Omalizumab for chronic spontaneous urticaria: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

June 2023

Abstract

Purpose

The PBAC requested an update of the June 2020 DUSC predicted versus actual analysis of omalizumab for chronic spontaneous urticaria (CSU), including additional analyses on the trend in prescribing a higher dose (600 mg) of omalizumab for CSU and the age distribution of PBS patients.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Omalizimuab was first listed on the PBS for severe CSU on 1 September 2017.

Data Source / methodology

Authorities data and prescriptions data was extracted from the prescription database and Authorities database maintained by the Department of Health and Aged Care, processed by Services Australia from between 28 March 2023 and 5 April 2023, respectively. Data were extracted based on the date of supply.

Key Findings

- The number of patients supplied omalizumab for CSU was [redacted] than predicted over the first five years of listing.
- For both initial and continuing treatment, the majority of prescriptions supplied were for 300 mg. The number of cases where first initiating or continuing prescriptions for 150 mg was negligible.
- Only a small proportion of patients were found to down titrate from 300 mg to 150 mg.
- While median, mode, and minimum dosing supplied for both initial and continuous treatment have remained stable since listing, the mean and maximum doses have increased over time.
- The median time on treatment including breaks was estimated to be 863 days and excluding breaks was estimated to be 697 days.

- Most prescriptions dispensed were prescribed by an immunologist, allergist or dermatologist.
- Approximately one third of prescriptions were provided by specialities outside of those listed in the restriction.
- The most common sequence of treatment is omalizumab without any prior PBS-listed therapy identified.

Purpose of analysis

The PBAC requested an update of the June 2020 DUSC predicted versus actual analysis of omalizumab for CSU including additional analyses on the trend in prescribing a higher dose of omalizumab for CSU and the age distribution of PBS patients.

Background

Clinical situation

CSU refers to wheals arising spontaneously on most days of the week for six weeks or more (ASCIA 2020). The urticarial (hives) may be intensely itchy, and the appearance of the rash can be distressing for sufferers.

Under the lining of the skin are mast cells that contain the chemical histamine. When released into the skin, histamine can irritate nerve endings to cause itching and make blood vessels expand and leak fluid to cause redness and swelling of the skin. CSU mainly occurs from the activation of mast cells in the skin involving histamine-releasing factors (ASCIA 2020).

Most cases of hives are resolved without the need for any specific treatment. Antihistamines are commonly used to reduce the severity of itching. When the hives become chronic and severe, medicines that reduce the inflammation in the skin may be required. Currently there is no evidence that the available drugs cause remission or cure of urticaria, however they can control or suppress symptoms, including suppression of itch, visible rash and prevention of angioedema episodes (ASCIA 2020). Medicines that are commonly used for the management of urticaria are summarised in Table 1.

Table 1: Commonly used drugs for the management of urticaria

Drug class	Generic drug names
Antihistamines	(non-sedating) cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine, (sedating) diphenhydramine, hydroxyzine, promethazine, chlorpheniramine, dexchlorpheniramine
H2 antagonists	Famotidine, nizatidine, cimetidine
Leukotreine receptor antagonists (LTRA)	Montelukast
Anxiolytics, sedatives	Doxepin
Immunosuppressants	Omalizumab, cyclosporine, sulfasalazine, mycophenolate, methotrexate

Sources:
Australasian Society of Clinical Immunology and Allergy (ASCIA) 2020 Position Paper – Chronic Spontaneous Urticaria. Accessed on 9 March 2023 at: www.allergy.org.au.
Therapeutic Guidelines: Dermatology. Accessed on 8 March 2023 at Topic | Therapeutic Guidelines (tg.org.au).

The ASCIA (2020) Position Paper – *Chronic Spontaneous Urticaria and the Therapeutic Guidelines: Dermatology for the definition, classification, diagnosis and management of urticaria* recommends the use of omalizumab as third line treatment in clinical practice, as depicted in Figure 1.

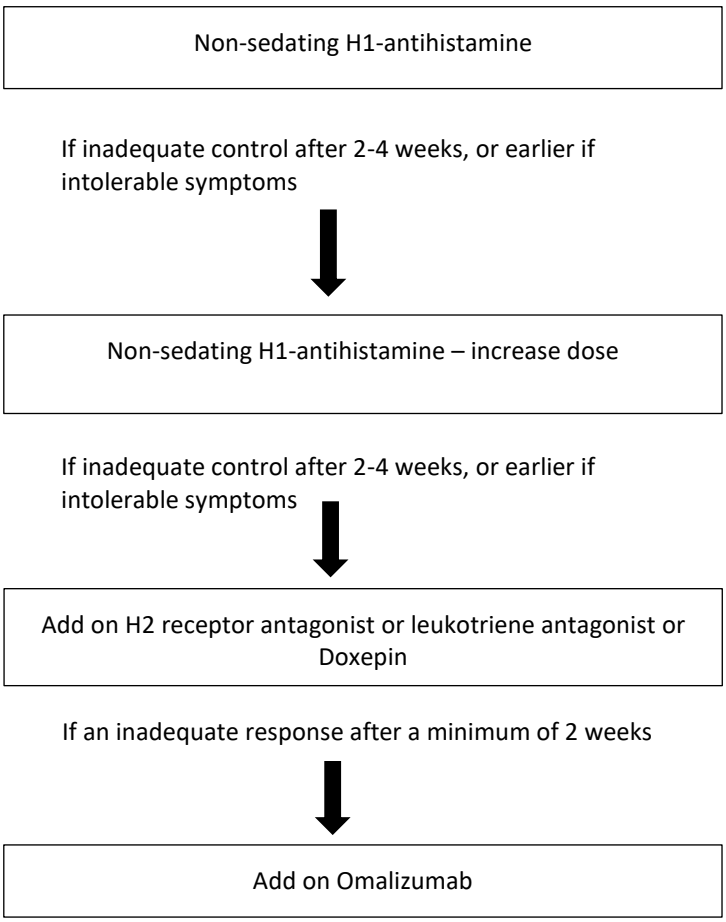

Figure 1: Treatment algorithm for urticaria

Source: Adapted from PBS indication accessed 8 March 2023, ASCIA (2020) and Therapeutic Guidelines: Dermatology accessed on 8 March 2023.

To be prescribed omalizumab under the current PBS restriction, prior to being authorised to be supplied omalizumab a patient must have failed to achieve a response to standard therapy after a minimum of two weeks. A failure to respond is defined as an Urticaria Activity Score (UAS) equal to or greater than 28 with an itch score greater than 8. The sum of scores for wheals and itch is measured over 7 days using the scoring system shown in Table 2.

Table 2: Urticaria Activity Score (UAS7) to assess disease activity in chronic spontaneous urticaria

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 hours)	Mild (present but not troublesome)
2	Moderate (20-50 wheals/24 hours)	Moderate (troublesome but does not interfere with normal daily activity or sleep
3	Intense (>50 wheals/24 hours or large confluent areas of wheals)	Intense (sufficiently troublesome to interfere with normal daily activity or sleep)

Source: Reproduced from the ASCIA 2020 guidelines, Table 1 p6.

The PBS clinical criteria defines standard therapy as a combination of therapies that includes H1 antihistamines at maximally tolerated doses in accordance with clinical guidelines, and one of the following:

- A H2 receptor antagonist (150 mg twice per day); or
- A leukotriene receptor antagonist (10 mg per day); or
- Doxepin (up to 25 mg three times a day).

If the requirement for standard therapy cannot be met because of contraindications and/or intolerances of a severity necessitating permanent treatment withdrawal, details must be provided in the authority application.

Pharmacology

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It works by blocking immunoglobulin E (also known as IgE) which is produced by the body. As a consequence, the activity of specific receptors and/or cells in the body which play a key role in causing chronic spontaneous urticaria are reduced.

Therapeutic Goods Administration (TGA) approved indications

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

Omalizumab is also registered for the following indications:

- In children aged 6 to less than 12 years, as add-on therapy to improve asthma control in patients with severe allergic asthma.

- Adults and adolescents 12 years of age and above for the management of moderate to severe allergic asthma, who are already being treated with inhaled steroids.
- As add-on treatment in adult patients (18 years of age and above) for the treatment of severe chronic rhinosinusitis with nasal polyps with inadequate response to intranasal corticosteroids.

Dosage and administration

The recommended dose is 300 mg by subcutaneous injection every four weeks. Some patients may achieve control of their symptoms with a dose of 150 mg every four weeks.

Prescribers are advised to periodically reassess the need for continued therapy.

Clinical trial experience of long-term treatment beyond 6 months in this indication is limited.

Xolair should be used as add-on therapy to H1 antihistamine treatment.

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 1 April 2023)

Omalizumab was listed on the section 100 Highly Specialised Drugs (HSD) Program with a Complex Authority Required listing on 1 September 2017 for severe CSU. Prescribers are required to obtain Written Authority approval for initial prescriptions. Applications for authorisation for continuing treatment can be made by using the Online PBS Authorities system or by telephone.

The current PBS listings for omalizumab for the treatment of CSU are presented in Table 3 below.

Table 3: PBS listing of Omalizumab

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11175E [Private Hospital]	omalizumab 150 mg/mL injection, 1 mL syringe	2	2	$860.62[a]	Xolair, Novartis Pharmaceuticals Australia Pty Limited
11176F [Public Hospital]	omalizumab 150 mg/mL injection, 1 mL syringe	2	2	$820.00[a]	Xolair, Novartis Pharmaceuticals Australia Pty Limited
11163M [Private Hospital]	omalizumab 150 mg/mL injection, 1 mL syringe	2	2	$860.62[a]	Xolair, Novartis Pharmaceuticals Australia Pty Limited
11168T [Public Hospital]	omalizumab 150 mg/mL injection, 1 mL syringe	2	2	$820.00[a]	Xolair, Novartis Pharmaceuticals Australia Pty Limited

Source: the PBS website.
Note:[a] Special pricing arrangements apply.

Restriction

Omalizumab for CSU has a complex restriction. An abridged version is presented.

Initial treatment of severe chronic spontaneous urticaria is by a clinical immunologist, allergist, dermatologist or general physician with expertise in the management of chronic CSU. Patients must meet the following criteria:

- The condition must be based on both physical examination and patient history (to exclude any factors that may be triggering the urticaria).
- Patient must have experienced itch and hives that persist on a daily basis for at least 6 weeks despite treatment with H1 antihistamines.
- Patient must have failed to achieve an adequate response after a minimum of 2 weeks treatment with a standard therapy.
- Patient must not receive more than 12 weeks of treatment under this restriction.

Continuing treatment of severe chronic spontaneous urticarial is by a clinical immunologist, allergist, dermatologist or general physician with expertise in the management of CSU. Patients must meet the following criteria:

- Patient must have demonstrated a response to the most recent PBS-subsidised treatment with this drug for this condition.
- Patient must not receive more than 24 weeks per authorised course of treatment under this restriction.

The continuing listing also includes the following note: A proportion of patients respond to 150 mg 4-weekly so where a substantial improvement has been obtained with a 300 mg dose it is reasonable to back-titrate dose after initial treatment.

The Australian Government implemented a temporary measure from 1 May 2020 to 30 June 2022 to allow some flexibility around PBS restrictions for eligible PBS medicines to ensure continued treatment for patients during the COVID-19 crisis.

Exemption included:

Omalizumab - Injection 75 mg in 0.5 mL single dose pre-filled syringe

Omalizumab - Injection 150 mg in 1 mL single dose pre-filled syringe

Where a treating medical professional considered that a patient taking an eligible PBS medicine should be exempt from any specific Authority Required PBS restriction requirement, as it may put the patient at increased risk of contracting COVID-19, or cannot be completed due to social distancing or isolation requirements, a request for exemption for that PBS restriction requirement was able to be lodged with Services Australia (Medicare) from 1 May 2020 to 30 June 2022. The request for exemption needed to be included with the authority request through the normal process.

This measure only applied to continuation prescriptions for patients who had previously received a script for the eligible PBS medicine, and all other PBS restriction criteria that were not affected by the COVID-19 pandemic still applied.

It was a legal requirement that the prescriber note the reasons for the proposed waiver and how it relates to the COVID-19 pandemic.

This measure was implemented based on the advice of the expert Pharmaceutical Benefits Advisory Committee in light of the COVID-19 pandemic. The measure was repealed on 30 June 2022, following advice provided by the Pharmaceutical Benefits Advisory Committee.

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

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

Omalizumab was first considered by the PBAC for the treatment of chronic idiopathic urticaria (CIU) in November 2015. The PBAC recommended the listing on the basis that it should only be available under Section 100 (Highly Specialised Drugs Program). The recommendation was formed on the basis of a cost-minimisation analysis compared with cyclosporin, where the equi-effective doses were omalizumab 300 mg and cyclosporin 3 mg/kg. The DUSC considered that the estimates presented in the submission and updated in the Pre-Sub-Committee Response were slightly overestimated.

For further details, refer to the Public Summary Document (PSD) from the November 2015 PBAC meeting.

A minor resubmission in November 2016 requested the reassessment of the PBAC recommended equi-effective dose of omalizumab compared with cyclosporin and the updated condition name from chronic idiopathic urticarial to chronic spontaneous urticaria (CSU). The PBAC recommended that the equi-effective doses are omalizumab 300 mg and

cyclosporin 4 mg/kg, based on the un-titrated trial doses for both drugs. The PBAC noted that both products were likely to be down titrated in clinical practice, and noted the information provided in the submission to support the proposed rate of down-titration, but considered that the actual proportion of patients who would down titrate remained uncertain.

For further details, refer to the Public Summary Document (PSD) from the November 2016 PBAC meeting.

A minor resubmission in March 2018 requested the expansion of the listing to include a Section 85 Authority Required (Written) and Authority Required (Telephone) for the initial and continuing treatment respectively. The PBAC recommended the listing, and advised that the Sponsor should reduce the ex-manufacturer price of omalizumab to ensure that the impact to government would remain cost neutral for the dual S85 and S100 listing.

For further details, refer to the Public Summary Document (PSD) from the March 2018 PBAC meeting.

Note: To date, the S85 listings have not been implemented on the PBS.

At its 24 January 2023 meeting, the PBAC Executive noted the high cost of treatment at the 300 mg dose, the trend in prescribing higher doses (600 mg) and uncertainty around the equi-effective doses. The PBAC Executive supported updating the June 2020 Drug Utilisation Sub-Committee (DUSC) review, including an analysis of age distribution.

Approach taken to estimate utilisation

The financial estimates were developed using an epidemiological approach.

[redacted]

[redacted]

Previous reviews by the DUSC

June 2020

Omalizumab for CSU

Key Findings

- The number of patients supplied omalizumab for CSU was more than predicted in its first two years of listing. In Year 2 of listing, a total of 2,206 patients were supplied omalizumab.
- The proportion of patients continuing on omalizumab was less than anticipated and the number of packs per patient was lower than predicted.
- Only a small proportion of patients (2%) were identified as having their dose down-titrated from 300 mg to 150 mg.

For details of the DUSC consideration of omalizumab for CSU refer to the Public Release Document Omalizumab for chronic spontaneous urticaria: predicted versus actual analysis from the June 2020 DUSC meeting.

Methods

Authorities data and prescriptions data maintained by the Department of Health and Aged Care, processed by Services Australia, was extracted from 1 September 2016. Data was extracted based on the date of supply. Unless otherwise specified data is presented by listing year for the period September – August.

Patient level analysis

The number of prevalent patients was determined by counting the number of people supplied at least one PBS prescription using person specific numbers (non-identifying) in the data for the specified time periods. Patient initiation was defined as the date of supply of the first PBS or RPBS prescription.

Patient age was derived as the age at first supply.

Predicted versus actual analysis

Predicted versus actual analysis of the number of patients treated, prescriptions dispensed, annual contribution rates and benefits paid, net cost to government (exclusive of co-payment). The projected figures were adjusted to the period September to August (i.e. by listing year) to align with the first listing date of omalizumab. Actual utilisation for these parameters was extracted by listing year.

The differences in actual compared to predicted utilisation was determined using the following calculation:

Difference (%) = ((Actual – Predicted)/Predicted) x 100.

Dose analysis

Omalizumab is administered as monthly injections. The total amount of drug dispensed was calculated as the product of the mass per unit of drug supplied by the PBS quantity dispensed.

The dose dispensed was examined separately for initial scripts and continuing scripts.

The PBS listing note suggests patient down titration of doses. Dose transitions were investigated for all patients initiating omalizumab for urticaria with follow-up to the end of February 2023 (excluding patients initiating in the last 6 months, i.e. on or after 1 September 2022).

Treatment duration analysis

Time (days) on treatment for all patients initiating omalizumab for urticaria with follow-up to the end of February 2023 (excluding patients initiating in the last 6 months, i.e. on or after 1 September 2022). Kaplan-Meier analysis was undertaken to analyse the time on treatment. Time on treatment was determined with and without treatment breaks.

Patients were assumed to have had a break in therapy if there was a period of no supply equivalent to three times the median time between supplies (i.e. 90 days, 3 x 30 days).

Patients who had a supply within 90 days of the analysis end date were assumed to be continuing on therapy. These patients were censored from the Kaplan-Meier analysis.

Prescription analysis

Distribution and percentages of the number of ordered repeats on original prescriptions by listing year. The last listing year is only included as a percentage of the scripts so a valid comparison can be made due to the data being immature.

Prescriber analysis

Number and proportion of prescriptions dispensed by prescriber type over time by specialities.

Standard therapy analysis

To determine the sequence of standard therapies prior to initiating omalizumab, prescription data for the drugs listed in Appendix A were extracted from September 2016 to the end of February 2023. These data were merged with patients who had been supplied omalizumab. Each omalizumab patient has had at least 12 months of standard therapy opportunity as the first omalizumab initiation was in September 2017.

Patients with no prior PBS listed standard therapies were excluded from the time on standard therapy estimation.

Results

Analysis of actual versus predicted utilisation

The number of predicted patients was significantly [redacted] than actual patients (Table 4 and 5).

Table 4 compares the predicted versus the actual utilisation of omalizumab over the first five years of listing.

Table 4: Comparison of predicted versus actual utilisation of omalizumab for each year of listing

	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]
Number of patients					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual	1,267	2,206	3,172	4,230	5,133
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of packs					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual	13,451	30,135	45,827	66,510	84,486
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: [redacted]

Note:

[a] The figures are presented in listing years (September to August).

[redacted]

Table 5 compares the predicted treatment uptake rate with the actual treatment uptake rate.

Table 5: Treatment uptake rate

	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patients under proposed restriction	5,332	5,423	5,514	5,606	5,697
Actual Incident patients	1,267	1,189	1,461	1,696	1,735
Actual treatment uptake rate	24%	22%	26%	30%	30%

Note:

[a] The data is presented in listing years for the period 1 September to 31 August.

Analysis of drug utilisation

Number of Authorities

Table 6 details the number of authority applications by listing year and compares the actual continuation rate to the assumed continuation rate for the first five years of listing. While the actual continuation rates have been lower then assumed over the first five years of listing they have been continually increasing.

Table 6: Number of Authority applications by listing year and Authority type

Application type	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]
Initial treatment	1,245	1,173	1,460	1,734	1,811
Grandfather treatment	131	2	1	1	-
Continuing treatment	1,056	2,584	3,861	5,677	7,087
Unknown	-	2	5	5	-
Actual Continuation rates	46%	69%	72%	77%	80%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**2,432**	**3,761**	**5,327**	**7,417**	**8,900**

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.

Number of patients

Table 7 and Figure 2 provide the incident and prevalent patient numbers by listing year.

Table 7: Number of incident (new) and prevalent (total treated) patients by listing year

	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]	Year 6[b]
Incident	1,267	1,189	1,461	1,696	1,735	879
Prevalent	1,267	2,206	3,172	4,230	5,133	4,827

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
[b] Utilisation in year to date from 1 September 2022 to 28 February 2023 based on date of supply.

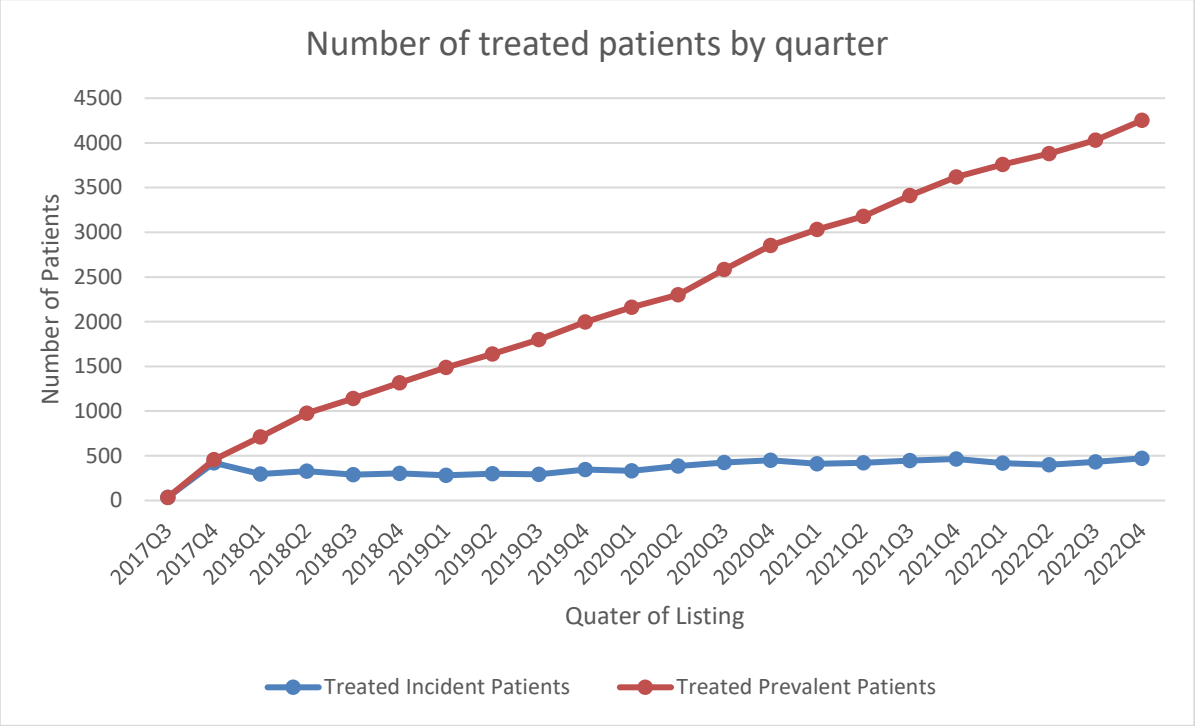

Figure 2: Number of treated incident patients and treated prevalent patients by quarter

Figure 2 shows that the number of initiating patients is relatively stable but the number of treated patients is growing each quarter indicating that patients are remaining on therapy.

Patient age

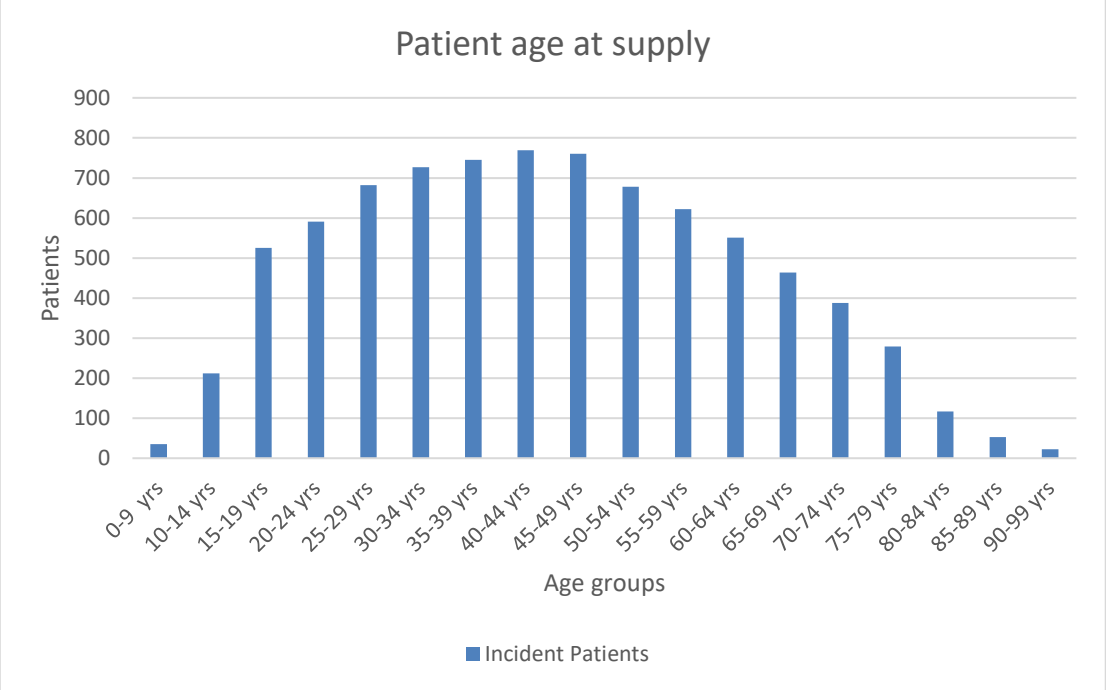

Figure 3: Incident patients by 5-year age group

Figure 3 provides a distribution of omalizumab supply by age. Of the 8,227 incident patients supplied omalizumab from September 2017 to February 2023, 85 (1.0%) were aged less than 12 years. For the period September 2021 to August 2022, 24 (1.4%) of the 1,735 incident and 45 (0.9%) of the 5,141 prevalent patients aged less than 12 years were supplied omalizumab.

Dosing

While median, mode, and minimum dosing supplied for both initial and continuous treatment have remained stable over the period since listing, the mean and maximum doses have increased over time (Table 8 and 9).

Table 8: Doses (mg) supplied during initial treatment

Year	Number of Prescriptions	Mean	Median	Mode	Min	Max
1[a]	2,788	300	300	300	150	600
2[a]	3,207	300	300	300	150	750
3[a]	3,800	304	300	300	150	600
4[a]	4,803	304	300	300	150	1,200
5[a]	5,023	306	300	300	150	1,200
6[b]	2,591	309	300	300	150	1,500

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
[b] Utilisation in year to date from 1 September 2022 to 28 February 2023 based on date of supply.

Table 9: Doses (mg) supplied during continuing treatment

Year	Number of Prescriptions	Mean	Median	Mode	Min	Max
1[a]	3,813	310	300	300	150	600
2[a]	11,697	304	300	300	150	600
3[a]	17,875	320	300	300	150	900
4[a]	25,220	338	300	300	150	1200
5[a]	31,828	350	300	300	150	1350
6[b]	17,942	356	300	300	150	1800

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
[b] Utilisation in year to date from 1 September 2022 to 28 February 2023 based on date of supply.

For both initial and continuing treatment, the majority of prescriptions supplied were for a dose of 300 mg (Table 10 and 11 and Figure 4). The number of prescriptions for 150 mg in both initial and continuing was negligible (Table 10 and 11). [redacted]. A small proportion of prescriptions were dispensed with a dose higher than 300 mg (Table 10 and 11). There was a steady increase in the dosage supplied to continuing patients over time (Figure 4).

Table 10: Number of prescriptions dispensed for initial treatment by dose dispensed

	Dose	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]	Year 6[b]
Prescriptions	150mg	22	35	<20	<20	<20	<20
	300mg	2,752	3,151	3,716	4,704	4,894	2,487
	450mg	<20	<20	42	39	39	23
	600mg	<20	<20	36	43	77	66
	other	<20	<20	<20	<20	<20	<20
Total Prescriptions		**<2,848**	**<3,269**	**<3,840**	**<4,843**	**<5,063**	**<2,633**

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
[b] Utilisation in year to date from 1 September 2022 to 28 February 2023 based on date of supply.

Table 11: Number of prescriptions dispensed for continuing treatment by dose dispensed

	Dose	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]	Year 6[b]
Prescriptions	150mg	81	179	225	330	444	214
	300mg	3,565	11,262	15,887	20,178	23,911	13,132
	450mg	<20	46	1,008	2,884	4,214	2,495
	600mg	153	227	785	1,813	3,259	2,128
	other	<20	<20	<20	45	88	39
Total Prescriptions		**<3,858**	**11,734**	**<17,930**	**25,250**	**31,916**	**18,008**

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
[b] Utilisation in year to date from 1 September 2022 to 28 February 2023 based on date of supply.

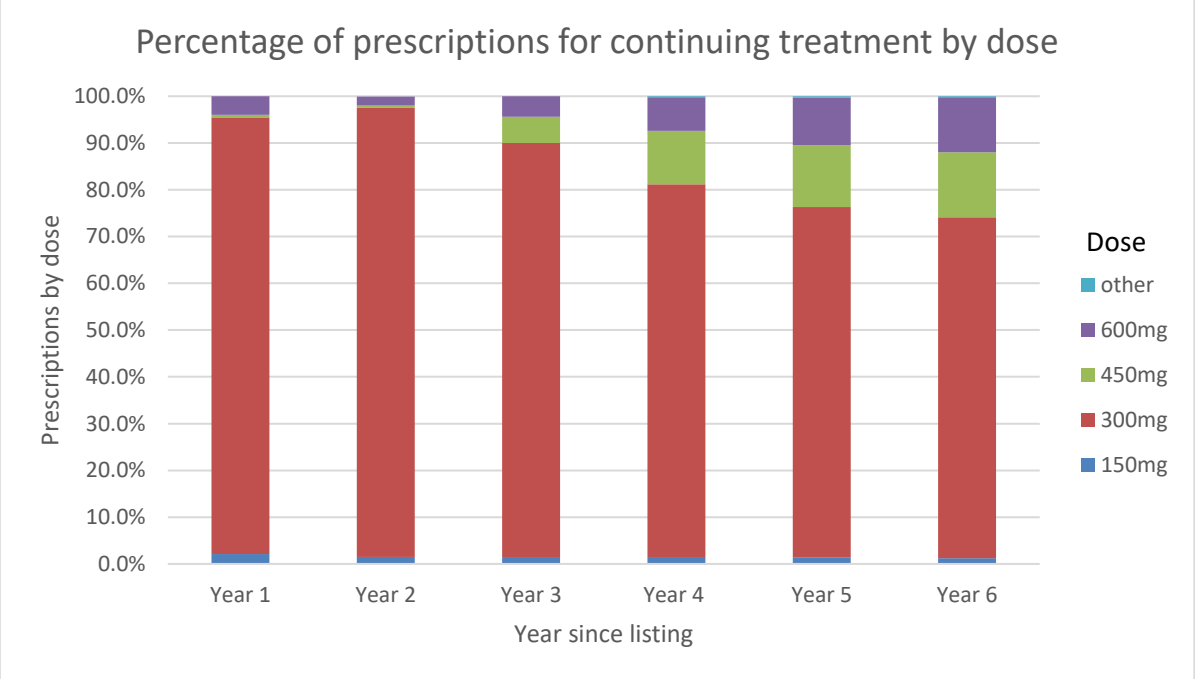

Figure 4: Percentage of prescriptions for continuing treatment by dose prescribed
The data is presented in listing years for the period 1 September to 31 August.

Table 12 through 14 provide information on the sequence of dose titration. Dose titration was examined for all patients with follow-up to 28 February 2023 (excluding patients initiating in the last 6 months, i.e. on or after 1 September 2022). The majority of patients (74%) initiated and remained on 300 mg (Tables 12 to 14). Only a small proportion of patients (1.1%) down titrated from 300 mg to 150 mg (Table 13). The proportion of patients continuing on a 300 mg dose increased in year 5, and the proportion of patients down titrating from 300 mg to 150 mg decreased while there was a small increase in the proportion of patients up titrating in the same time period (Table 14.)

Table 12: Dose sequencing for all patients

Dose sequences	Number of patients	Proportion (%)
300mg	5,406	73.6%
300mg-> 450mg	583	7.9%
300mg-> 600mg	276	3.8%
600mg	232	3.2%
300mg-> 450mg-> 600mg	171	2.3%
300mg-> 450mg-> 300mg	91	1.2%
300mg-> 150mg	82	1.1%
300mg-> 150mg-> 300mg	74	1.0%
Other	428	5.8%
Total	7,343	99.9%[1]

Note:
[1]Less than 100% due to rounding.

Table 13: Dose sequencing for all patients by therapy initiation year

Dose sequence	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]
300mg	949	890	1011	1217	1339
300mg-> 450mg	83	61	116	151	172
300mg-> 600mg	26	36	52	75	87
600mg	42	40	60	44	46
300mg-> 450mg-> 600mg	26	24	38	50	33
300mg-> 450mg-> 300mg	<20	<20	28	32	<20
300mg-> 150mg	<20	23	29	<20	<20
300mg-> 150mg-> 300mg	26	<20	<20	<20	<20
Other	94	79	115	101	39
Total	<1,306	<1,226	<1,860	<1,736	<1,795

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.

Table 14: Dose sequencing as a proportion of all patients by therapy initiation year

Dose sequence	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]
300mg	75.0%	75.0%	69.2%	71.8%	77.2%
300mg-> 450mg	6.6%	5.1%	7.9%	8.9%	9.9%
300mg-> 600mg	2.1%	3.0%	3.6%	4.4%	5.0%
600mg	3.3%	3.4%	4.1%	2.6%	2.7%
300mg-> 450mg-> 600mg	2.1%	2.0%	2.6%	2.9%	1.9%
300mg-> 450mg-> 300mg	0.4%	1.2%	1.9%	1.9%	0.7%
300mg-> 150mg	1.2%	1.9%	2.0%	0.8%	0.1%
300mg-> 150mg-> 300mg	2.1%	1.6%	0.8%	0.7%	0.3%
Other	7.4%	6.7%	7.9%	6.0%	2.2%

Note:

[a] The data is presented in listing years for the period 1 September to 31 August.

Treatment duration

Time (days) on treatment for all patients initiating omalizumab for urticaria with follow-up to the end for February 2023 (excluding patients initiating in the last 6 months, i.e. on or after 1 September 2022). Time on treatment was analysed with and without treatment breaks with the break length removed (Figure 5).

Percent censored excluding and including breaks was 47.5%. The mean LOT excluding breaks was 928 days, compared to a LOT including breaks of 990 days. Median LOT excluding breaks 697 days, LOT including breaks 863 days. This may indicate that a subset of patients are spending significantly more time on treatment than originally assumed.

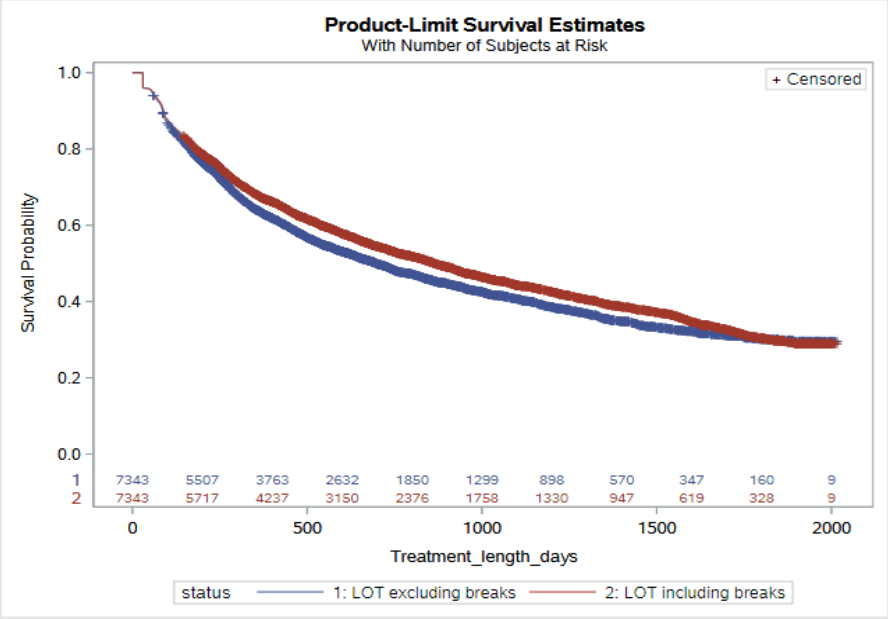

Figure 5: Time (days) on omalizumab for an initiating cohort in September 2017-August 2018 with follow-up to 28 February 2023

Prescribers

The restrictions for omalizumab specify that only the following prescribers are authorised to prescribed subsidised therapy: a clinical immunologist, allergist, dermatologist; or general physician with expertise in the management of CSU. Since 2017, most prescriptions dispensed were prescribed by an immunologist, allergist or dermatologist (Table 15 and Figure 6). Over the first five years of listing the overall proportion of prescriptions written by immunologists and allergists decreased and those written by dermatologists increased (Table 16 and Figure 7).

Table 15: Number of prescriptions supplied by prescriber type

Prescriber Group	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]	Total
Immunology and Allergy	3,157	6,210	9,093	12,949	16,131	47,540
Dermatology	1,111	2,667	3,695	6,149	7,721	21,343
Pathology	485	1,148	1,554	2,451	3,203	8,841
Respiratory and Sleep Medicine	465	934	1,373	1,750	2,019	6,541
NONVRGP	458	842	448	547	2,476	4,771
Paediatric Medicine	387	858	1,168	1,345	1,531	5,289
Internal Medicine	312	844	1,193	1,809	1,987	6,145
GP Unclassified	93	49	<20	<20	<20	<20
VRGP	80	300	283	434	510	1,607
GP Trainee	<20	34	53	53	22	<188
Other	25	967	2,795	2,496	1,244	7,527
Total	**<6,599**	**14,853**	**<21,675**	**<30,003**	**<36,864**	**<109,994**

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
NONVRGP – Non-vocationally registered GP
VRGP - Vocationally registered GP

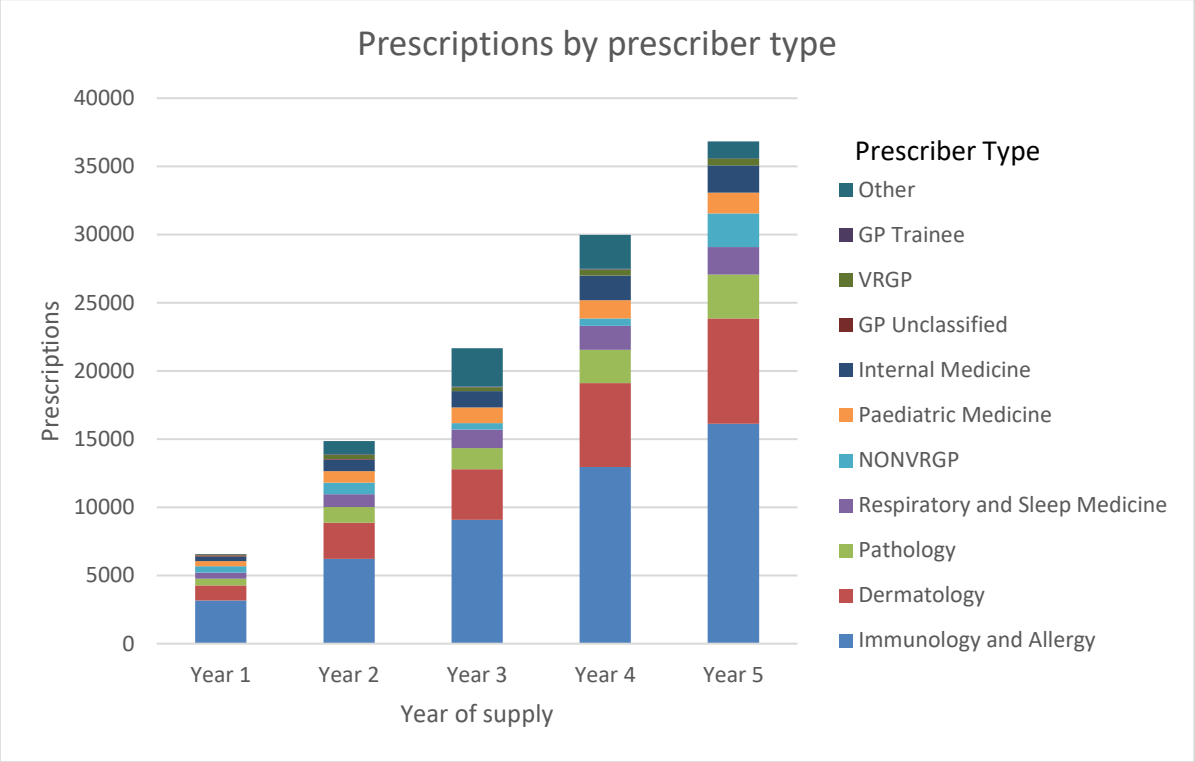

Figure 6: Number of prescriptions supplied by prescriber type

Note:
The data is presented in listing years for the period 1 September to 31 August.
NONVRGP – Non-vocationally registered GP
VRGP - Vocationally registered GP

Table 16: Proportion of prescriptions supplied by prescriber type

Prescriber Group	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]
Immunology and Allergy	48.0%	41.8%	42.0%	43.2%	43.8%
Dermatology	16.9%	18.0%	17.1%	20.5%	21.0%
Pathology	7.4%	7.7%	7.2%	8.2%	8.7%
Respiratory and Sleep Medicine	7.1%	6.3%	6.3%	5.8%	5.5%
NONVRGP	7.0%	5.7%	2.1%	1.8%	6.7%
Paediatric Medicine	5.9%	5.8%	5.4%	4.5%	4.2%
Internal Medicine	4.7%	5.7%	5.5%	6.0%	5.4%
GP Unclassified	1.4%	0.3%	0.0%	0.0%	0.0%
VRGP	1.2%	2.0%	1.3%	1.5%	1.4%
GP Trainee	0.1%	0.2%	0.2%	0.2%	0.1%
Other	0.4%	6.5%	12.9%	8.3%	3.4%

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
NONVRGP – Non-vocationally registered GP
VRGP - Vocationally registered GP

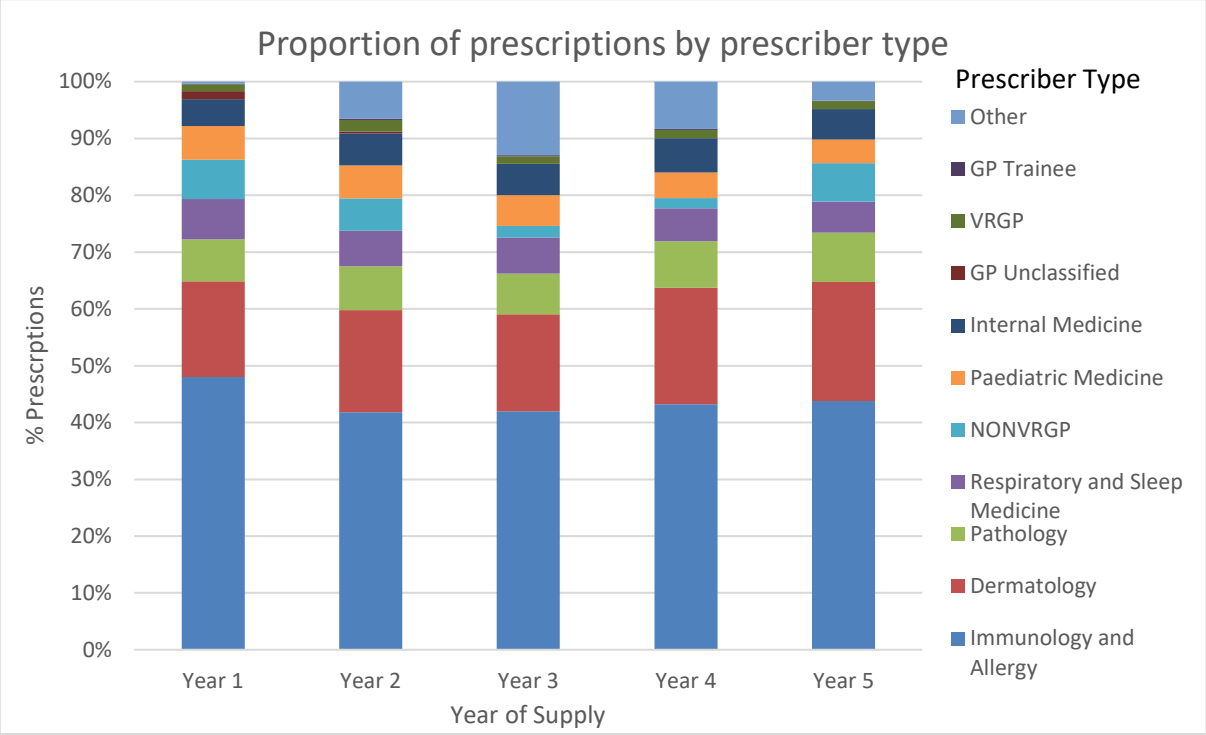

Figure 7: Proportion of prescriptions supplied by prescriber type

Note:
The data is presented in listing years for the period 1 September to 31 August.
NONVRGP – Non-vocationally registered GP
VRGP - Vocationally registered GP

Repeats

Table 17 provides the number of repeats ordered for initial and continuing treatment over time.

Table 17: Number of repeats ordered for initial and continuing treatment over time

Repeats by Treatment Phase	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]	Total
Initial	<1,156	<1,213	<1,449	<1,745	<1,831	**<7,394**
0	<20	<20	<20	<20	<20	**<100**
1	<20	<20	<20	<20	20	**<100**
2	1,015	1,070	1,281	1,562	1,631	**6,559**
3	<20	<20	<20	<20	<20	**<100**
5	21	23	48	63	80	**235**
6	<20	<20	<20	<20	<20	**<100**
7	<20	<20	<20	<20	<20	**<100**
Continuing	<1,193	<2,508	<3,702	<5,079	<6,312	**<18,794**
0	<20	<20	30	19	30	**<118**
1	<20	<20	<20	<20	<20	**<100**
2	72	81	85	100	168	**506**
3	<20	<20	<20	41	74	**<175**
4	<20	<20	<20	52	101	**<181**
5	1,001	2,308	3,487	4,839	5,879	**<17,514**
6	<20	<20	<20	<20	<20	**<100**
7	<20	<20	<20	<20	<20	**<100**
Total	<2,349	<3,721	<5,151	<6,824	<8,143	**<26,188**

Note:

[a] The data is presented in listing years for the period 1 September to 31 August.

The most frequent repeats ordered (Tables 17 and 18) for initial treatment was two which represented 95% of initial treatment phase prescriptions in year one decreasing to 93% by year six with the corresponding increase in prescriptions written with five repeats. The most frequent repeats ordered for continuing treatment has been five which represented 91% of continuing treatment phase prescriptions in year one increasing to 94% by year six with the corresponding decrease in prescriptions written with two repeats.

Treatment with a standard therapy

Table 18 provides information on PBS-listed standard therapies supplied before or after the supply of omalizumab, Table 19 the proportion of patients without an identified supply of a PBS-listed standard therapy prior to initiating on omalizumab by listing year, and Table 20 the time on PBS-listed standard therapies prior to initiating on omalizumab.

Table 18: Standard therapy drug initiation sequences for omalizumab patients

Treatment initiating sequence	Patients	% Patients
OMALIZUMAB	3,008	36.6%
RANITIDINE->OMALIZUMAB	1,175	14.3%
NIZATIDINE->OMALIZUMAB	913	11.1%
DOXEPIN->OMALIZUMAB	546	6.6%
FAMOTIDINE->OMALIZUMAB	394	4.8%
RANITIDINE->OMALIZUMAB->NIZATIDINE	174	2.1%
RANITIDINE->NIZATIDINE->OMALIZUMAB	153	1.9%
OMALIZUMAB->NIZATIDINE	152	1.8%
RANITIDINE->DOXEPIN->OMALIZUMAB	143	1.7%
MONTELUKAST->OMALIZUMAB	87	1.1%
OMALIZUMAB->FAMOTIDINE	80	1.0%
RANITIDINE->OMALIZUMAB->FAMOTIDINE	80	1.0%
Other	1,317	16.0%
Total	8,222	100.0%

Note:
List of medications taken as standard therapy are listed at Appendix A.

Table 19: Patients initiating omalizumab with no prior standard therapy by year

Treatment Initiation Sequence	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]	Year 6[b]
Omalizumab						
Patients	403	326	561	738	647	333
Percentage of total	31.8%	27.5%	38.5%	43.6%	37.3%	37.9%
Omalizumab -> Other treatment						
Patients	102	60	78	100	55	11
Percentage of total	8.1%	5.1%	5.3%	5.9%	3.2%	1.3%

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.
[b] Utilisation in year to date from 1 September 2022 to 28 February 2023 based on date of supply.

The most common sequence of treatment is omalizumab without any prior PBS-listed therapy identified.

Table 20: Time (days) on standard therapies prior to initiating on omalizumab

	Patients	Mean	Median	Min	Max
Year 1[a]	761	193	161	1	365
Year 2[a]	800	183	135.5	4	365
Year 3[a]	820	198	161	4	365
Year 4[a]	856	199	162	1	365
Year 5[a]	1032	180	118	1	365

Note:
[a] The data is presented in listing years for the period 1 September to 31 August.

Discussion

The number of patients supplied omalizumab was [redacted] than predicted (Table 4). The sponsor estimated that [redacted] patients would first initiate on omalizumab within the first listing year, however there were 1,245 (not including 131 grandfathered patients) Authority applications approved for initial treatment (Table 6). DUSC (November 2015) considered that the applicability of the international data sources to the Australian PBS population was unclear, and this may have led to the [redacted]. DUSC considered the proportion of patients treated was likely to have been [redacted] because the analysis in Zazzali et al. (2012) was based on insurance claims, and as such, the data may not have captured all treatments received by CSU patients. It was also unclear whether the assessments of disease severity in Thenie (2015) aligned with the PBS listing Urticaria Activity Score (UAS7) of 28 or more. DUSC also considered there was a potential for use outside the restriction in milder disease because the Urticaria Activity Score assessment test used to determine severity is subjective. Actual treatment uptake rates (Table 5) were [redacted] that predicted which may indicate that there was an underestimate of severe cases then initially assumed or that milder cases are being treated.

The original November 2015 submission estimated 59% of patients would move to the continuing treatment phase based on the 59% response rate from the trial. The sponsor also incorporated the continuation criteria from the trial into the proposed restriction. PBAC considered that it would be difficult to implement the continuation criteria in practice and recommended that this criterion was removed from the PBS restriction. The August 2016 submission increased the response rate to [redacted] with the average continuation rate at [redacted] over the first 5 years. The average continuation rate in practice (Table 6) was 69% over the first 5 years with continuation rates increasing year on year.

PBAC (November 2016) recommended omalizumab on a cost-minimisation basis to cyclosporin. In considering the equi-effective doses, PBAC noted that both drugs were likely to be down-titrated in practice but the proportion of patients who would down titrate was uncertain. PBAC recommended the equi-effective doses of omalizumab 300 mg and cyclosporine 4 mg/kg based on the un-titrated trial doses for both drugs. Based on the analysis of initial and continuing prescriptions, the majority of patients (84%) were supplied

300 mg (Table 12). Only a small proportion of patients (5%) were identified as having down titrated from 300 mg to 150 mg (Tables 13 and 14). [redacted].

In the July 2020 ASCIA guidelines for the treatment of CSU it was noted that multiple trials have shown increased effectiveness of omalizumab at higher and/or more frequent fortnightly doses particularly in obese, elderly (>57 years), and prior ciclosporin users. Dosing for continuing patients appears to be increasing year on year (Table 9, 11, and Figure 4). Initiation on 300 mg increased during listing year 5 and up titrations from 300 mg to 450 mg or 600 mg are becoming more common (Tables 13 and 14). There does not seem to have been any change in treatment patterns of omalizumab for CSU during the COVID-19 crisis in relation to the temporary measure to allow some flexibility around PBS restrictions for eligible PBS medicines to ensure continued treatment for patients.

Omalizumab is restricted to patients aged 12 years or over. The June 2020 DUSC analysis of omalizumab found that of the 2,502 patients supplied omalizumab in 2019, 14 patients (0.6%) were aged less than 12 years. The current analysis found that for the period September 2021 to August 2022, 24 incident (1.4%) and 45 prevalent (0.9%) patients aged less than 12 years were supplied omalizumab.

Under the current restrictions for initial treatment, patients must not receive more than 12 weeks of treatment and continuing patients must not receive more than 24 weeks of treatment. Estimates of length on treatment (Figure 5) indicate that patients are on treatment for longer than these periods.

The medical specialities involved in prescribing were generally consistent with those eligible under the restrictions (Table 15). Over the first five years of listing prescriptions were mainly written by immunologists or allergists (43%) followed by dermatologists (19%), with approximately one third of prescriptions being written by specialists outside of the current restriction (Table 16). This result is similar to the June 2020 DUSC review.

Approximately 41.5% of patients did not have an identified supply of a PBS-listed standard therapy prior to initiating on omalizumab. It is not possible to tell whether patients were taking non-PBS listed standard therapies prior to omalizumab initiation. The information provided in relation to patients on standard therapies prior to commencement on omalizumab is complicated by the fact that it does not include H1-antihistamines available over the counter which are therefore not included in this analysis. Further, the H2 receptor antagonist market over this time period was impacted by the suspension of ranitidine from the Australian Register of Therapeutic Goods. Some patients appear to be on standard therapy and omalizumab concurrently, which is consistent with clinical guidelines.

DUSC consideration

DUSC noted that the number of patients supplied omalizumab for CSU, the length on treatment and dose varied from the predicted over the first five years of listing. DUSC considered that these variations were due to several factors including patient awareness,

clinician enthusiasm, use in symptom control as opposed to being curative, possible flares (exacerbation) due to COVID infection, vaccination and anxiety, uncertainties in initial prediction of the population and possible leakage into milder case due to the subjectivity of the diagnostic criteria. The establishment of allergy clinics may have resulted in more patients being treated for CSU with omalizumab than previously anticipated taking into consideration the treatment resources available at the time of listing.

DUSC noted that patients were initiating and continuing on doses that varied from initial expectations and that the variation in expected down titrations was possibly due to the recent updating of Australasian Society of Clinical Immunology and Allergy guidelines. DUSC further noted that clinical experience indicates that CSU is a relapsing condition and that omalizumab is not a disease modifying agent but one used for symptom control. As such, an increase in flares prevents down titration and an increase in flares with down titration normally results in re-up titration to the previous or a higher dose and that ceasing treatment when the condition has been stabilised can lead to flare ups. DUSC noted that clinical experience indicated a dose of 300 mg for initiation and continuing treatment was probably more appropriate than 150 mg. DUSC noted that treatment requirements are unpredictable and that patients may be able to take a break in treatment when they enter remission which could last a few years but then have to re-initiate after relapse. DUSC noted that there was an incentive to prescribing the 300 mg dose for the patient as well as extending dosing time or interval between doses which can in effect lead to down titration through the less frequency of dosing.

DUSC noted that most of the prior treatment required to meet the PBS restriction for the initiation of treatment with omalizumab for CSU are not PBS listed and would therefore not be identified in the analysis of PBS data. DUSC considered that patients were likely to be undertaking treatment with over-the-counter antihistamines as per the restriction prior to treatment with omalizumab.

DUSC noted the Department of Health and Aged Care was conducting a systematic literature review to evaluate the evidence on the comparative clinical effectiveness of omalizumab and cyclosporin, with regard to the equi-effective doses for the treatment of CSU (the review).

DUSC actions

DUSC suggested that the review consider the following:

- clarification of the rationale for the 24-week treatment restriction for continuing patients;
- seeking clinical input from Australasian Society of Clinical Immunology and Allergy; and
- an analysis of the time between scripts.

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

Context for analysis

The DUSC is a Sub Committee of the 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

Novartis Pharmaceuticals Australia Pty Limited: 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.

To the extent provided by law, the Department of Health and Aged Care makes no warranties or representations as to accuracy or completeness of information contained in this report.

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Appendices

Appendix A: PBS Listed Standard Therapies

Medications available over the counter are **bolded**

Cimetidine
Ranitidine
Famotidine
Nizatidine
Brompheniramine Maleate
Promethazine
Cetirizine
Loratadine
Fexofenadine
Doxepin
Montelukast
Hydroxyzine Embonate
Meclozine Hydrochloride

Addendum: Omalizumab for chronic spontaneous urticaria

1. Purpose

At its June 2023 meeting, DUSC considered a predicted versus actual analysis of omalizumab for chronic spontaneous urticaria (CSU), including additional analyses on the trend in prescribing a higher dose (600 mg) of omalizumab for CSU and the age distribution of PBS patients.

This addendum presents the requested additional analysis of time between prescriptions for omalizumab.

Analysis of the time between scripts

DUSC considered that the original dosing analysis which included the distribution of dose (i.e. mass of medicine) per script over time and dose sequencing, could be enhanced by having regard to the time between script supply. Specifically to determine if dose titration was effectively occurring via changing the time between re-supply of prescriptions.

2. Methods and sources

PBS Authority Approval data and prescriptions data maintained by the Department of Health and Aged Care, processed by Services Australia, was extracted from 1 September 2016 to the end of February 2023 (the same period as used in the Item 7.2 analysis considered by the June 2023 DUSC meeting). Data was extracted based on the date of supply.

Dose analysis

Omalizumab is administered as monthly injections. The total amount of drug dispensed was calculated as the product of the mass per unit of drug supplied by the PBS quantity dispensed.

Time to resupply analysis

Time to resupply calculated for a prescription is the number of days from the supply of that prescription to the supply of the next prescription of the same medicine (regardless of the strength or treatment phase of the next prescription).

3. Results

Figure 1 presents a distribution of the number of days to resupply by the phase of treatment (initial and continuing).

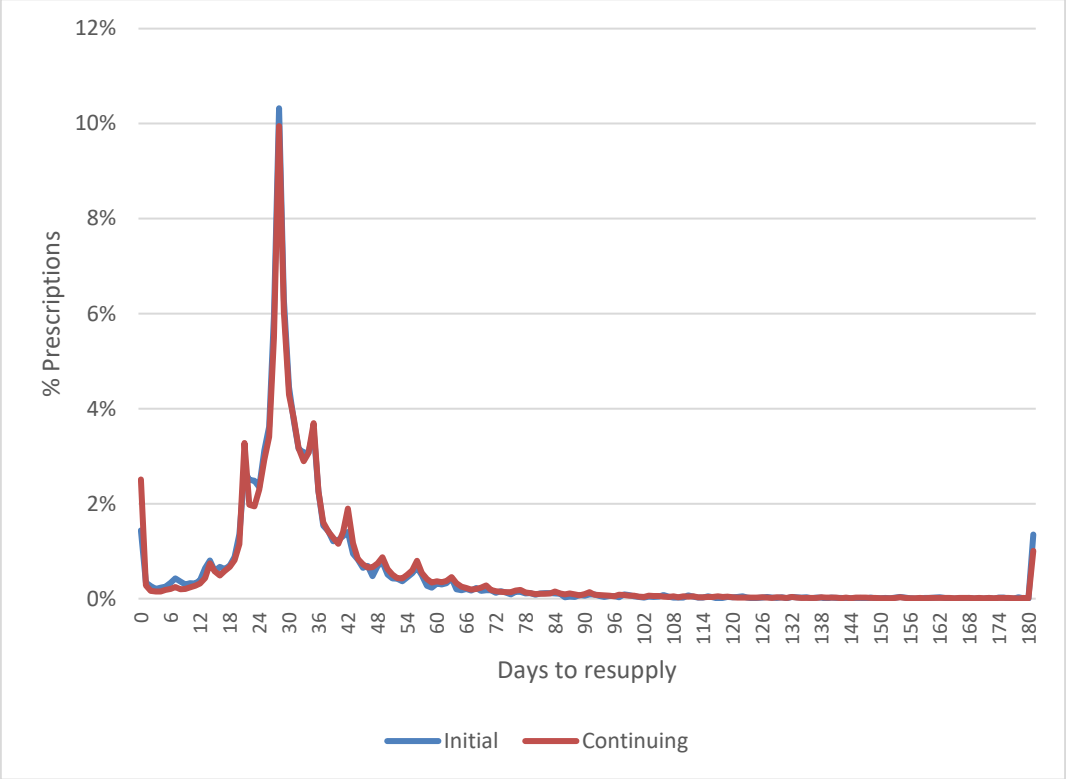

Figure 1: Distribution of days to resupply by treatment phase

Initial treatment phase items are;
11176F - omalizumab 150 mg/mL injection, 1 mL syringe (HSD Public, 2 repeats); and
11175E - omalizumab 150 mg/mL injection, 1 mL syringe (HSD Private, 2 repeats)

Continuing treatment phase items are;
11168T - omalizumab 150 mg/mL injection, 1 mL syringe (HSD Public, 5 repeats); and
11163M - omalizumab 150 mg/mL injection, 1 mL syringe (HSD Private, 5 repeats)

Generally the initial treatment phase consists of the first three prescriptions. It can be seen from Figure 1 that the distribution of days to resupply does not seem to differ much between the initial and continuing phases. A possible exception is that continuing scripts have a higher proportion with 0 days to resupply (i.e. two scripts filled on the same day). Some scripts have resupply after more than 90 days. It may be more correct to regard these scripts the last before a break in treatment, rather than scripts where the dosing has been extended over a long period of time. The tail of the distribution rises as there is a >180 days category on the end.

Tables 1 and 2 show the proportion of prescriptions that were resupplied within 31 days, between 32 to 62 days, more than 62 days and within a window ±7 days of two months from the prior supply, for initial and continuing treatment respectively.

Table 1: Proportion of prescriptions by resupply time for initial treatment, 2022

	Proportion
Proportion 31 days or less	56.5%
Proportion 32 to 62 days	37.0%
More than 62 days	6.5%
Within 7 days of two months from the last supply (days 55-69)	4.8%

Table 2: Proportion of prescriptions by resupply time for continuing treatment, 2022

	Proportion
Proportion 31 days or less	54.7%
Proportion 32 to 62 days	36.9%
More than 62 days	8.4%
Within 7 days of two months from the last supply (days 55-69)	6.0%

Figure 2 shows that the distribution of days to resupply does not differ much between the years of supply. A possible exception is that the more recent years have a higher proportion with 0 days to resupply.

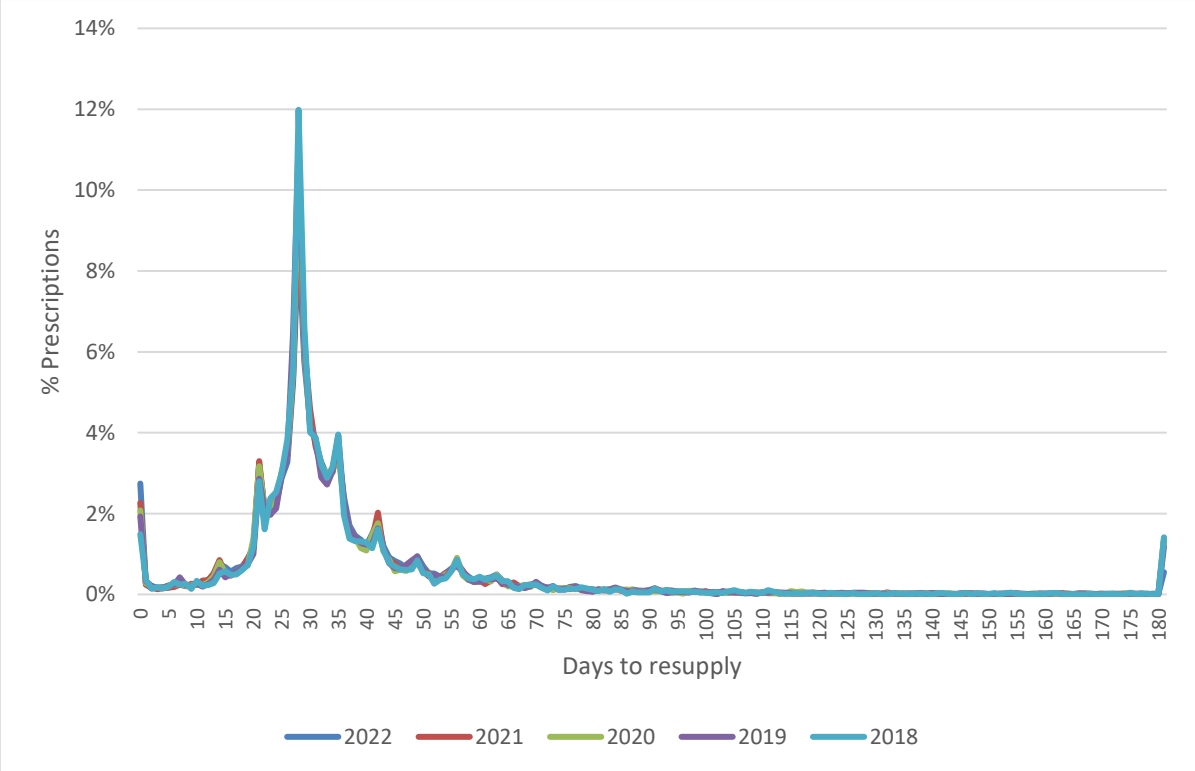

Figure 2: Distribution of days to resupply by year of supply

Figure 3 shows that the distribution of days to resupply does not differ much between different milligrams (mg) dispensed per script. An exception is that the 150mg scripts have a higher proportion with 0 days to resupply and a lower proportion resupplied around 21 days.

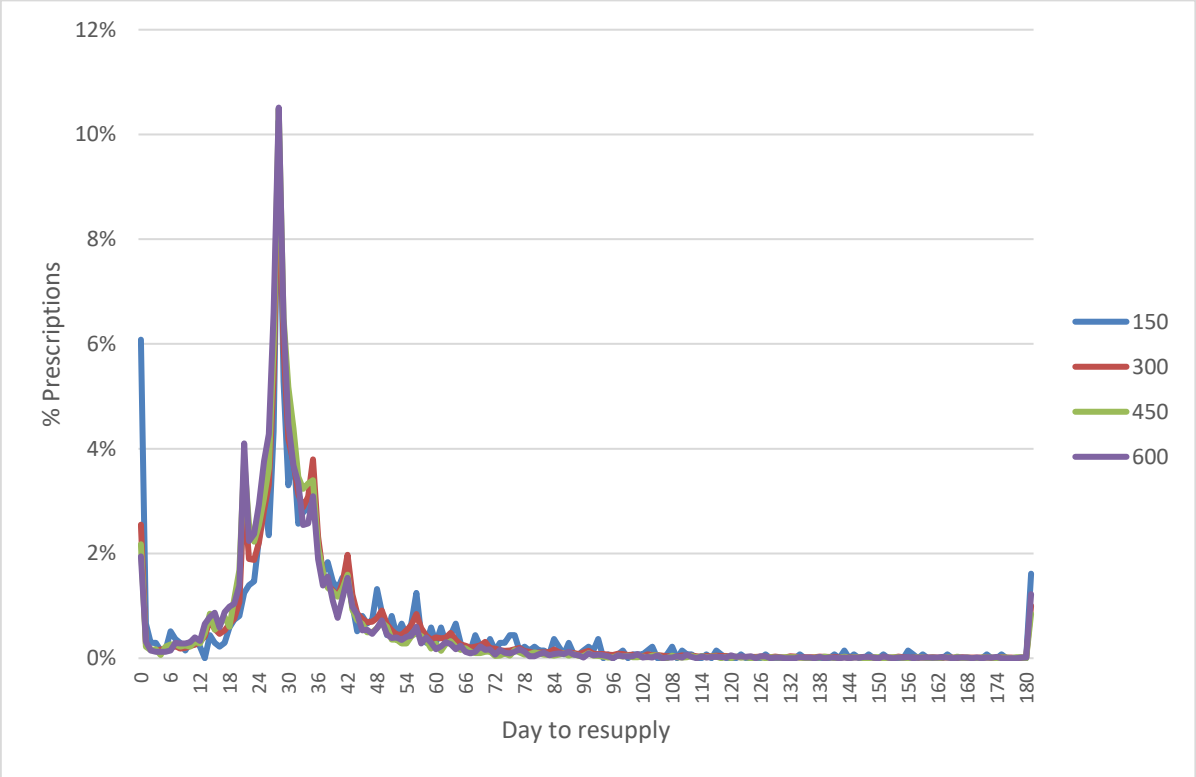

Figure 3: Distribution of days to resupply by omalizumab mg dispensed per script

Tables 3 and 4 show the proportion of prescriptions that were re-supplied within 31 days, between 32 to 62 days, more than 62 days and within a window ±7 days of two months from the prior supply, for 300 mg and 600 mg scripts respectively.

Table 3: Proportion of prescriptions by re-supply time for 300 mg scripts, 2022

	Proportion
Proportion 31 days or less	53.7%
Proportion 32 to 62 days	37.7%
More than 62 days	8.6%
Within 7 days of two months from the last supply (days 55-69)	6.2%

Table 4: Proportion of prescriptions by re-supply time for 600 mg scripts, 2022

	Proportion
Proportion 31 days or less	59.7%
Proportion 32 to 62 days	33.2%
More than 62 days	7.1%
Within 7 days of two months from the last supply (days 55-69)	4.9%

The scale of the x-axis of Figure 4 below has been limited to 90 days to better discern the differences in the very similar distributions. A small difference is that the proportion of first scripts resupplied between 21 and 28 days is higher than for subsequent scripts. Only plots for the first 6 scripts are shown to aid readability of the figure.

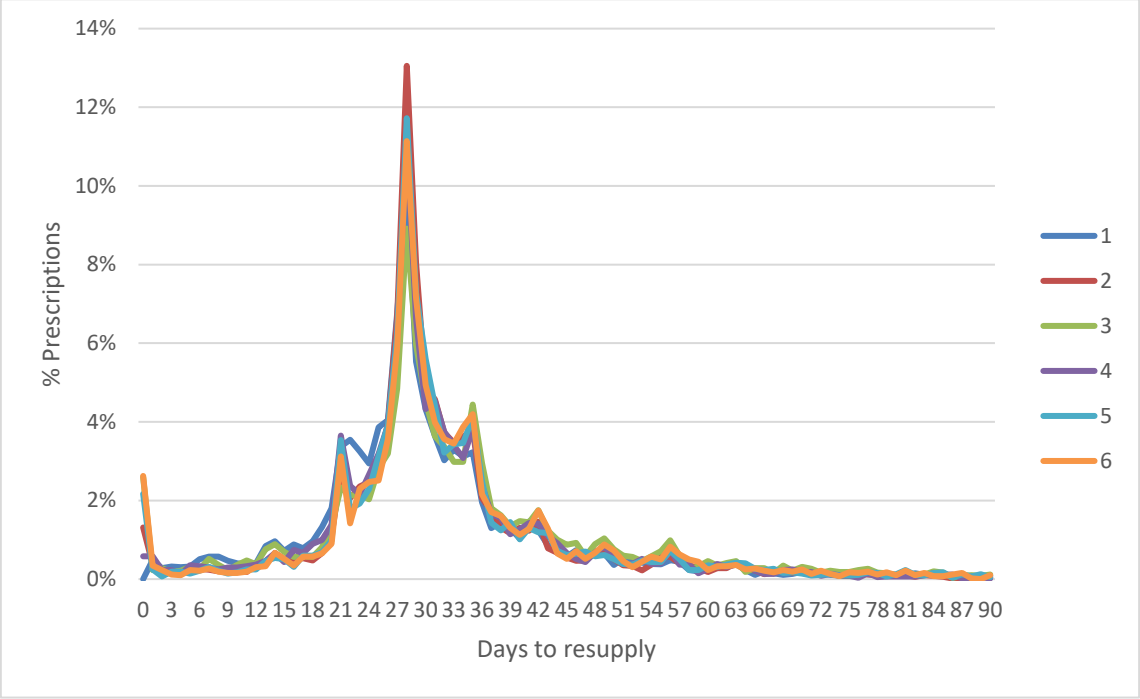

Figure 4: Distribution of days to resupply by prescription number

Figure 5 shows the average days to resupply for the distributions shown in Figure 4. It also shows these averages by year of supply. The averages were based on scripts whose time to resupply was 90 days or less. It was considered that scripts with longer time to resupply may include a break in treatment and so should be excluded from the average.

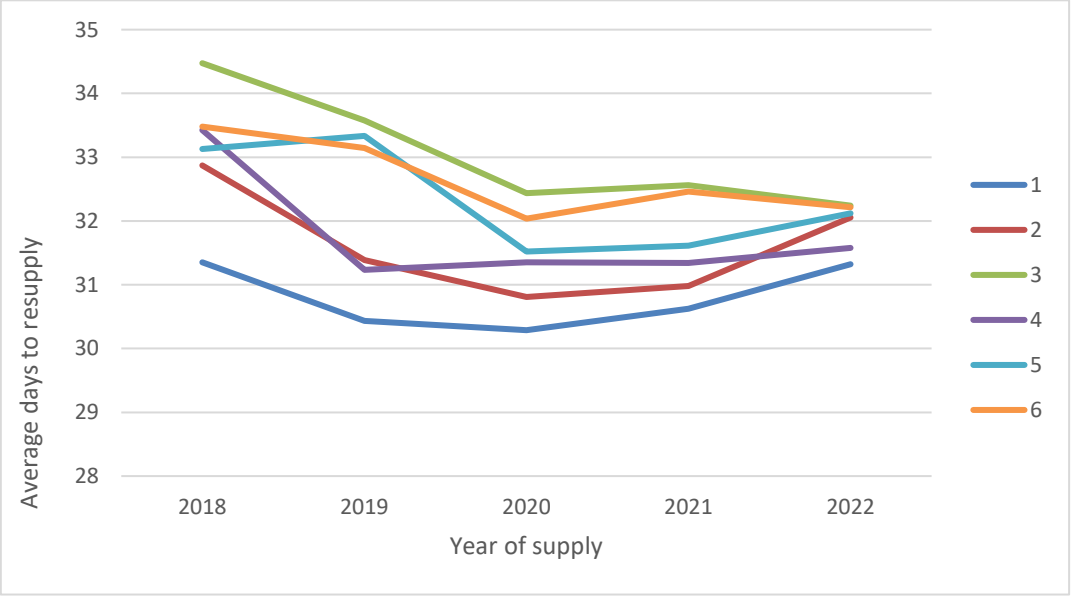

Figure 5: Average days to resupply by year and prescription number

Figure 5 shows a general trend of decreasing days to resupply from 2018 to 2020 and then relatively constant from 2020 to 2022. In the most recent three years to 2022 the trend has been for the days to resupply to increase through the initial treatment phase (scripts 1 to 3)

and then drop slightly at the start of the continuing phase (script 4) and increase again for scripts 5 and 6.

Omalizumab mg per day

An alternative measure of medicine utilisation is to calculate omalizumab mg per day for each script by dividing the mg dispensed per script by the days to resupply.

In Figure 6, for years 2021 and 2022 it appears there is a pattern of slight dose decrease between script 1 and scripts 2 & 3. This is repeated for the continuation phase where the first script (script 4) is slightly higher than scripts 5 & 6.

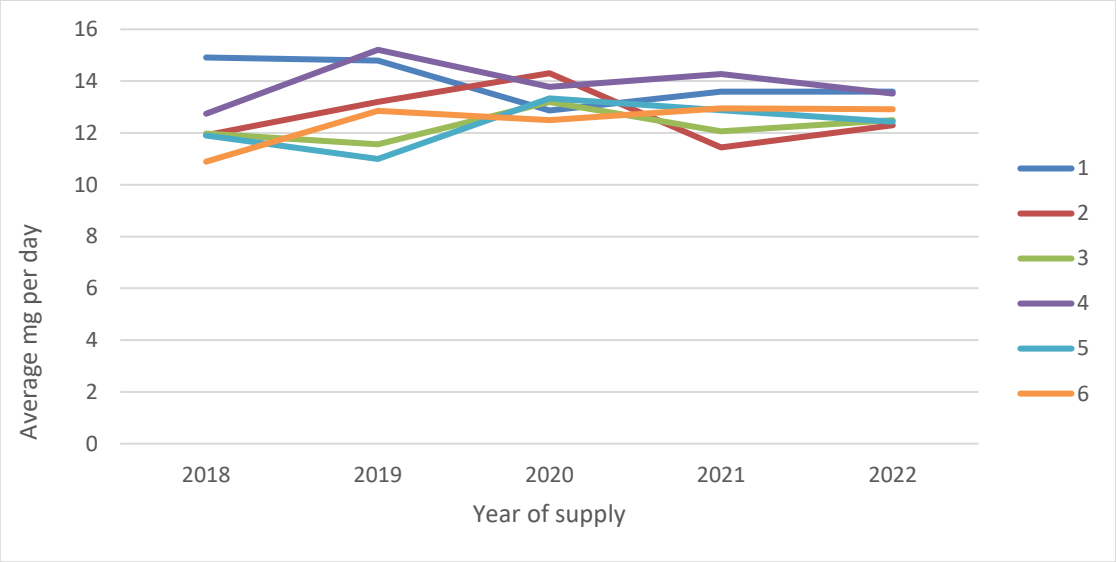

Figure 6: Average mg per day by year and prescription number

4. Discussion

The trend in the time to resupply of omalizumab has been consistent over the last five years to 2022 (Figure 2). The majority of patients had a time to re-supply, as initial or continuing treatment, within a month (Figure 1).

A small proportion of patients had a resupply within a two month window for both initial treatment (4.8%, Table 1) and continuing treatment (6.0%, Table 2). The proportion of patients with a time to resupply of greater than two months was 6.5% for initial treatment and 8.4 % for continuing treatment (Tables 1 and 2, respectively).

An analysis of 300 mg scripts showed that the proportion of patients with a supply within a window of 7 days of two months was small (6.2%) and around 9% of patients had a time to resupply greater than 62 days (Table 3).

Overall, the practice of down titrating through increasing the time to resupply does not appear to be evident and if it is occurring it is most likely in a small proportion of the total population.