

Venetoclax for first-line treatment of chronic lymphocytic leukaemia or small lymphocytic lymphoma: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted and actual utilisation of venetoclax for first-line treatment of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) since its listing on the Pharmaceutical Benefits Scheme (PBS) and how the listing effected the second-line treatments for CLL and SLL.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Venetoclax in combination with obinutuzumab was listed for first-line treatment for CLL or SLL on 1 December 2020.

Data Source / methodology

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

Key Findings

- The actual uptake of venetoclax in combination with obinutuzumab for first-line treatment of CLL/SLL was ████████ over the first two years of listing than predicted.
- The actual substitution rate of chlorambucil in combination with obinutuzumab for venetoclax in first-line therapy is ████████ than predicted over the first two years of listing.
- The overall use of second-line therapies for CLL/SLL appears to have remained stable since the listing of venetoclax for first-line therapy. However, there appears to be a shift away from the use of ibrutinib towards venetoclax (as either monotherapy or in combination with rituximab) and to a lesser extent acalabrutinib for second-line therapy.
- The median time on treatment including breaks in supply was estimated to be 360 days and excluding breaks was estimated to be 315 days.

Purpose of analysis

To compare the predicted and actual utilisation of venetoclax for first-line treatment of CLL or SLL since its listing on the PBS and how the listing effected the second-line treatments for CLL and SLL.

Background

Clinical situation

CLL/SLL is a slow-growing cancer in which immature B-lymphocytes (B-cells) are found in the blood and bone marrow and/or in the lymph nodes. CLL and SLL are the same disease, but in CLL cancer cells are found mostly in the blood and bone marrow. In SLL cancer cells are found mostly in the lymph nodes. CLL/SLL is a type of non-Hodgkin lymphoma.

Data from the Australian Institute for Health and Welfare (AIHW) indicates that CLL had:

- an age-standardised incidence rate of 7.3 cases per 100,000 persons in 2022;
- a 5-year relative survival rate of 85.4%;
- an age-standardised rate in males of all ages being 9.7 cases per 100,000;
- an age-standardised rate in females of all ages being 5.1 cases per 100,000; and
- a mean age at diagnosis of 71.0 years (72.4 years for females and 70.2 years in males) in 2018.

At any time, the population of untreated CLL/SLL is made up of three subpopulations. Those who are asymptomatic but will require treatment sometime in the future, those who are asymptomatic and never require treatment and those who are symptomatic and currently require treatment.

Venetoclax is indicated for CLL or SLL for the treatment of patients who are considered unfit or unsuitable for chemo-immunotherapy.

Venetoclax is also indicated for:

- in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy.
- as monotherapy for the treatment of:
 - patients with relapsed or refractory CLL with 17p deletion, or
 - patients with relapsed or refractory CLL for whom there are no other suitable treatment options.
- in combination with azacitidine or low-dose cytarabine, for the treatment of adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy.

Other PBS listed treatments for CLL include:

Fludarabine appropriate

- First-line – fludarabine with cyclophosphamide and rituximab, bendamustine with rituximab.
- Second-line for Relapsed or Refractory (RR) – fludarabine with cyclophosphamide and rituximab.

Fludarabine inappropriate

- First-line – venetoclax and obinutuzumab, obinutuzumab and chlorambucil, rituximab and chlorambucil.
- Second-line for RR – venetoclax, venetoclax and rituximab, ibrutinib, acalabrutinib, idelalisib and rituximab.

Pharmacology

Venetoclax is a small-molecule inhibitor of B-cell lymphoma (BCL)-2. Overexpression of BCL-2 has been demonstrated in CLL cells, as well as various other haematological and solid tumour malignancies, and has been implicated in resistance to certain therapeutic agents. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins, triggering mitochondrial outer membrane permeabilisation, the release of cytochrome c from mitochondria and the activation of caspases.

Therapeutic Goods Administration (TGA) approved indications

Venetoclax was registered on the Australian Register of Therapeutic Goods (ARTG) on 5th of January 2017 in combination with obinutuzumab for the treatment of patients with CLL or SLL who are considered unfit or unsuitable for chemo-immunotherapy.

Venetoclax is also registered on the ARTG for the following indications:

- in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy
- as monotherapy for the treatment of:
 - patients with relapsed or refractory CLL with 17p deletion, or,
 - patients with relapsed or refractory CLL for whom there are no other suitable treatment options.
- in combination with azacitidine or low-dose cytarabine, for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Venetoclax product information includes a black triangle indicating that it is subject to additional monitoring in Australia. By being included in the Black Triangle scheme, this reminds health professionals and consumers to report suspected adverse events.

Dosage and administration

5-week ramp-up schedule

The starting dose of venetoclax is 20 mg once daily for 7 days. The venetoclax dose must be administered according to a weekly ramp-up schedule to the daily dose of 400 mg over a period of 5 weeks as shown in Table 1. The 5-week ramp-up schedule is designed to gradually reduce tumour burden (debulking) and decrease the risk of tumour lysis syndrome (TLS).

Table 1: Dosing schedule including ramp-up phase for patients with CLL/SLL

Week	Venetoclax daily dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

Source: Venclaxta® (Venetoclax). Australian Approved Product Information. [pdf \(tga.gov.au\)](https://www.tga.gov.au)

First line CLL/SLL:

Venetoclax should be given for a total of 12 cycles (28 days in each cycle) as shown in Table 2.

Table 2: Dosing Schedule for venetoclax in combination with obinutuzumab

Cycle, Day	Obinutuzumab	Venetoclax
Cycle 1, Day 1	Day 1: 100 mg Followed by 900 mg which may be administered on Day 1 or Day 2.	
Cycle 1, Day 8	1000 mg	
Cycle 1, Day 15	1000 mg	
Cycle 1, Day 22 – 28		20 mg daily ^a
Cycle 2, Day 1 – 7	Day 1 only: 1000 mg	50 mg daily ^a
Cycle 2, Day 8 – 14		100 mg daily ^a
Cycle 2, Day 15 – 21		200 mg daily ^a
Cycle 2, Day 22 – 28		400 mg daily ^a
Cycles 3 - 6, Day 1 - 28	Day 1 only: 1000 mg	400 mg daily
Cycles 7 - 12, Day 1 – 28		400 mg daily

Source: Venclaxta® (Venetoclax). Australian Approved Product Information. [pdf \(tga.gov.au\)](https://www.tga.gov.au)

Note:

^a5 week ramp-up (see Table 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 (as at 1 July 2023)

Table 3: PBS listing of venetoclax for first-line treatment of CLL or SLL

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11648C General Schedule	Venetoclax 50 mg tablet, 7 tablets	1	0	\$254.81 ^a	Venclexta [®] , AbbVie Pty Ltd
12188L General Schedule	Venetoclax 10 mg tablet [14 tablets] (&) venetoclax 50 mg tablet [7 tablets] (&) venetoclax 100 mg tablet [7 tablets] (&) venetoclax 100 mg tablet [14 tablets], 1 pack.	1	0	\$1791.55 ^a	Venclexta [®] , AbbVie Pty Ltd
12199C General Schedule	Venetoclax 100 mg tablet, 120 tablets.	1	5	\$7784.30 ^a	Venclexta [®] , AbbVie Pty Ltd
12205J General Schedule	Venetoclax 100 mg tablet, 120 tablets.	1	4	\$7784.30 ^a	Venclexta [®] , AbbVie Pty Ltd
12999E General Schedule	Venetoclax 10 mg tablet, 2 tablets	7	0	\$107.85 ^a	Venclexta [®] , AbbVie Pty Ltd

Source: the [PBS website](#).

Note:

^aSpecial Pricing Arrangement is in place.

Restriction

Initial treatment in first-line therapy - Dose titration (weeks 1 to 4 of a 5-week ramp-up schedule).

Clinical criteria:

- The condition must be untreated, AND
- Patient must be inappropriate for fludarabine based chemo-immunotherapy, AND
- The treatment must be in combination with obinutuzumab, AND
- Patient must have a creatinine clearance 30 mL/min or greater, AND
- Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage); OR
- Patient must have a creatinine clearance less than 70 mL/min.

First continuing treatment (treatment cycles 2 to 6 inclusive) of first-line therapy.

Clinical criteria:

- Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND

- The treatment must be in combination with obinutuzumab, AND
- The treatment must cease upon disease progression.

Second and final continuing treatment prescription (treatment cycles 7 to 12 inclusive) of first-line therapy.

Clinical criteria:

- Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND
- The treatment must cease upon disease progression; OR
- The treatment must cease upon completion of 12 cycles of treatment with this drug for this condition, whichever comes first.

Notes:

No increase in the maximum quantity or number of units may be authorised.

No increase in the maximum number of repeats may be authorised.

Special Pricing Arrangements apply.

Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

For details of the current PBS listing refer to the [PBS website](#).

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

The PBAC first considered venetoclax in March 2020. The submission was not recommended as the incremental cost-effectiveness ratio (ICER) was difficult to ascertain based on the economic model provided and the financial estimates were highly uncertain.

For further details refer to the [Public Summary Document \(PSD\)](#) from the March 2020 PBAC meeting.

After considering a minor resubmission requesting listing for venetoclax, which took into consideration the advice that PBAC provided in relation to the March 2020 submission, PBAC recommended the listing of venetoclax at its July 2020 meeting.

For further details refer to the [Public Summary Document \(PSD\)](#) from the July 2020 PBAC meeting.

Approach taken to estimate utilisation

An epidemiological approach was applied in estimating the utilisation and financial implications resulting from the listing of venetoclax.

Australian Bureau of Statistics (ABS) data was used to estimate the projected total Australian population.

CLL/SLL incidence rates were derived from reports of incidence and mortality statistics for cancers in the Australian Cancer Incidence and Mortality books (ACIM) produced by the AIHW. AIHW reported a CLL/SLL incidence rate of 7.2 per 100,000.

The July 2020 PBAC submission assumed that there is no prevalent population, instead a delay in the supply of the drug to incident patients was applied for [redacted] of patients as a watch and wait approach was often taken for CLL/SLL patients. Of those diagnosed [redacted] were estimated to receive treatment at some time, of these [redacted] of patients were assumed to initiate treatment immediately, [redacted] initiate treatment within [redacted] ([redacted]), and [redacted] would never initiate treatment based on clinical advice.

The proportion of patients unsuitable for fludarabine based chemo-immunotherapy was estimated to be [redacted] based on clinical advice and published literature.

[redacted]

It was expected that [redacted] of the patients who receive venetoclax would have otherwise received chlorambucil in combination with obinutuzumab, and there would be no substitution for rituximab in combination with chlorambucil.

Treatment duration under the restriction is fixed at 12 months.

The proportion of patients initiating second-line treatment each year after initiating venetoclax was assumed to decrease as compared to chlorambucil in combination with obinutuzumab as extrapolated from the randomised control trial (CLL-14) after 3.5 years.

Table 4: Proportion of patients initiating second-line treatment each year after initiating first-line treatment

Year	Venetoclax and Obinutuzumab	Chlorambucil and Obinutuzumab
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]

Source: Final version of the financial estimates model.

Previous reviews by the DUSC

October 2020

Ibrutinib for CLL and SLL: 24 month predicted versus actual analysis

Key Findings

- Since its listing in December 2017 the utilisation of ibrutinib had increased steadily. Data to June 2020 indicated approximately 1,000 prevalent patients and 40 incident patients were supplied ibrutinib per month.
- In the first year of listing, ibrutinib had 1,435 initiating patients. This was similar to the [REDACTED] patients that was estimated in agreed estimates model. There was a [REDACTED] decrease in incident patients in 2019 compared to year 2 of the estimates model.
- In 2019 the number of initiating patients is substantially less than predicted and due to this expenditure on ibrutinib was less than anticipated.
- The addition of venetoclax onto the PBS in March 2019 was likely to be the cause of reduction in ibrutinib incident patients.
- [REDACTED] The duration of ibrutinib was estimated to be 23.4 months, but median time on treatment was not reached in the first 942 days (~31 months) of PBS data with a mean time on ibrutinib of 21.75 months.
- There were negligible cases detected of ibrutinib use as first-line therapy. However there was some evidence to suggest that ibrutinib was potentially being used in combination with rituximab or venetoclax.
- Approximately 68% of incident patients did not have fludarabine in their dispensing history prior to starting ibrutinib, indicating that these patients may not have been suitable for treatment with a purine analogue. The sponsor estimated the number of patients who are not suitable for treatment or retreatment to be [REDACTED]. Since 68% does not include those patients who are not suitable for retreatment then in practice this number could be larger.
- A large portion of patients (19%) moved on to treatment with ibrutinib within six months of ceasing their previous line medications and 68% within 42 months. The group of patients starting treatment within six months were potentially refractory, followed by a consistent amount of potentially relapsing patients in the 7- 42 months group after which the rate of relapsing patients steadily declined.

For details of the DUSC consideration of Ibrutinib for CLL/SLL refer to the [Public Release Document](#) from the October 2020 DUSC meeting

Methods

Data extracted from the PBS claims database maintained by the Department of Health and Aged Care and processed by Services Australia were used for the analyses. Prescription data were extracted from 1 December 2017 up to and including 31 May 2023. Data for the

analysis of treatment sequence and duration was extracted from 1 January 2017 to 31 August 2023.

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 ([REDACTED]) was undertaken from the date of listing. The benefits paid and net cost to government are based on the published list prices. The projected figures were adjusted to the period December to November (i.e. by listing year) to align with the first listing date of venetoclax. 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.

Treatment sequence and treatment duration

The following PBS listings were included in the data extraction:

- Venetoclax first-line (in combination with obinutuzumab): 11648C, 12188L, 12199C, 12205J and 12999E.
- Venetoclax second-line: 11624T, 11630D and 11639N.
- Acalabrutinib for relapsed/refractory (RR) patients: 12117R and 13318Y.
- Ibrutinib for RR: 11213E.
- Idelalisib for RR: 11170X and 11162L.

The data was sorted by the unique de-identified patient identifier and the date of supply.

Patients were identified who had a first ever supply of venetoclax for first-line treatment. A lookback period to 1 January 2017 was used to identify new patients first initiating on venetoclax first-line. All supplies to this initiating cohort, including further first-line venetoclax claims and claims for RR listings, were followed up to 31 August 2023.

The sequence of supply by date order and drug regimen was analysed from the first ever supply of venetoclax for first-line to the analysis end date.

The treatment duration was based on the time when a patient was first ever supplied venetoclax for first-line treatment to their last supply of their first episode on venetoclax. A

lookback period to 1 January 2017 was used to identify new patients first initiating on a first-line listing for venetoclax.

The median time between supplies of venetoclax first-line was obtained (29 days). A patient was assumed to be taking a break in treatment if they did not have a re-supply within 87 days of their last supply (i.e. three times the median time between supplies). A patient was assumed to be continuing on venetoclax first-line if they had a supply within 87 days of the analysis end date of 31 August 2023.

Kaplan-Meier analysis was undertaken to determine the mean, median, lower 95%CI and upper 95%CI time of supply of venetoclax first-line.

Results

Analysis of drug utilisation

Table 5 provides the incident and prevalent patient numbers by listing year.

Table 5: Number of venetoclax incident (new) prevalent (total treated) patients and scripts by listing year

	Year 1 ^a	Year 2 ^a	Year 3 ^b
Incident patients	553	563	317
Prevalent patients	553	934	742
Total scripts supplied	2,682	4,539	2,750

Note:

^a The figures are presented in listing years (December to November).

^b Utilisation in year to date from 1 December 2022 to 31 May 2023 based on date of supply.

Patient age and Gender

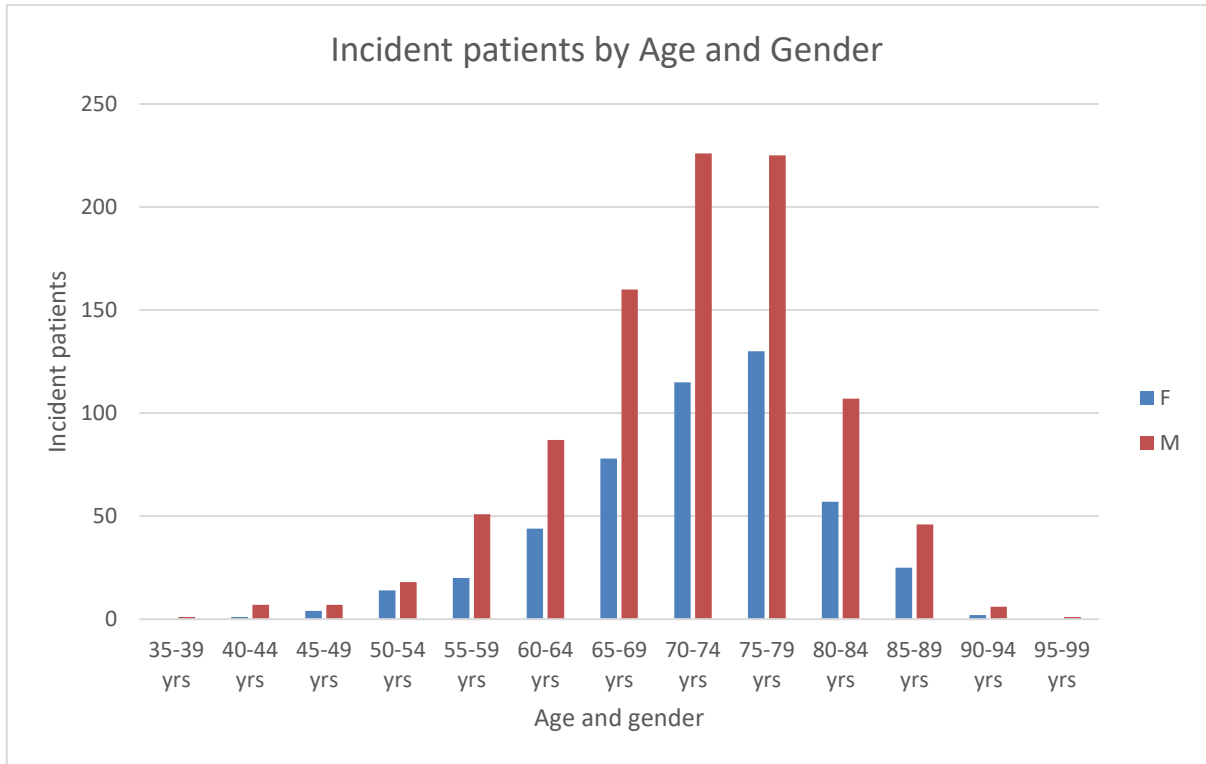


Figure 1: Incident patients by gender and 5-year age group

Figure 1 provides a distribution of venetoclax supply by age and gender from 1 December 2020 to 31 May 2023.

Changes in the use of other drugs

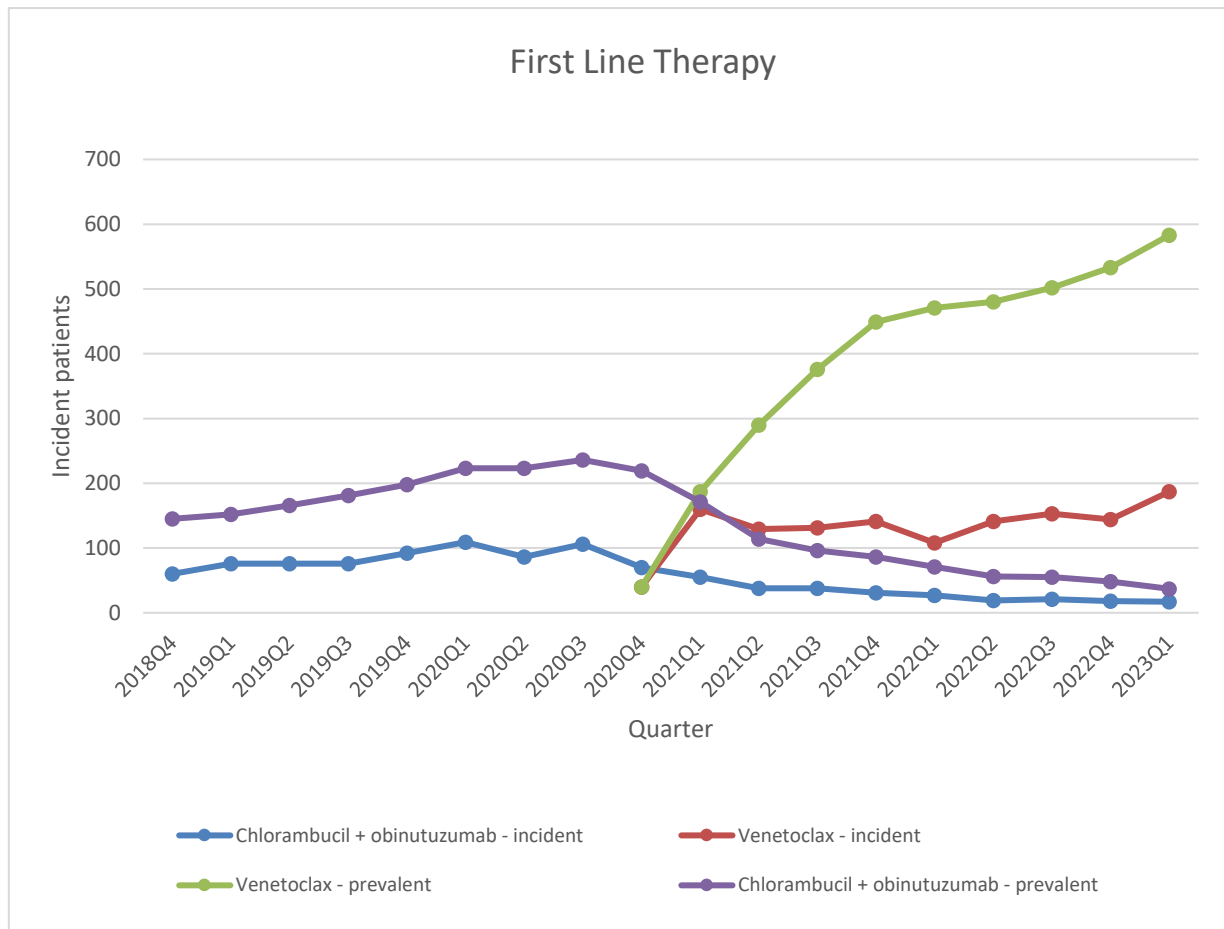


Figure 2: Number of treated incident patients and treated prevalent patients by quarter with first-line therapy

Note:

For patients who are not appropriate for fludarabine based therapy.

Does not include rituximab in combination with chlorambucil.

Figure 2 shows that the number of initiating patients for venetoclax is relatively stable while the number of treated prevalent patients is growing each quarter. There is a decrease in the number of initiating and treated patients on chlorambucil in combination with obinutuzumab occurring at the same time.

Table 7 compares the predicted substitution rate to the actual substitution rate of chlorambucil in combination with obinutuzumab for venetoclax and the assumed uptake rate to the actual uptake rate of venetoclax in first-line therapy for CLL/SLL. Substitution of chlorambucil in combination with obinutuzumab for venetoclax has [REDACTED] as predicted but is increasing year-on-year. Actual uptake was significantly [REDACTED] than expected in the first year of listing.

Table 7: Substitution of chlorambucil in combination with obinutuzumab for venetoclax in first line therapy

	Year	Year1 ^a	Year2 ^a
A	Actual venetoclax incident patients	553	563
B	Actual chlorambucil and obinutuzumab incident patients	173	88
C	Total incident patients treated ^c	726	651
D	Substitution rate ^b	76%	86%
E	Predicted substitution rate	■	■
F	Predicted patients eligible for 1st line treatment ^d	■	■
G	Actual uptake	83%	83%
H	Assumed uptake ^e	■	■

Source: The assumed eligible for 1st line treatment and substitution, and uptake were sourced from the final version of the financial estimates model.

Note:

^aThe figures are presented in listing years (December to November) and given for years prior to and post listing.

^bReplacement of chlorambucil in combination with obinutuzumab for venetoclax in 1st line treatment assumes no change in other 1st line treatments. Calculated as a percentage of A/C.

^cTotal first line treatment not including rituximab in combination with chlorambucil.

^d2020 taken as year for eligible population for year 1.

^eCalculated as a percentage of A/F.

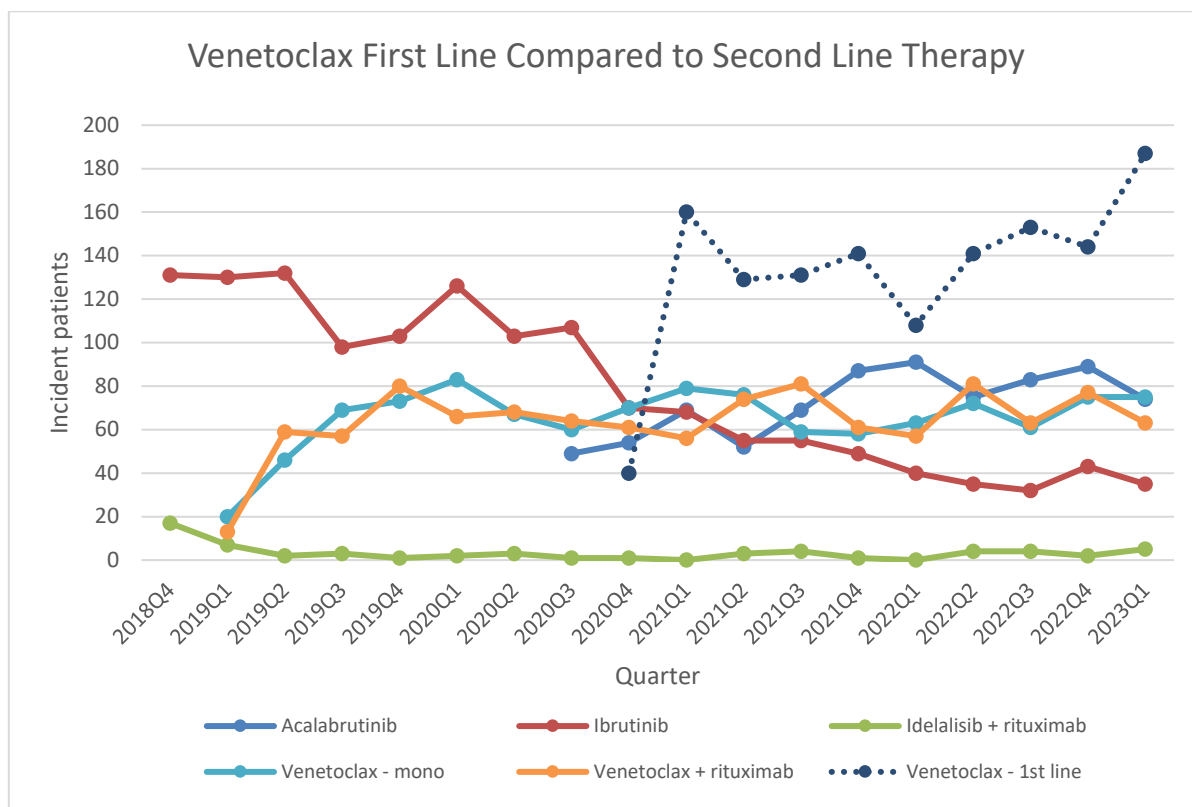


Figure 3: Number of treated incident patients by quarter with second line therapy and venetoclax for first line therapy

Figure 3 and Table 8 shows the possible effect of venetoclax for first-line treatment of CLL/SLL on the utilisation of second-line treatments for CLL/SLL. The total number of patients initiating second-line therapy has remained stable since listing of venetoclax for first-line therapy.

Table 8: Number of treated incident patients with venetoclax and 2nd line therapies

	Year-2 ^a	Year-1 ^a	Year1 ^a	Year2 ^a
Venetoclax for 1 st line Therapy	NA	NA	553	563
Total 2 nd line Therapies	872	1,053	1,034	1,063

Note:

^aThe figures are presented in listing years (December to November) and given for years prior to and post listing.

For patients who are not appropriate for fludarabine based therapy.

Treatment sequence

Tables 9 provides information on treatment sequence for venetoclax for first-line therapy and other second-line therapies for CLL/SLL for fludarabine inappropriate patients.

Table 9 indicates that since first listing on 1 December 2020 to 31 August 2023, for patients whose first ever supply of venetoclax was for first-line therapy for CLL/SLL, the majority of patients were only supplied venetoclax for first-line therapy. Only a small proportion of

patients had a further supply of venetoclax for the treatment of second-line (relapsed or refractory (RR)) CLL/SLL.

Table 9 Sequence of CLL and SLL listing supplied for patients first initiating on venetoclax for first-line treatment

Sequence of drug regimen	Patient count	Proportion of initiating patients
Venetoclax with Obinutuzumab first line	1,172	92.4
Venetoclax with Obinutuzumab first line -> Venetoclax RR	88	6.9
Other sequences:	8	0.6
Venetoclax with Obinutuzumab first line -> Acalabrutinib RR		
Venetoclax with Obinutuzumab first line -> IbrutinibRR		
Venetoclax with Obinutuzumab first line -> Venetoclax RR -> Acalabrutinib RR		
Venetoclax with Obinutuzumab first line -> Venetoclax RR -> Ibrutinib RR		

Table 10 shows the treatment pathway patients commenced upon once they had completed the first 6 cycles of therapy with venetoclax for the first two years of listing. The patient count is 1,030 of the 1,116 initial patients as some patients were still continuing cycles 1 to 6 of treatment.

Table 10: Treatment pathway for patients who have completed cycles 1 to 6

Treatment pathway	Patients ^a
Continue onto Cycles 7 to 12	705
Commence 2 nd line treatment	68
Cease treatment	257

Note:

^aExcludes patients who commenced in cycle 1-6 after 18 months from the listing of venetoclax as these patients would likely still be continuing treatment when the data was extracted.

Treatment duration

Time (days) on treatment for all patients initiating venetoclax with follow-up to the end for August 2023. Time on treatment was analysed with and without treatment breaks with the break length removed (Table 11, Figure 4). From 1 December 2020 to 31 August 2023, a total of 1,268 patients first initiated on a venetoclax listing for first-line treatment. Of these patients, 41.8 percent of patients were identified as having a continuing supply of venetoclax for first-line and these patients were censored from the Kaplan-Meier analysis (Table 11).

Including breaks in supply, the mean time on venetoclax for first-line treatment was 378 days (median 360 days), (Table 11). Only a small number of patients had a treatment break

(Table 2). When excluding treatment breaks, the mean time on venetoclax first-line was reduced to 288 days (median 315 days), (Table 11).

Percent censored including treatment breaks was 32.6% and excluding breaks was 42.1%.

Table 11: Estimated length of treatment from Kaplan-Meier analysis in patients who initiated first-line venetoclax treatment

	Number of patients	Censored	Mean (days)	Median (days)	95% confidence interval (days)	
Including breaks	46	15	378.1	360	300	479
Excluding breaks	1,222	515	287.7	315	309	320

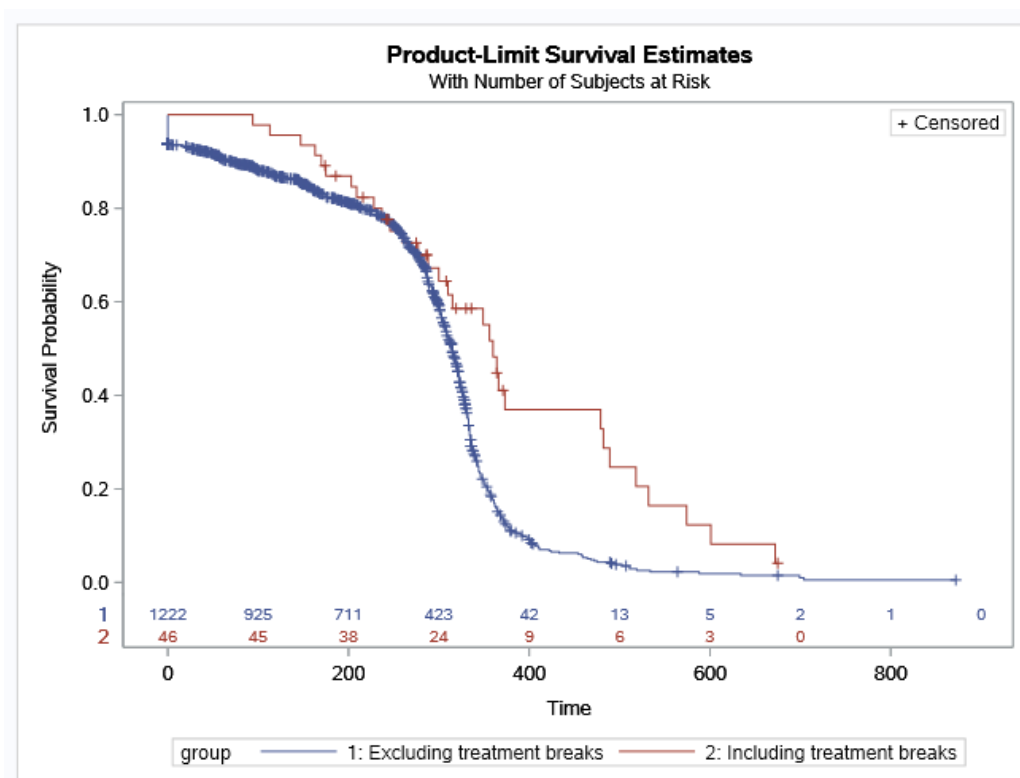


Figure 4: Kaplan-Meier analysis of the number of days patients were supplied venetoclax, excluding and including treatment breaks.

Analysis of actual versus predicted utilisation

Table 12 compares the predicted versus the actual utilisation and cost to government of venetoclax over the first two years of listing. The number of predicted patients was significantly [REDACTED] than actual patients as was the net cost to government in the first year of listing.

Table 12: Comparison of predicted versus actual utilisation of venetoclax for each year of listing

	Year 1 ^a	Year 2 ^a
Number of patients		
Predicted ^d	[REDACTED]	[REDACTED]
Actual	553	563
Difference ^b	[REDACTED]	[REDACTED]
Number of scripts		
Predicted ^d	[REDACTED]	[REDACTED]
Actual	2,682	4,539
Difference ^b	[REDACTED]	[REDACTED]
Net cost to government^c		
Predicted	[REDACTED]	[REDACTED]
Actual	[REDACTED]	[REDACTED]
Difference ^b	[REDACTED]	[REDACTED]

Source: The predicted figures were sourced from the final version of the financial estimates model.

Note:

^a The figures are presented in listing years (December to November).

^b Difference is calculated as: $((\text{Actual} - \text{Predicted}) / \text{Predicted}) \times 100$.

[REDACTED]

^d Source: Years 1 and 2 of Risk Sharing Agreement.

Discussion

The mean age of incident (new) patients on venetoclax was 72 years, with males being slightly younger (71.8 years) than females (72.3 years). The majority of incident patients on venetoclax were males (66%) as compared to females (34%) (Figure 1). This age and gender distribution is consistent with AIHW data on CLL.

The actual uptake rate was [REDACTED] in the first two years of listing then assumed with an actual uptake rate of 83% in year 1 compared to an assumed uptake rate of [REDACTED] the rate of uptake appears to have remained steady in year 2 at 83% which is still [REDACTED] than the [REDACTED] assumed (Table 7 and Figure 2). The actual substitution rate of chlorambucil in combination with obinutuzumab for venetoclax is [REDACTED] than predicted over the first 2 years of listing (Table 7).

The use of ibrutinib in second-line therapy of CLL/SLL has decreased (Figure 3). This decrease appears to have commenced with the increased use of venetoclax (monotherapy) and venetoclax in combination with rituximab for second-line therapy after March 2019 and appears to have accelerated around the same time as the listing of acalabrutinib for second-line therapy on 1 September 2020 and venetoclax for first-line therapy on 1 December 2020. The overall use of second-line therapies for CLL/SLL appears to have remained stable since the listing of venetoclax for first-line therapy possibly as result of the introduction of acalabrutinib for second-line therapy just prior to that of venetoclax for first-line therapy (Figure 3 and Table 8). Overall, there appears to be a shift away from the use of ibrutinib towards venetoclax (as either monotherapy or in combination with rituximab) and to a lesser extent acalabrutinib for second-line therapy (Figure 3). Of those patients who completed cycles 1 to 6 of venetoclax during the first two years of listing approximately 63.2% (705) continued onto cycles 7 to 12, a further 6.1% (68) commenced on second-line therapy, and 23% (257) ceased treatment (Table 10), with the remainder likely continuing to be in cycles 1 to 6 of therapy.

Under the current restriction for venetoclax patients must not receive more than 12 cycles of treatment, with each cycle consisting of 28 days (Table 2) this gives a total length of treatment of 336 days. Estimates of actual length of treatment (Table 11, Figure 4) indicate that only a small minority of patients are on treatment longer than this period of time.

The actual number of patients on venetoclax was [REDACTED] over the first two years of listing than predicted (Table 12) which may be due to a combination of the [REDACTED] substitution rate counterbalanced by a [REDACTED] uptake rate (Table 7).

DUSC consideration

DUSC noted that there had been a number of changes to the restrictions of PBS listed therapies for first and second-line (relapsed/refractory) treatments for CLL/SLL that commenced on 1 September 2023. These changes included removing the requirement for venetoclax in first-line therapy for patients to be, in effect, unfit for chemo-immunotherapy. DUSC noted that this will have the effect of broadening the restriction to include patient populations that were ineligible to be treated with venetoclax for first-line

therapy under the previous restriction. And the listing of zanubrutinib for first and second-line treatment for CLL/SLL. DUSC considers that these changes will affect the use of venetoclax in both first and second-line therapy, the use of other second-line treatments, and that the use of chemo-immunotherapy will be greatly reduced in both first and second-line therapy.

DUSC noted that the uptake of venetoclax for first-line therapy was different than first predicted and that the substitution of chlorambucil in combination with obinutuzumab by venetoclax in first-line therapy was different than predicted. DUSC considered that there may have been a small amount of usage in patients who would have otherwise been appropriate for chemo-immunotherapy as first-line therapy under the pre-1 September 2023 restriction, that most patients respond well to venetoclax, that venetoclax was likely to be more beneficial than chemo-immunotherapy in all patients, and that it was likely that the preference for the use of venetoclax and Bruton tyrosine kinase (BTK) inhibitors over chemo-immunotherapy will increase over time in both first and second-line therapy.

DUSC considered that the data for venetoclax's effect on second-line therapies was not mature at the time of the report, as those patients currently on second-line treatments would have likely used first-line therapies other than venetoclax, and given that the report covered the first 24-months since listing, of the cohort of patients that have had the full 12 month course of venetoclax as first-line therapy only a small number would have commenced second-line therapy.

DUSC agreed that it was clinically unlikely that patients were being treated with venetoclax in second-line therapy after they have used venetoclax in first-line therapy and that the apparent treatment sequence could be the result of confounding with second-line utilisation data.

DUSC noted that patient numbers and script numbers did not matchup. DUSC considered that this mismatch may be due to reductions in dose and/or time on treatment as a result of toxicity.

DUSC actions

DUSC suggested that a further analysis be undertaken to examine dose by age, and co-morbidities.

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

Context for analysis

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

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

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

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

Sponsors' comments

AbbVie Pty Ltd: AbbVie notes that the DUSC report found the estimated treatment length with venetoclax in first-line CLL or SLL is aligned with what is expected under the fixed duration restriction (median duration of 315 days versus expected 336 days). AbbVie agrees with DUSC that the recent removal of the requirement for patients to be unfit for chemotherapy will have the effect of broadening the restriction to include patient populations that were ineligible to be treated with venetoclax for first-line therapy under the previous restriction.

Disclaimer

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

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

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