Omalizumab for chronic spontaneous utricaria: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

June 2020

Abstract

Purpose

To compare the predicted and actual utilisation of omalizumab for severe chronic spontaneous urticaria (CSU) since it was PBS listed for this indication.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Omalizimuab was first listed on the PBS for severe chronic spontaneous urticaria on 1 September 2017.

Data Source / methodology

Authorities data and prescriptions data was extracted from the Services Australia prescription database and Authorities database from 1 September 2017, respectively. Data were extracted based on the date of supply.

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.

Purpose of analysis

To compare the predicted and actual utilisation of omalizumab for severe chronic spontaneous urticaria since it was PBS listed on 1 September 2017 for this indication.

Background

Clinical situation and management

Chronic spontaneous urticaria (CSU) is a condition characterised by a rash of raised wheals or hives arising spontaneously on most days of the week for six weeks or more (ASCIA 2019). 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 2019).

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 2019). 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	Cetirizine, desloratadine, loratadine, fexofenadine, promethazine, levocetirizine, cyproheptadine, dexchlorpheniramine, pheniramine, trimeprazine
H2 antagonists	Ranitidine, famotidine
Leukotreine receptor antagonists (LTRA)	Montelukast, pranlukast
Anxiolytics, sedatives	Doxepin, diphenhydramine
Immunosuppressants	Omalizumab, cyclosporine, sulfasalazine

Sources:
Drugs.com. Accessed on 11 April 2020 at www.drugs.com
De Silva et al. (2014)
eTG Complete. Accessed on 14 April 2020 at https://tgldcdp.tg.org.au/viewTopic?topicfile=urticaria-angioedema&guidelineName=Dermatology&topicNavigation=navigateTopic#toc_d1e64

The EAACI/GA^{2}LEN/EDF/WAO guideline (Zuberbier et al., 2018) for the definition, classification, diagnosis and management of urticaria recommends the use of omalizumuab as third line treatment in clinical practice, as depicted in Figure 1.

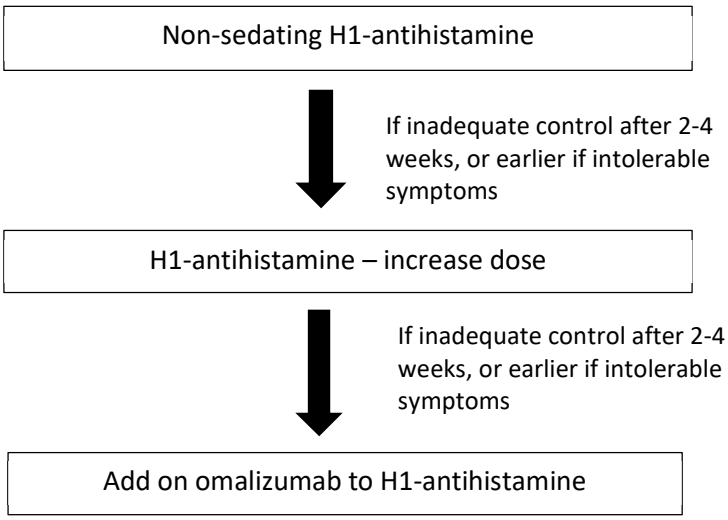

Figure 1: Treatment algorithm for urticaria

Source: Adapted from ASCIA (2019) and EAACI/GA2LEN/EDF/WAO guidelines (Zuberbier et al., 2018).

Under the 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 2019 guidelines, Table 1 p6.

The PBS clinical criteria defines standard therapy as H1 antihistamines at maximally tolerated recommended doses 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 treatment with H1 antihistamines and a H2 antagonist, or a leukotriene receptor antagonist or doxepin cannot be met because of contraindications according to the relevant TGA-approved Product Information and/or intolerances of a

severity necessitating permanent treatment withdrawal, details of the contraindication and/or intolerance 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).[1] It works by blocking a substance called 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.[2]

Therapeutic Goods Administration (TGA) approved indications

Omalizumab is indicated for adults and adolescent patients (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:

Add-on therapy for children 6 to less than 12 years of age with severe allergic asthma.

Management of adult and adolescent patients (greater than or equal to 12 years of age) with moderate to severe allergic asthma who are already being treated with inhaled corticosteroids.

Dosage and administration

The recommended dose for chronic spontaneous urticaria is 300 mg by subcutaneous injection every 4 weeks. Some patients may achieve control of their symptoms with a dose of 150 mg every 4 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.[2]

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

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[1] Xolair (omalizumab). Australian Approved Product Information. Novartis Pharmaceuticals Australia Pty Limited. Approved 13 June 2003, updated 22 January 2020. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2009-PI-00304-3&d=202004091016933

[2] Xolair (omalizumab). Australian Approved Consumer Medicines Information. Novartis Pharmaceuticals Australia Pty Limited. January 2020. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-CMI-05307-3

PBS listing details (as at 1 April 2020)

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

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	$860.19 [a]	Xolair, Novartis Pharmaceuticals Australia Pty Limited
11176F [Public Hospital]	Omalizumab 150mg/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	5	$860.19 [a]	Xolair, Novartis Pharmaceuticals Australia Pty Limited
11168T [Public Hospital]	Omalizumab 150 mg/mL injection, 1 mL syringe	2	5	$820.00 [a]	Xolair, Novartis Pharmaceuticals Australia Pty Limited

[a]Special pricing arrangement is in place
Source: the PBS website.

Abridged Restriction

Omalizumab 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 spontaneous urticaria (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 utricaria).
- 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 chronic spontaneous urticaria (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.

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

- Patient must have received non-PBS subsidised treatment with this drug for this condition prior to 1 September 2017
- Patient must have documented history of itch and hives that persisted on a daily basis for at least 6 weeks despite treatment with H1 antihistamines prior to commencing non-PBS subsidised treatment with this drug for this condition
- Patient must have documented history of failure to achieve and adequate response after a minimum of 2 weeks treatment with a standard therapy prior to commencing non-PBS subsidised treatment with this drug for this condition
- Patient must not receive more than 24 weeks of treatment under this restriction

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, with the equi-effective doses are 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. This PBAC recommendation has not been implemented yet. For further details, refer to the Public Summary Document (PSD) from the March 2018 PBAC meeting.

Approach taken to estimate utilisation

The financial estimates were developed using an epidemiological approach.

Commercial-in-confidence

[redacted]

[redacted]

End commercial-in-confidence

Methods

Authorities data and prescriptions data was extracted from the Services Australia prescription database and Authorities database from 1 September 2017, respectively. Data was extracted based on the date of supply.

Patient level analyses

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 supply.

Predicted versus actual analysis

The forecast utilisation for patients, packs and net cost to government (exclusive of copayments) was obtained from the final financial estimates model. 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 analyses

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 was investigated in patients who first initiated on a continuing script in 2018 with follow up to 31 December 2019.

Treatment duration

A cohort of patients first initiating on omalizumab between January to June 2019 was selected. Kaplan-Meier analysis was undertaken to analyse the time on treatment. Drug supply to each patient was followed up to 31 December 2019. 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.

Results

Analysis of actual versus predicted utilisation

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

	Year 1	Year 2
Number of patients		
[redacted]	[redacted]	[redacted]
Actual	1,267	2,206
[redacted]	[redacted]	[redacted]
Number of packs		
[redacted]		
[redacted]	[redacted]	[redacted]
Actual	13,461	30,171
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Net cost to government (exclusive of copayments)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

The number of patients was underestimated, mainly from an underestimate of continuing patients. [redacted] The actual number of Authorities approved for grandfathering treatment was 126 in Year 1.

Analysis of drug utilisation

Number of Authorities

Table 5: Number of Authority applications by listing year and Authority type

Application type	Year 1[a]	Year 2[a]	Year 3[b]
Initial treatment	1,214	1,146	662
Grandfather treatment	126	<5	0
Continuing treatment	832	1,628	1,600

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 2019 to 31 January 2020 based on date of approval.

Number of patients

Table 6: Number of incident (new) and prevalent (total treated) patients by listing year

	Year 1[a]	Year 2[a]	Year 3[b]
Incident	1,267	1,189	545
Prevalent	1,267	2,206	2,201

[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 2019 to 31 January 2020 based on date of supply.

Since 2018, the number of initiators to omalizumab has remained steady at around 100 patients per month (Figure 2). The number of total (prevalent) patients supplied omalizumab has grown linearly since its first listing in September 2017 (Figure 2).

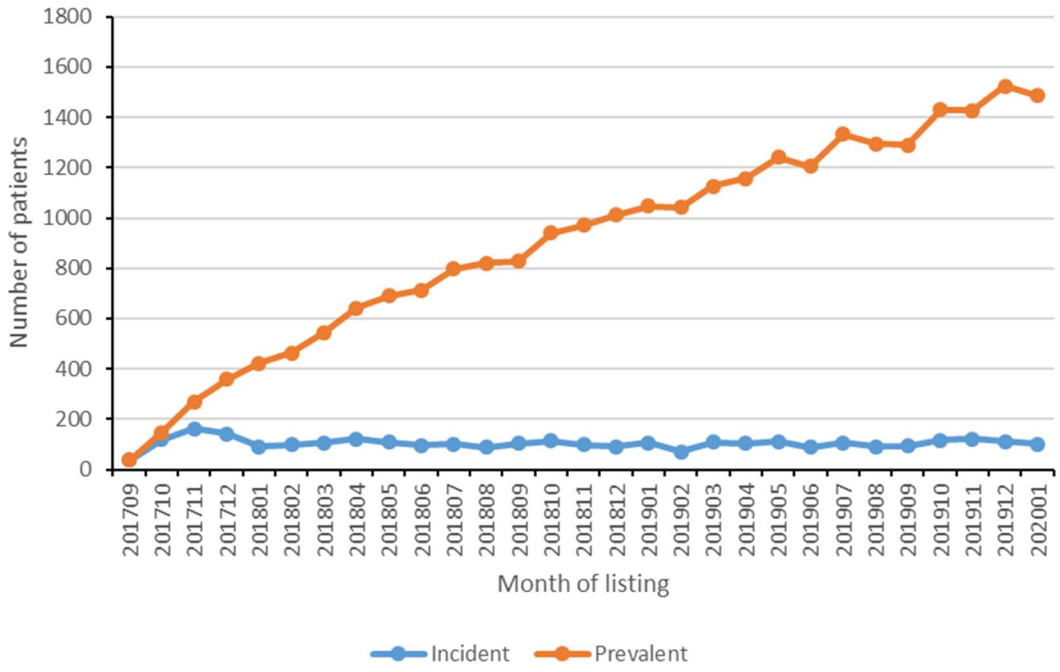

Figure 2: Number of incident (new) and prevalent (total treated) patients by month

Patient age

Omalizumab is restricted to patients aged 12 years or over. The age of patients supplied omalizumab in 2019 was examined. Of the 2,502 patients supplied treatment, only 14 cases (0.6%) were identified where patients were aged less than 12 years.

Dosing

In 2019, for both initial and continuing treatment the majority of prescriptions supplied were for 300 mg (Table 9). The number of cases where first initiating prescriptions were for

the 150 mg strength was negligible (Table 9). A small proportion of prescriptions were identified where an amount of drug higher than 300 mg was dispensed (Table 9).

Dose titration was examined in a six-month cohort of patients first initiating on omalizumab in January-June 2018 with follow-up to 31 December 2019. Only a small proportion of patients were found to down titrate from 300 mg to 150 mg (Table 10).

Table 7: Daily doses supplied during initial treatment, 2019

n	mean	median	min	max
3287	302.2	300	150	600

Table 8: Daily doses supplied during continuing treatment, 2019

n	mean	median	min	max
13767	305.9	300	150	600

Table 9: Proportion of prescriptions dispensed for initial and continuing treatment by dose dispensed, 2019

	Initial		Continuing	
	n	Proportion (%)	n	Proportion (%)
150mg	18	0.5%	205	1.5%
300mg	3230	98.2%	13145	95.3%
450mg	16	0.5%	131	1.0%
600mg	25	0.8%	306	2.2%
Total	3,289	100.0%	13,787	100.0%

Table 10: Sequences of doses dispensed to patients initiating in January to June 2018 with follow-up to 31 December 2019

Dose sequences	Number of patients	Proportion (%)
300	927	89.8
600	38	3.7
300 -> 450	26	2.5
300 -> 150	20	1.9
150 -> 300	7	0.7
300 -> 600	5	0.5
Other	9	0.9

Treatment duration

Time on omalizumab was examined in a cohort of patients initiating on omalizumab between January to June 2019 with follow-up to 31 December 2019. Time on treatment was analysed with and without treatment breaks (Figure 3).

The data was too immature to examine time on omalizumab with median survival not reached with the inclusion of breaks as at December 2019 (Figure 3).Of the 1,798 initiators, 1,125 (63%) were censored as they were identified as continuers.

The analysis showed early indications that the time on therapy in practice is less than assumed in the financial estimates. The predicted annual continuation rate of 80% whereas there were a lower proportion of patients continuing PBS treatment after one year (Figure 3).

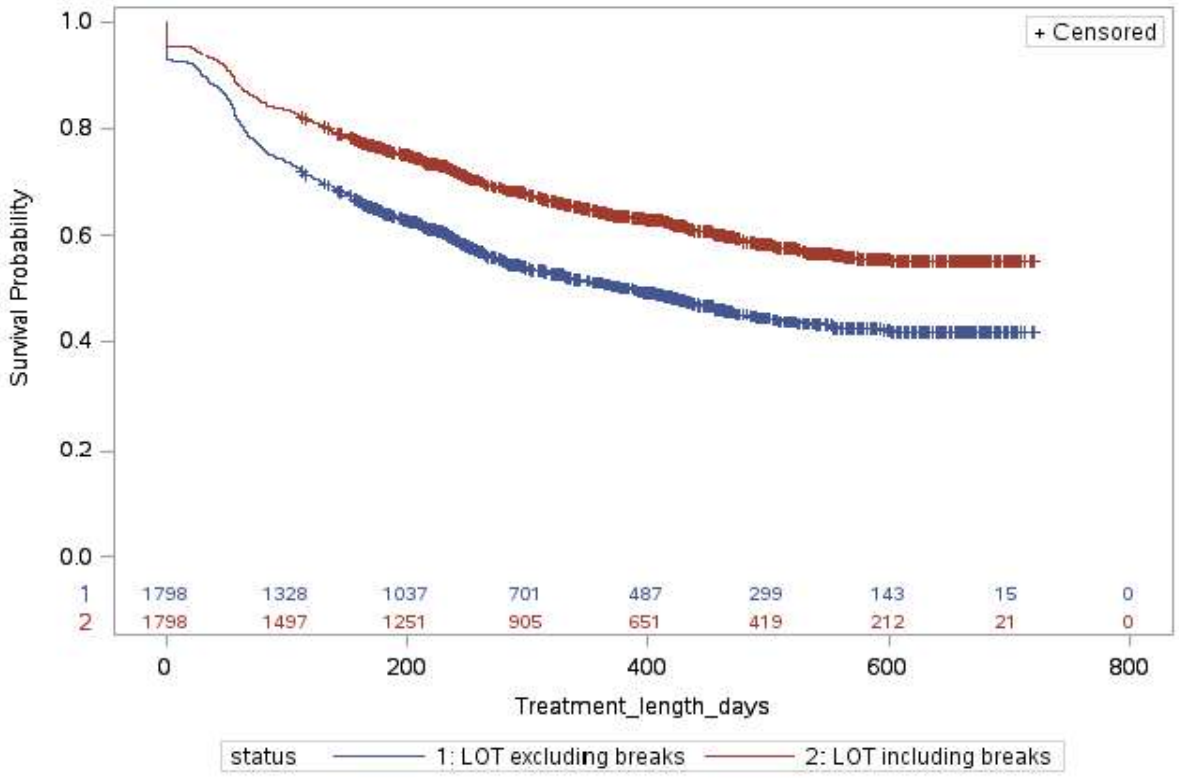

Figure 3: Time (days) on omalizumab for an initiating cohort in January-June 2018 with follow-up to 31 December 2020

Prescribers

The restrictions for omalizumab specify that only the following prescribers are authorised to prescribed subsidised therapy: clinical immunologist, allergist, dermatologist; or general physician with expertise in the management of CSU. In 2019, most prescriptions dispensed were prescribed by an immunologist, allergist or dermatologist (Table 11).

Table 11: Summary of prescriptions supplied by prescriber type, 2019

Prescriber Group	Scripts supplied	Proportion
Immunology and Allergy	7152	41.9%
Dermatology	2958	17.3%
Pathology	1358	8.0%
Respiratory and Sleep Medicine	1108	6.5%
Paediatric Medicine	1062	6.2%
Internal Medicine	933	5.5%
Non-vocationally registered GP	553	3.2%
Vocationally registered GP	320	1.9%
GP Trainee	42	0.2%
Rheumatology	11	0.1%
Gastroenterology and Hepatology	10	0.1%
GP Unclassified	8	0.05%
Other	1539	9.0%
Total	17054	100.0%

Discussion

The number of patients supplied omalizumab was more than predicted (Table 4). The sponsor estimated that [redacted] patients would first initiate on omalizumab within the first listing year, however there were 1,214 Authority applications approved for initial treatment (Table 5). This could indicate that one or more of the following assumptions was underestimated:

- The proportion of patients diagnosed and treated [redacted]; or
- the proportion of the treated population having severe disease [redacted]; or
- treatment uptake rate assumptions of [redacted] in Year 1 and [redacted] in Year 2.

DUSC (November 2015) considered that the applicability of the international data sources to the Australian PBS population was unclear. DUSC considered the proportion of patients treated was likely to have been underestimated 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 UAS7 score 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. Further, the number of grandfathered patients was underestimated (90 patients versus 126 actual Authority applications, Table 5).

The original November 2015 submission used the trial-based response rate of 59%, accounting for continuation criteria in the trial, to estimate the proportion of patients continuing on omalizumab. PBAC considered that it would be difficult to implement the continuation criteria in practice and recommended that this criteria was moved from the PBS restriction. The sponsor increased the estimate of the continuation rate to [redacted] percent after the removing of the continuation criteria from the restriction. Based on the treatment duration of patients first initiating on omalizumab between January to June 2018, a lower proportion of patients have persisted on treatment (Figure 3). As such, the number of packs per patient was less than predicted resulting in a relatively small difference in the actual versus predicted expenditure ([redacted]) despite a larger difference in the actual versus predicted number of patients ([redacted]), (Table 4).

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 in 2019, the majority of patients (over 95%) were supplied 300 mg (Table 9). Only a small proportion of patients (2%) first initiating on omalizumab in 2018 were identified as having down-tritrated from 300 mg to 150 mg (Table 10). These results suggest setting the equi-effective dose for omalizumab at 300 mg is appropriate.

The medical specialities involved in prescribing were generally consistent with those eligible under the restrictions (Table 11). In 2019, prescriptions were mainly written by immunologists or allergists (42%) followed by dermatologists (17%), (Table 11).

DUSC consideration

DUSC noted there was an increase in the number of patients receiving prescriptions, due to lower than expected continuation, however the increase in cost was only 9%. The variation in usage was related to the estimations in the utilisation analysis where there were issues in applicability of overseas data to Australian populations, uncertainty in continuation rates and also reduced frequency of dosage as advised by the Australasian Society of Clinical Immunology and Allergy (ASCIA).

DUSC noted that other areas that may need consideration are:

- Leakage into less severe groups due to the CSU scale being subjective.
- Approximately one third of prescriptions being provided by specialities outside of those listed in the restriction.
- Patient preference to stretch out dosing intervals as per stakeholder feedback.
- Limited usage in the PBS restriction of 12 weeks for initial scripts and 24 for continuing treatment.

Consumer input was sought from Allergy and Anaphylaxis Australia (A&AA). The response explained the A&AA rarely have members with CSU so they have limited understanding of their management in the community. A&AA suggested the Department consider a survey and call out to members which could be implemented through the A&AA social media pages, however due to the short lead time this was not undertaken. A&AA additionally suggested accessing the International group through social media for consumer input. The social media group had some discussions of omalizumab and the inconvenience of going to the doctor to get a regular injection.

Actions undertaken by the DUSC Secretariat

The report was provided to the sponsor of omalizumab.

DUSC actions

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

Context for analysis

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

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

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

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

Sponsors' comments

Novartis Pharmaceuticals Australia Pty Limited: The sponsor has no comment.

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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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