to omalizumab and mepolizumab in close to a 1:1 ratio, with little expenditure for benralizumab (listed 1 December 2018).
- There has been a high rate of growth in the number of treated prevalent severe eosinophilic asthma patients since the listing of mepolizumab, with the rate of growth further increasing with the listing of benralizumab in December 2018. These patients exceeded the number of patients supplied omalizumab for severe allergic asthma in the first half of 2019.
- In quarter 2 of 2019, prescriptions dispensed for eosinophilic asthma exceeded prescriptions dispensed for allergic asthma for the first time.
- Use of mepolizumab was higher than predicted in the first two years of PBS listing.

Purpose of analysis

DUSC requested a review of biologics for uncontrolled severe asthma when 24 months of data were available since the listing of mepolizumab. When DUSC last considered omalizumab for review (September 2017), it decided to delay further review of omalizumab until sufficient mepolizumab data were available.

DUSC noted a stakeholder meeting regarding severe asthma was held on 14 December 2018. A preliminary analysis of omalizumab, mepolizumab and benralizumab use was provided to attendees. DUSC noted that there had been a steep increase in the number of treated patients and prescriptions. DUSC further noted it was suggested that switching between agents may be prolonging time on therapy and increasing the number of prevalent patients. DUSC considered it was timely to review the use of biologics for the treatment of severe uncontrolled asthma.

Background

Clinical situation[1]

There are currently three biologic medicines listed on the PBS for the treatment of severe asthma. Omalizumab was the first biologic medicine listed on the PBS for uncontrolled severe allergic asthma. PBS eligibility criteria were developed based predominantly on relevant omalizumab clinical trials presented to the PBAC and stakeholder consultation. The PBS restrictions for mepolizumab and benralizumab for the treatment of eosinophilic asthma were developed for consistency with the omalizumab PBS listing.

An article published in the American College of Allergy, Asthma & Immunology journal in 2016[2], not limited to severe asthma, examined the frequency and overlap of atopic, eosinophilic, and T helper 2 (TH2)-high asthma phenotypes, the latter using a non-standard definition (IgE ≥100 IU/L and blood eosinophils ≥140/µl). The study included 269 children and 310 adults aged 6-64 years across the spectrum of asthma severity. At a higher eosinophil cut-off point, a greater proportion of eosinophilic asthma can be classified as atopic or TH2-high, but a lower proportion of atopic or TH2-high asthma can be classified as eosinophilic. Approximately 70% or more of children and adults with asthma were 1 of these 3 phenotypes.

Pharmacology

Omalizumab is a monoclonal antibody that blocks a substance produced by the body called immunoglobulin E (IgE). IgE is involved in causing symptoms of allergic asthma.[3]

Mepolizumab[4] and benralizumab[5] both target the interleukin-5 (IL-5) pathway. Mepolizumab is a monoclonal antibody that blocks a protein called IL-5. Benralizumab is a monoclonal antibody that binds to the IL-5 receptor thus blocking IL-5 activity. These medicines both limit the production of eosinophils (a type of white blood cell) from the bone marrow. Some people with severe asthma have too many eosinophils in the blood and lungs, causing inflammation of the airways. Mepolizumab and benralizumab lower the

number of eosinophils in the bloodstream and lungs to prevent worsening asthma symptoms and flare-ups.

Therapeutic Goods Administration (TGA) approved indications

Omalizumab[6] is indicated for the management of adult and adolescent patients with moderate to severe allergic asthma, who are already being treated with inhaled steroids, and who have serum immunoglobulin E levels corresponding to the recommended dose range. In children aged 6 to <12 years, omalizumab is indicated as add-on therapy to improve asthma control in patients with severe allergic asthma who have documented exacerbations despite daily high dose inhaled corticosteroids, and who have immunoglobulin E levels corresponding to the recommended dose range.

Omalizumab is also indicated for adults and adolescents (12 years of age and above) with chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment.

Mepolizumab[7] is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over. Mepolizumab is also indicated as an add-on treatment for relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients aged 18 years and over; but is not PBS listed for this indication.

Benralizumab[8] is indicated as add-on therapy in patients aged 12 years and over with severe eosinophilic asthma (blood eosinophil count ≥300 cells/µL or ≥150 cells/µL if on oral corticosteroid treatment).

Dosage and administration

Omalizumab[6] is administered subcutaneously by a healthcare provider every two or four weeks. Doses and dosing frequency are determined by baseline serum total IgE level, measured before the start of treatment, and body weight. The dose range is 75 mg - 600 mg once per four weeks, or 225 mg - 375 mg every two weeks.

Mepolizumab[7] should be prescribed by a specialist experienced in the diagnosis and treatment of severe asthma. Mepolizumab should be reconstituted and administered subcutaneously by a health care professional. The recommended dose is 100 mg of mepolizumab administered by subcutaneous injection once every 4 weeks.

Benralizumab[8] should be prescribed by a health care professional in consultation with a specialist physician experienced in the diagnosis and treatment of severe asthma. The recommended dose is 30 mg of benralizumab by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. Benralizumab is intended for long-term treatment. A decision to continue therapy should be made at least annually based on disease severity and level of exacerbation.

The half-lives of the biologics used to treat severe asthma are as follows:

- Benralizumab = 15 days
- Mepolizumab = 16-22 days
- Omalizumab = 22 days (±8 days)

Therefore these medications would not be expected to be eliminated from the body until 75-110 days (2.5-4 months) after the last injection (based on clearance requiring five elimination half-lives).[1]

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 (August 2019)

Omalizumab, mepolizumab and benralizumab are listed on the Section 100 (S100) Highly Specialised Drugs (HSD) Program with Complex Authority Required listings. Prescribers are required to obtain written authority approval for initial and continuing prescriptions from Services Australia before prescribing on the PBS.

Table 1: PBS listing of omalizumab for severe allergic asthma

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
10109C; 10973M (paed)	OMALIZUMAB omalizumab 150 mg/mL injection, 1 mL syringe (Public)	1	0	$410.00	Xolair® Novartis Pharmaceuticals Australia Pty Limited
10122R; 10968G (paed)	OMALIZUMAB omalizumab 150 mg/mL injection, 1 mL syringe (Private)	1	0	$433.69	Xolair® Novartis Pharmaceuticals Australia Pty Limited
10118M; 10967F (paed)	OMALIZUMAB omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe (Public)	1	0	$205.00	Xolair® Novartis Pharmaceuticals Australia Pty Limited
10110D; 10956P (paed)	OMALIZUMAB omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe (Private)	1	0	$220.49	Xolair® Novartis Pharmaceuticals Australia Pty Limited

Source: PBS website. Special Pricing Arrangements apply. Excludes item codes for chronic spontaneous urticaria. Paed = paediatric. Note: the number of repeats for some omalizumab item codes were changed in December 2019 to better reflect authority approvals in practice. Refer to the PBS website for current listing information.

Table 2: PBS listing of mepolizumab for severe eosinophilic asthma

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11003D (private, initiating)	MEPOLIZUMAB 100 mg injection, 1 vial	1	7	$1685.29	Nucala® GlaxoSmithKline Australia Pty Ltd
11014Q (private, continuing)	MEPOLIZUMAB 100 mg injection, 1 vial	1	5	$1685.29	Nucala® GlaxoSmithKline Australia Pty Ltd
10996R (public, initiating)	MEPOLIZUMAB 100 mg injection, 1 vial	1	7	$1638.00	Nucala® GlaxoSmithKline Australia Pty Ltd
10980X (public, continuing)	MEPOLIZUMAB 100 mg injection, 1 vial	1	5	$1638.00	Nucala® GlaxoSmithKline Australia Pty Ltd

Source: PBS website. Special Pricing Arrangements apply.

Table 3: PBS listing of benralizumab for severe eosinophilic asthma

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11523L (private, initiating)	BENRALIZUMAB benralizumab 30 mg/mL injection, 1 mL syringe	1	4	$3358.29	Fesenra® AstraZeneca Pty Ltd
11504L (private, continuing)	BENRALIZUMAB benralizumab 30 mg/mL injection, 1 mL syringe	1	2	$3358.29	Fesenra® AstraZeneca Pty Ltd
11549W (public, initiating)	BENRALIZUMAB benralizumab 30 mg/mL injection, 1 mL syringe	1	4	$3311.00	Fesenra® AstraZeneca Pty Ltd
11529T (public, continuing)	BENRALIZUMAB benralizumab 30 mg/mL injection, 1 mL syringe	1	2	$3311.00	Fesenra® AstraZeneca Pty Ltd

Source: PBS website. Special Pricing Arrangements apply.

Restrictions (abridged)

The criteria for initial PBS-subsidised treatment with biologics for severe asthma are:

- Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma
- Patient must be under the care of the same physician for at least 6 months OR patient must have been diagnosed by a multidisciplinary severe asthma clinic team
- Patient must have a diagnosis of asthma defined by: (i) forced expiratory volume (FEV1) reversibility or (ii) airway hyperresponsiveness or (iii) peak expiratory flow (PEF) as defined in the restriction
- Patient must have a duration of asthma of at least 1 year
- Patient must have forced expiratory volume (FEV1) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months
- Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented
- The treatment must not be used in combination with, or within 6 months of treatment with, other PBS-subsidised biologics for severe asthma
- Patient must be aged 12 years or older

For allergic asthma (omalizumab):

- Patient must have past or current evidence of atopy, documented by skin prick testing or RAST
- Patient must have total serum human immunoglobulin E greater than or equal to 30 IU/mL

For eosinophilic asthma (mepolizumab and benralizumab):

- Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months

The maximum duration of initial treatment is 32 weeks for mepolizumab and benralizumab, with response assessed at 26-30 weeks for mepolizumab and 20-24 weeks for benralizumab. The maximum duration of initial treatment is 28 weeks for omalizumab, with response assessed at 22-26 weeks. For the purposes of continuing to receive PBS-subsidised treatment with biologics for severe asthma, an adequate response is defined as:

(a) a reduction in the Asthma Control Questionnaire (ACQ-5) score of at least 0.5 from baseline, OR

(b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ-5 score from baseline, OR

An additional continuation criterion for omalizumab patients transitioned from the paediatric to the adolescent/adult restriction:

(c) a reduction in the time-adjusted exacerbation rates compared to the 12 months prior to baseline

There are separate PBS restrictions for omalizumab in patients aged 6 to <12 years.

For full details of the current PBS listings refer to the PBS website.

Date of listing on PBS

- Omalizumab: 1 July 2011
- Mepolizumab: 1 January 2017
- Benralizumab: 1 December 2018

Changes to listing

Table 4: Changes to PBS listing for severe asthma biologics

Date	Change to listing
July 2011	Omalizumab listed
August 2014	Omalizumab pre-filled syringe added
May 2015	Omalizumab – amendment to allow patients to initiate if they have received a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months
June 2016	Omalizumab – Baseline IgE level reduced from 75 IU/mL to 30 IU/mL
December 2016	Omalizumab new item for children 6-11 years (accounted for 2.7% of omalizumab use in 2017)
January 2017	Mepolizumab added
	Omalizumab • Change to clinical criteria to reduce the requirement to document FEV1 <80% on 3 or more occasions in the previous 12 months to one or more occasions in the last 12 months. • Addition: 'The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised mepolizumab.'
June 2018	Omalizumab <u>Alteration note</u> • Initial treatment note …iii) A patient has received prior PBS-subsidised mepolizumab and wishes to commence treatment with omalizumab after a treatment break of at least 6 months. All applications for initial treatment ~~for non-grandfathered patients~~ will be limited to provide for a maximum of 28 weeks of therapy of omalizumab… <u>Alteration restriction</u> Amalgamated initial treatment balance of supply with continuing treatment amalgamation of supply, with the requirements for under these restrictions otherwise unchanged.
July 2018	Mepolizumab - extended eosinophil blood test validity period from 6 weeks to 12 months (to align with the omalizumab listing for uncontrolled severe allergic asthma).
December 2018	Benralizumab added
	Omalizumab - 'The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised benralizumab or mepolizumab.' Mepolizumab - 'The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised benralizumab or omalizumab.'
February 2019	Benralizumab - change to grandfathered restriction: • Patient must have demonstrated an adequate response if the patient has received at least 24 weeks of treatment of non-PBS subsidised benralizumab for this condition • Change to "Optimised asthma therapy" definition - failure to achieve adequate control and assessment for continuing eligibility more fully described

Current PBS listing details are available from the PBS website.

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

This section focuses on PBAC considerations for mepolizumab, and for severe asthma generally. Information regarding the PBAC considerations for omalizumab is available in the Public Release Document from the June 2014 DUSC meeting or the Public Summary Documents. Details of the recommendation for benralizumab are available in the March 2018 Public Summary Document.

Mepolizumab - March 2016

The PBAC rejected the listing of mepolizumab on the basis of high and uncertain cost-effectiveness in the comparison with standard of care, and inappropriate equi-effective doses proposed in the cost-minimisation analysis against omalizumab. The PBAC accepted that mepolizumab had a clinical place in the treatment of eosinophilic asthma, noting advice received from the TSANZ clarifying that there is sufficient distinction to allow recognition and application of different therapies to this distinct asthma phenotype.

The PBAC agreed with the DUSC's estimates of the financial implications, noting that although the DUSC considered Year 1 estimates to be underestimated, the DUSC considered the total estimate of use over five years may be reasonable.

For further details refer to the Public Summary Document from the March 2016 PBAC meeting.

Mepolizumab - July 2016

The minor resubmission presented a revised budget impact which incorporated DUSC revisions and the updated costs associated with omalizumab administration and monitoring.

The PBAC recommended the listing of mepolizumab on a cost-minimisation basis with omalizumab. The PBAC noted that the minor resubmission and sponsor's pre-PBAC response presented arguments for incorporating utilisation data into the calculation of equi-effective doses, but maintained their previous view that the equi-effective doses should be derived from clinical trial data. The equi-effective doses accepted by PBAC were mepolizumab 100 mg and omalizumab 398 mg.

For further details refer to the Public Summary Document from the July 2016 PBAC meeting.

Mepolizumab - November 2017

The PBAC recommended extending the eosinophil blood test validity period from 6 weeks to 12 months in the mepolizumab listing to align with the omalizumab listing for uncontrolled severe allergic asthma.

For further details refer to the Public Summary Document from the November 2017 PBAC meeting.

March 2018[1]

The current PBS restrictions for biologics for severe asthma do not permit use of a biologic in combination, or within six months of treatment with another PBS-subsidised biologic. The six-month treatment break was originally based on the omalizumab restriction, and related to re-trial of omalizumab in patients with inadequate response, and this requirement was subsequently also applied to switching between different biologics. The treatment interval applies regardless of the reason for switching, including if the switch is due to adverse events, partial or non-responsiveness, or patient/clinician choice.

The PBAC received two minor submissions at the March 2018 PBAC meeting requesting removal of the six-month interval when switching between biologic therapies. At this time, the PBAC noted that support for the change was provided by two organisations: the Thoracic Society of Australia and New Zealand; and the Centre of Research Excellence in Severe Asthma, both proposing that the six-month interval between switching be removed or replaced with a shorter (1-2 month) interval. The input noted potential risks associated with a six-month treatment interval in patients with severe asthma including:

- Increased risk of asthma exacerbations.
- Increased requirements for oral corticosteroids, with corresponding increase in risk of adverse events.

The PBAC deferred making a decision about the request to remove the six-month treatment break when switching between biologics, noting that further stakeholder consideration of the issue should take into account the inter-related issues associated with re-trialling, switching and cycling of biologics in asthma.

For further details refer to the Public Summary Documents for benralizumab and mepolizumab from the March 2018 PBAC meeting.

Severe Asthma Stakeholder Meeting - December 2018

In December 2018, a severe asthma stakeholder meeting was held to receive advice and clinical perspectives on the treatment of severe asthma within the context of effective use of biologic medicines. Participants provided advice regarding initiation criteria, continuation criteria and re-trialling, switching and cycling of biologics in asthma. Stakeholders highlighted the importance of the following key issues:

- Reducing exacerbations and OCS use in the severe asthma population
- Having a suitable method to assess patients' response and/or symptom control
- Re-examining certain aspects of the PBS restriction for biologic medicines to ensure that those most at risk are not excluded.

The PBAC Chair stated the outcomes of the meeting would be used to inform future PBAC considerations on this issue. The PBAC Chair indicated a willingness of the PBAC to work with the Department and sponsors with a view to amending certain aspects of the PBS criteria for biologic medicines.

Approach taken to estimate utilisation

The March 2016 submission used both epidemiological and market share approaches to estimate the expected utilisation of mepolizumab:

- A market share approach was used for patients eligible for both mepolizumab and omalizumab, and in whom mepolizumab would replace omalizumab;
- An epidemiological approach was used for patients eligible for both mepolizumab and omalizumab, and in whom mepolizumab would not replace omalizumab; and
- An epidemiological approach was used for patients eligible for mepolizumab only.

The population in whom mepolizumab would replace omalizumab was calculated using DUSC utilisation data[9] and clinical criteria from the IDEAL Study. The epidemiological approach first calculated the number of patients with severe, uncontrolled asthma who were compliant with inhaled corticosteroids/long-acting beta agonists (ICS/LABA) therapy, using predominantly Australian data sources. IDEAL Study data was then used to ascertain the number eligible for mepolizumab.

While DUSC did not agree with all of the submission's inputs to the financial model, the total estimate of use over the five years may be reasonable. However, DUSC considered the Year 1 estimates presented in the submission to be under-estimated. The main issues were:

- The population clinical criteria, derived from the IDEAL study, might not be representative of the Australian severe asthma population.
- DUSC considered it more straightforward to use a prevalence only approach for estimating PBS usage and financial implications of mepolizumab.
- The proportion of patients treated with an inhaled corticosteroid/long-acting beta agonist (ICS/LABA) combination product (35%), might be underestimated. DUSC considered the Reddel (2015) [10] estimate for patients using an ICS/LABA therapy (49.6%) as more appropriate than the 2008-2009 BEACH general practice data.
- DUSC considered the application of a continuation rate of 80% for mepolizumab would be a more appropriate estimate, consistent with the omalizumab continuation rate in practice.

DUSC provided revised estimates which used:

- a prevalence only approach;
- a higher estimate of asthma patients treated with ICS/LABA combination from the Reddel (2015)[10] study;
- a grouped cohort of patients with eosinophils ≥ 300 cells/mL and therefore eligible for mepolizumab (33.5%) instead of three separate cohorts;
- an uptake rate of 2%; and
- a continuation rate of 80% based on omalizumab continuation rate.[11]

The Pre-PBAC Response accepted most of DUSC's comments regarding the structure and inputs to the financial model, however the sponsor did not accept the application of omalizumab's real world continuation rate of 80%, as the sponsor claimed that this should be treatment specific.

For further details refer to the Public Summary Document from the March 2016 PBAC meeting.

The July 2016 minor resubmission presented a revised budget impact which incorporated DUSC revisions and the updated costs associated with omalizumab administration and monitoring.

For further details refer to the Public Summary Document from the July 2016 PBAC meeting.

Previous reviews by the DUSC

At its February 2013 meeting, DUSC examined the utilisation of omalizumab in its first 12 months of PBS listing. The analysis found utilisation in the first year of listing to be much lower than expected. DUSC noted the comprehensive and informative responses provided by the sponsor and clinicians outlining the reasons for low uptake. DUSC did not consider that safety concerns or an uncertain place in therapy were the reasons for low utilisation. DUSC considered that possible reasons may include:

- Overestimation of the eligible population;
- Difficulty for clinics to collect patient data to fulfil administrative requirements for eligibility;
- Reluctance by clinicians and patients to use long-term oral corticosteroids due to toxicity; and
- Low continuation rate, noting that patients who commenced treatment in the second half of the year would not have had an opportunity to be assessed for response and seek approval for continuing treatment.

DUSC recommended reviewing use after 24 months of data were available. The committee considered the use of omalizumab could be better understood by assessing response and continuation rates in the PBS population when further data were available and using the Australian Xolair Register data when available.

At its June 2014 meeting, DUSC considered the use of omalizumab in the first 24 months of PBS listing. Use continued to be lower than expected. The majority of patients who start omalizumab continue treatment. DUSC considered that ongoing lower uptake of omalizumab was most likely due to reluctance to use oral corticosteroids at relatively high dose for at least 6 weeks due to concerns about tolerability and a likely overestimation of the eligible population.

For details of the DUSC consideration of omalizumab refer to the Public Release Document from the June 2014 DUSC meeting.

Methods

The analyses used data from the PBS supplied prescriptions database, managed by Services Australia, for dates of supply up to and including 30 June 2019; extracted 30 July 2019. The PBS supplied prescriptions database includes data submitted to Services Australia for payment of a PBS or RPBS subsidy by the Government by all approved pharmacies in Australia. This dataset contains de-identified information that includes a unique patient identification number (PIN), dates and quantities of supply of all PBS listed drugs, prescriber and pharmacy information.

Analyses in the report include:

- New and prevalent patient counts by indication (Figure 1 and Table 6)
- New and prevalent patient counts by drug (Figure 2)
- Prescriptions by indication (Figure 3)
- Prescriptions by drug (Figure 4)
- Treatment sequence (Table 7)
- Switching (Figure 5)
- Length of treatment (Figure 6)
- Prescriber type (Figure 7)
- Predicted versus actual analysis (Table 8)
- Hospital setting (public or private) based on the dispensing pharmacy

A patient was defined as an initiator (or 'new patient') based on the date of first supply of PBS subsidised therapy from 1 July 2011 (omalizumab date of listing). This included patients who were naïve to therapy and 'grandfathered' patients; i.e. patients who obtained therapy through other means prior to listing on the PBS and then commenced PBS-subsidised treatment.

The length of treatment analyses used the Kaplan Meier (aka Product-Limit) method. Two ways of measuring length of treatment were undertaken to account for patients stopping medicine for periods of time (called a 'break' in therapy). One analysis excluded the time of any breaks in treatment (i.e. reports the total time a patient is actually receiving regular supplies of the medicine) and the other did not. A patient was deemed to have a break in treatment if the time between two of their supplied prescriptions was more than 3 times the median time to resupply (i.e. 3 x 28 days), which is an estimated break in treatment of at least 2 times the median time to resupply.

A censoring definition was applied in the length of treatment analysis, to account for the end of the data observation period where patients who might be continuing supply appear to stop treatment (because there is no further data for supplies). A patient was deemed to be continuing treatment (classified as censored in the Product-Limit method) at the end of the data period (i.e. the end of June 2019) if their last prescription was within 3 times the median time to resupply of this end date. Otherwise, the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply.

Prescriber type was attributed to the de-identified approval number of the prescriber by Services Australia and was based on the major field of specialty, derived from the

combination of the current registered specialty and the most PBS services provided per quarter. Prescribers can work in several different specialties but are allocated by Services Australia to one major field of specialty per quarter.

Data manipulation was undertaken using SAS.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available PBS date of processing data.[12]

Omalizumab, mepolizumab and benralizumab are listed on the PBS as Section 100 (S100) highly specialised drugs (HSDs). Prior to 1 July 2013, most HSD prescriptions supplied through public hospitals were processed through an offline processing system, for which only aggregated data was available, i.e. the number of packs supplied and the cost per quarter. Therefore the patient level analysis prior to 1 July 2013 may be incomplete. Omalizumab was the only severe asthma biologic listed in this period. To assess the extent of this, the DUSC HSD database was interrogated to determine the proportion of omalizumab packs recorded by bulk processing in the period from omalizumab listing (July 2011) to complete capture of HSD data (July 2013). The DUSC HSD database combines public hospital offline processed prescription data with public and private hospital online processed prescription data to give a complete picture of HSD drug utilisation. This analysis showed that from July 2013 to December 2014 inclusive, bulk processing accounted for 20-24% of omalizumab dispensing. This declined to 12% in the first quarter of 2013, after which there was complete capture of omalizumab dispensing in the line-by-line supplied prescriptions database.

Table 5: Omalizumab bulk versus line-by-line processing

Quarter of supply	Bulk packs	LBL scripts	Total	Bulk percentage
2011Q3	36	123	159	23%
2011Q4	154	486	640	24%
2012Q1	236	759	995	24%
2012Q2	253	938	1,191	21%
2012Q3	259	1,067	1,326	20%
2012Q4	354	1,238	1,592	22%
2013Q1	222	1,665	1,887	12%

Source: DUSC HSD Database, accessed August 2019. LBL = line-by-line.

Analysis for the period prior to July 2013 using an alternate method (counting authority approvals) is available in the omalizumab Public Release Document from the June 2014 DUSC meeting.

Results

Analysis of drug utilisation

Overall utilisation

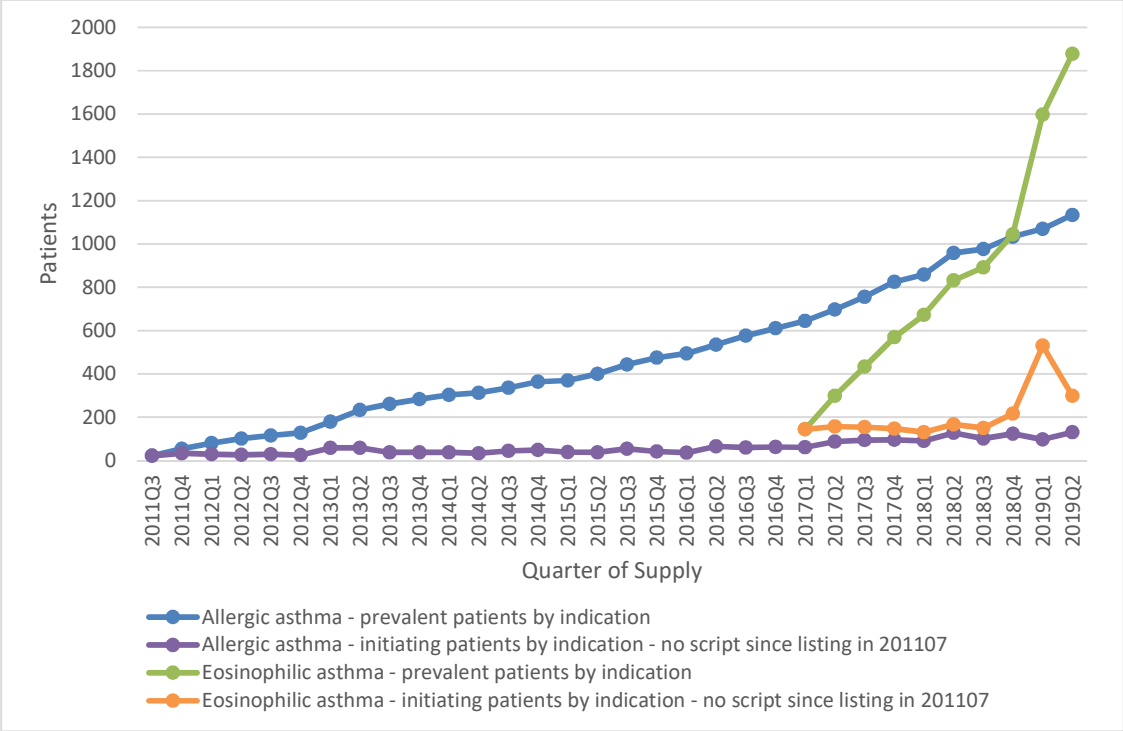

Figure 1: Prevalent and initiating patients by indication and quarter of supply

Note: Initiators are people supplied their first PBS-subsidised prescription. A look-back period to the omalizumab listing date (July 2011) was used to identify first initiators. Initiating and prevalent by indication; patients may appear in both allergic and eosinophilic categories.

Source: PIN count, PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

Table 6: Patients initiating and prevalent to indication by year

	Allergic Asthma		Eosinophilic Asthma	
Year	Prevalent	Initiating	Prevalent	Initiating
2011	55	55		
2012	162	110		
2013	318	192		
2014	435	164		
2015	519	173		
2016	693	224		
2017	936	340	604	604
2018	1,250	444	1,222	665
2019*	1,226	229	1,942	830

Note: *2019 Year to 30 June inclusive. Initiator look-back to omalizumab listing date (July 2011). Initiating and prevalent by indication – patients may appear in both allergic and eosinophilic.

Source: PIN count, PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

Table 6 and Figure 1 show that the number of people supplied biologics for severe asthma increased each year. In 2018, approximately the same number of people were treated with biologics for allergic asthma (n=1,250) and eosinophilic asthma (n=1,222). In the first half of 2019, more patients were supplied biologics to treat severe eosinophilic asthma (n=1,942) compared with severe allergic asthma (n=1,226). There has been a high rate of growth in the number of treated prevalent severe eosinophilic asthma patients since the listing of mepolizumab, with the rate of growth further increasing with the listing of benralizumab in December 2018.

Figure 2 shows that the number of patients supplied omalizumab for severe allergic asthma has steadily increased since its listing in 2011. The rate of growth in patients supplied mepolizumab and benralizumab was much faster than the omalizumab uptake. The PBS listing of mepolizumab did not appear to affect the number of patients supplied omalizumab. While the listing of benralizumab similarly did not appear to affect the number of patients supplied omalizumab, the rate of growth in mepolizumab patient numbers appears to have reduced slightly since the listing of benralizumab.

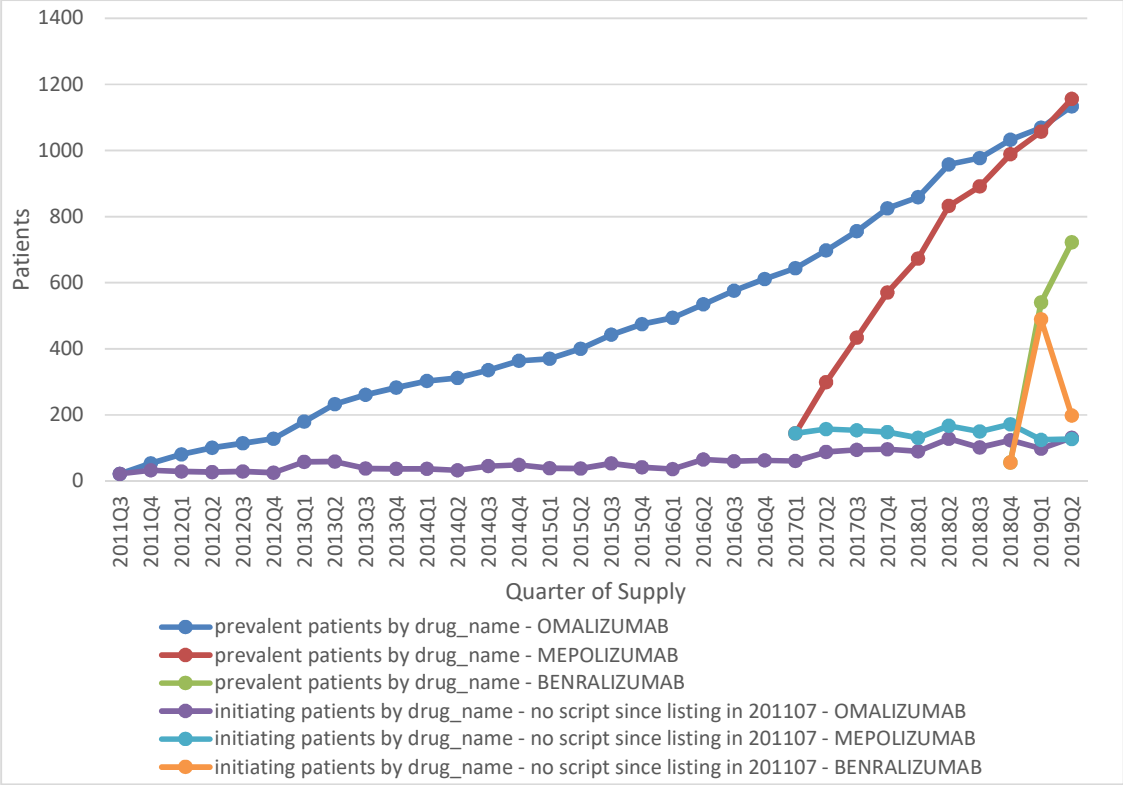

Figure 2: Prevalent and initiating patients by drug and quarter of supply

Note: Initiators are people supplied their first PBS-subsidised prescription. Initiator look-back to omalizumab listing date (July 2011). Initiating and prevalent by indication; patients may appear in both allergic and eosinophilic categories.

Source: PIN count, PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

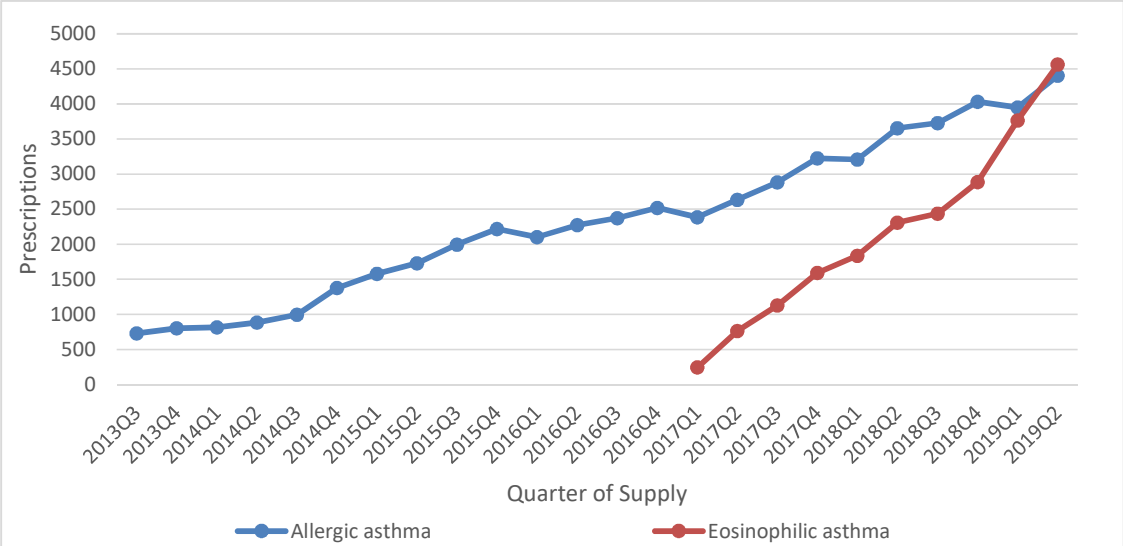

Figure 3: Prescriptions supplied for biologics for severe allergic and eosinophilic asthma

Source: PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

In the most recent quarter of available data (2019Q2), prescriptions dispensed for eosinophilic asthma exceeded prescriptions dispensed for allergic asthma for the first time (Figure 3). In considering prescription data, it should be noted that omalizumab is dosed every two or four weeks (depending on weight and baseline IgE), mepolizumab is given every four weeks and benralizumab is given every four weeks for the first three doses and then every eight weeks thereafter.

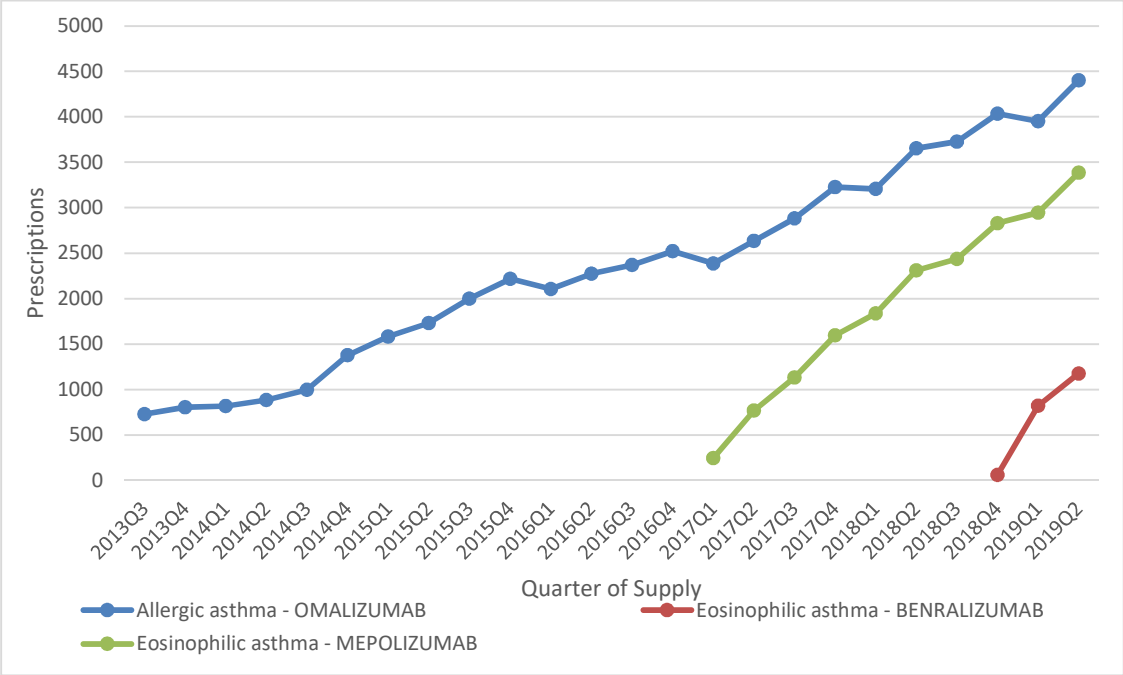

Figure 4: Prescriptions supplied for severe asthma biologic medicines

Source: PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

Sequence and switching analyses

The majority of patients (n=3,400) have been supplied one of the three severe asthma biologics. The number of patients who have switched once (n=343) was one-tenth the number supplied one medicine. Of the patients who switched once, over 70% (n=246) switched from a medicine for allergic asthma to one for eosinophilic asthma or vice-versa. Fewer than 30 patients have tried all three medicines.

Table 7: Drug initiation sequence

Sequence	Patients
OMALIZUMAB	1,665
MEPOLIZUMAB	1,203
BENRALIZUMAB	532
OMALIZUMAB -> MEPOLIZUMAB	147
MEPOLIZUMAB -> BENRALIZUMAB	97
OMALIZUMAB -> BENRALIZUMAB	92
OMALIZUMAB -> MEPOLIZUMAB -> BENRALIZUMAB	22
MEPOLIZUMAB -> OMALIZUMAB	7
MEPOLIZUMAB -> OMALIZUMAB -> BENRALIZUMAB	≤5

Note: Sequences from July 2011 to the end of May 2019
Source: PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

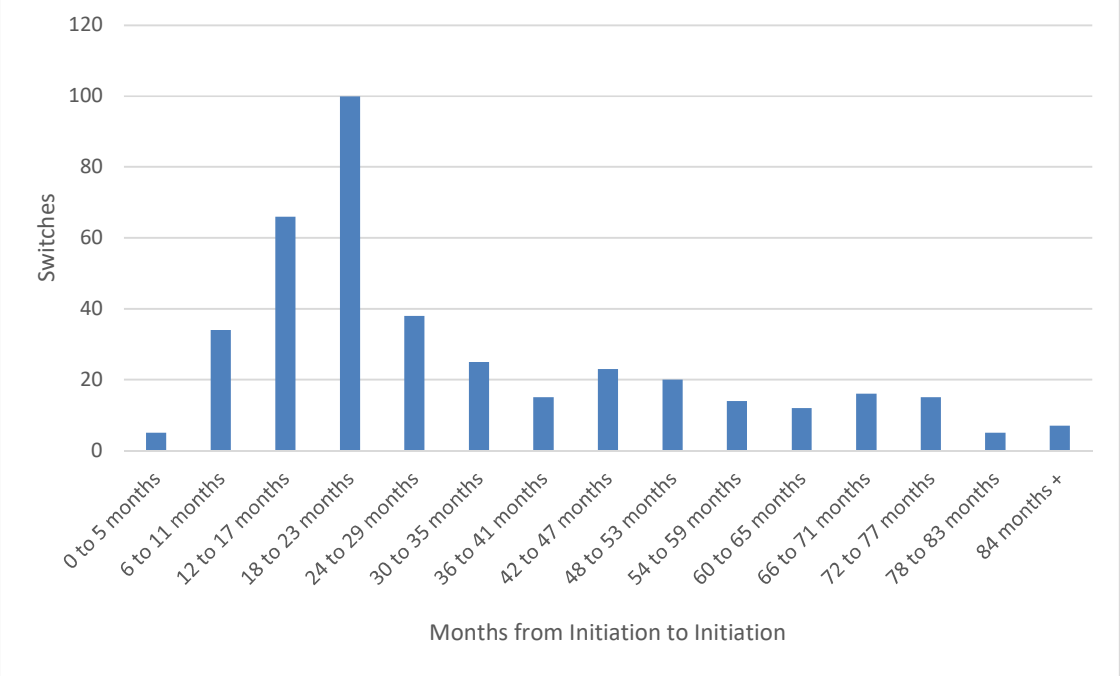

Figure 5: Time to switching

Note: Values equal to 5 may represent values ≤5.
Source: PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

Switching happened most often in the second year of treatment (Figure 5). The current PBS restrictions prohibit switching in the first 6 months from initiation of treatment, and it appears this happened very rarely (≤5 occasions).

Length of treatment

Figure 6 depicts the Kaplan Meier estimates for length of treatment with severe asthma biologics. Breaks in treatment were excluded. People who have been supplied more than one severe asthma biologic were included for each drug they have been supplied.

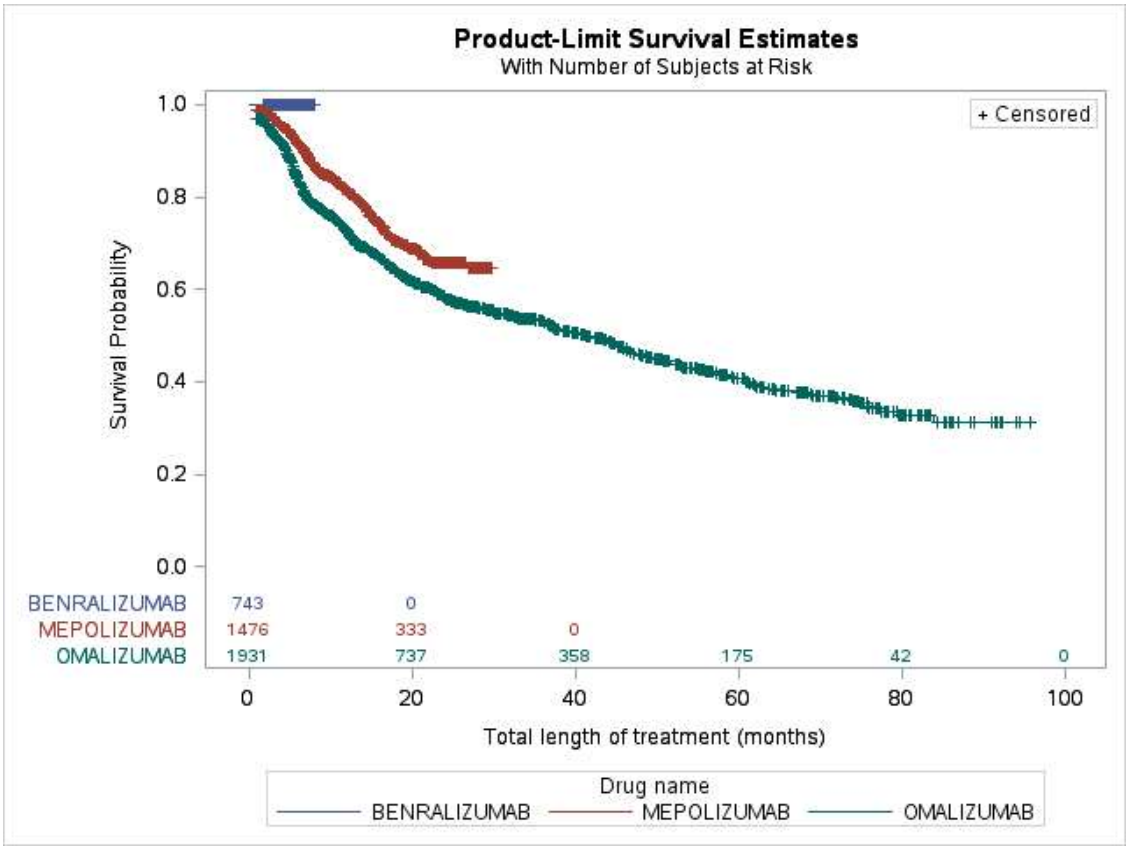

Figure 6: Length of treatment (months, excluding breaks) with severe asthma biologics

Source: PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

The probability of a patient remaining on treatment at 20 months from initiation was approximately 61% for omalizumab treatment and 69% for mepolizumab therapy. The median length of treatment for omalizumab was 41 months [36, 46]. The median length of treatment for mepolizumab has not been reached (30 months since listing). There are insufficient data for interpretation of benralizumab length of treatment (7 months since listing).

Utilisation by prescriber type

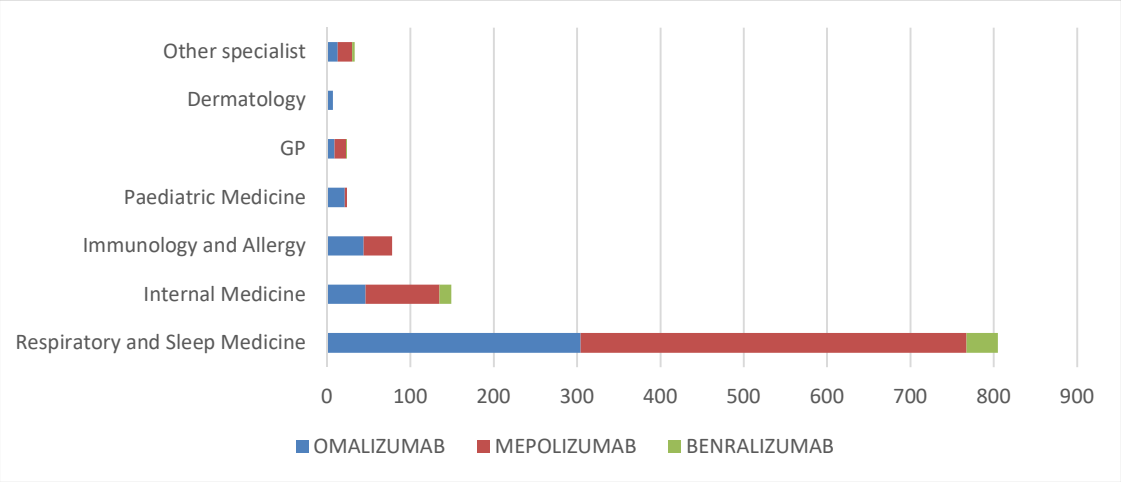

Figure 7: Prescriber type for initiating patients in 2018

Source: PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

Figure 7 shows that the majority of people starting a biologic for the treatment of severe asthma in 2018 had it firstly prescribed by a specialist in respiratory and sleep medicine (n=805; 72%). GPs prescribed 2% of first supplies. Other specialists included intensive care, pathology, medical oncology, gastroenterology, ENT, haematology and nephrology. The restriction text specifies that patients must be treated by a specialist from a limited number of prescriber specialties.

Analysis of expenditure

In 2018, expenditure for severe asthma biologics was $31.3 million based on the published prices (special pricing arrangements apply). This expenditure was mostly attributed to omalizumab and mepolizumab in close to a 1:1 ratio, with little expenditure for benralizumab (listed 1 December 2018).

As these analyses are based on date of supply, there may be small differences compared with publicly available PBS date of processing data.

Analysis of actual versus predicted utilisation

A comparison of the estimated versus actual use of mepolizumab in its first two years of PBS listing is presented in Table 8. Use of mepolizumab in terms of patients and prescriptions has been higher than estimated in both the first and second years of PBS listing.

Table 8: Analysis of actual versus predicted utilisation for mepolizumab

		Year 1	Year 2
Patients	Predicted	148	240
	Actual	604	1,177
	% Difference	+308%	+390%
Prescriptions	Predicted	1,775	2,880
	Actual	3,735	9,415
	% Difference	+110%	+227%

Source: PBS supplied prescriptions database to 30 June 2019; extracted 30 July 2019.

Expenditure (not presented) followed a similar predicted versus actual difference as prescriptions. Use by setting was predicted to be 79% public and 21% private. Over the whole period of mepolizumab listing to the most recent data, use has been 71% in the public setting and 29% private. This is similar to predicted and supports the conclusion that expenditure is driven by higher volumes not setting of supply.

Discussion and DUSC considerations

There has been a high rate of growth in the number of treated prevalent severe eosinophilic asthma patients since the listing of mepolizumab, with the rate of growth further increasing with the listing of benralizumab. These patients exceeded the number of patients supplied omalizumab for severe allergic asthma in the first half of 2019. In the most recent quarter of data (quarter 2 of 2019), prescriptions dispensed for eosinophilic asthma exceeded prescriptions dispensed for allergic asthma for the first time. Use of mepolizumab in terms of patients, prescriptions and expenditure has been higher than estimated in both the first and second years of PBS listing. DUSC noted that while the use of mepolizumab in the first two years of listing was higher than expected, the written authority means use is likely within the PBS restriction. DUSC considered respiratory physicians are now experienced with prescribing biologics and uptake of biologics in various treatment areas implies that subcutaneous injections are not a barrier for many patients. DUSC considered that the market for severe asthma biologics may continue to grow.

The mepolizumab sponsor suggested use of mepolizumab was higher than expected because the eligible population and uptake were underestimated. The sponsor considered the underestimated uptake related in part to the comparison to omalizumab, which seemed reasonable at the time, but has a number of differences in clinical profile, dosage and administration. The response also articulated how the treatment landscape for severe asthma has changed in recent years. This included a number of initiatives from local and global professional bodies to provide guidance and education in the diagnosis and management of severe asthma; leading to a greater understanding of severe asthma phenotyping (allergic, eosinophilic or both) and the role of biologics. The mepolizumab sponsor suggested that this changing landscape may have contributed to the identification and referral of severe eosinophilic asthma patients; and higher utilisation of mepolizumab than predicted. DUSC considered that the eligible population and uptake may have been

underestimated at the time of listing, partly due to the changing severe asthma treatment landscape and the assumptions that expected uptake would mirror omalizumab.

The PBS listing of biologics for the treatment of severe eosinophilic asthma did not create any substantial changes in the use of omalizumab for severe allergic asthma. A small proportion of patients switched between severe asthma biologics. However, of the people who switched, the majority moved from a medicine for allergic asthma to one for eosinophilic asthma or vice-versa. These patients represent the "overlap population" with both high eosinophil counts and high IgE.

The time to switching analysis showed that switching happened most often in the second year of treatment, but the tail of the graph indicated that switching occurred at various later points in the treatment course. These results are influenced by the time of listing, as people had more opportunity to have omalizumab than mepolizumab, and there has been little listing time for benralizumab. It is possible these patterns may change in the future, particularly if the restriction requirement that prohibits switching in the first 6 months from initiation of treatment was removed.

DUSC Actions

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

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

AstraZeneca Pty Ltd: The sponsor has no comment.

GlaxoSmithKline Australia Pty Ltd: The sponsor has no comment.

Novartis Pharmaceuticals Australia Pty Ltd: Novartis is pleased that patients with severe asthma are accessing PBS-subsidised biologic treatments, as described in the DUSC analysis. Amendments to the PBS restrictions, which took effect in December 2019, should enhance access to treatment for appropriate patients.

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 (DoH) 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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