

Ibrutinib for chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL): 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

Analysis of the predicted versus actual utilisation of ibrutinib 24 months following its addition as a streamline authority for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) and relapsed or refractory small lymphocytic lymphoma (SLL).

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Ibrutinib was listed on the PBS for CLL and SLL on 1 December 2017.

Data Source / methodology

PBS dispensing data for ibrutinib was extracted from the PBS data maintained by the Department of Health, processed by Services Australia. This data was used to establish the number of prevalent and incident patients utilising ibrutinib for relapsing or refractory CLL/SLL and time on therapy.

Key Findings

- Since its listing in December 2017 the utilisation of ibrutinib has increased steadily. Data to June 2020 indicates approximately 1,000 prevalent patients and 40 incident patients are supplied ibrutinib per month.
- In the first year of listing, ibrutinib had 1,435 initiating patients. This is similar to the [REDACTED] patients that was estimated in agreed estimates model. There is 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.
- 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%) move 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 could potentially be refractory, followed by a consistent amount of potentially relapsing patients in the 7- 42 months group after which the rate of relapsing patients steadily declines.

Purpose of analysis

Analysis of the predicted versus actual utilisation of ibrutinib 24 months following the addition of a streamline authority listing for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) and relapsed or refractory small lymphocytic lymphoma (SLL).

Background

Clinical situation

Chronic lymphocytic leukaemia (CLL) is a slowly progressing disease which affects B cells, causing them to become malignant with uncontrolled proliferation and accumulation in bone marrow, blood, lymphatic system, spleen, liver and other parts of the body.¹ These cells are unable to function normally and also interfere with normal blood cell production. Small lymphocytic lymphoma (SLL) refers to cases where these malignant B cells are located mostly in the lymph nodes.¹ The Australian Institute for Health and Welfare (AIHW) states CLL has an age-standardised incidence rate of 6.5 cases per 100,000 persons in 2016 and a 5-year relative survival rate of 83.3%.²

¹ The Leukaemia Foundation. Chronic Lymphocytic Leukaemia. < <https://www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/leukaemia/chronic-lymphocytic-leukaemia/> > Last Accessed 19/8/20

² The Australian Institute for Health and Welfare. Cancer summary data visualisation. < <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation> > Last Accessed 19/8/20.

Patients with relapsed or refractory CLL/SLL and known high-risk factors, such as 17p deletion have a poor prognosis and ibrutinib was introduced as targeted therapy for patients with CLL/SLL as well as mantle cell lymphomas.³ Treatment for relapsed or refractory CLL/SLL is dependent on a number of factors however it is possible to repeat first line treatment if the duration of the first remission exceeds 36 months.⁴ International guidelines indicate that treatments aside from ibrutinib which can be used in relapsed or refractory CLL/SLL and can be combined with rituximab are venetoclax, idelalisib, lenalidomide and alemtuzumab.² The only PBS listed alternatives to ibrutinib therapy are currently venetoclax (with or without rituximab) and idelalisib (with rituximab).

Pharmacology

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). BTK, a member of the Tec kinase family, is an important signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B cell malignancies, including MCL, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, and CLL/SLL. BTK's pivotal role in signalling through the B cell surface receptors results in activation of pathways necessary for B cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib inhibits B cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.⁵

Therapeutic Goods Administration (TGA) approved indications

Imbruvica is indicated for the treatment of:

- Patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy or as first line in patients with CLL with 17p deletion
- Patients with mantle cell lymphoma who have received at least one prior therapy.

Dosage and administration

The recommended daily dose of ibrutinib for CLL/SLL is 420 mg (i.e. three 140 mg capsules) taken once daily until disease progression or it is no longer tolerated by the patient.

For further information, see the current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

³ Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94(12):1353-1363. doi:10.1002/ajh.25638

⁴ Hallek, M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *Am J Hematol.* 2019; 94: 1266– 1287. <https://doi.org/10.1002/ajh.25595>

⁵ Imbruvica (ibrutinib). Australian Approved Product Information Macquarie Park: Janssen-Cilag Pty Ltd. Approved 20 April 2015. Updated 22 August 2019. Available from <<https://www.tga.gov.au/product-information-pi>>

PBS listing details (as at August 2020)

Table 1: PBS listing of Ibrutinib

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11213E	ibrutinib 140 mg capsule, 90 (PI, CMI)	90	5	\$8810.25	Janssen-Cilag Pty Ltd

Source: the PBS website. Special Pricing Arrangement is in place.

Restriction

Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)

Treatment Phase: Initial treatment

Clinical criteria:

- * The treatment must be the sole PBS-subsidised therapy for this condition,
AND
- * The condition must have relapsed or be refractory to at least one prior therapy,
AND
- * Patient must have a WHO performance status of 0 or 1,
AND
- * Patient must not have previously received PBS-subsidised treatment with this drug for this condition,
AND
- * Patient must be considered unsuitable for treatment or retreatment with a purine analogue.

A patient is considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:

- a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles;
- b) Age is 70 years or older;
- c) Age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen;
- d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia;
- e) Evidence of one or more 17p chromosomal deletions demonstrated by fluorescence in situ hybridisation (FISH).

Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)

Treatment Phase: Continuing treatment

Clinical criteria:

- * The treatment must be the sole PBS-subsidised therapy for this condition,
AND
- * Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
- * Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.

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

Date of listing on PBS

Ibrutinib was listed on the PBS for CLL and SLL on 1 December 2017.

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

The first submission for ibrutinib for CLL and SLL was rejected by the PBAC in July 2015. The PBAC considered that the patient population and clinical place of ibrutinib were not adequately defined, the size of the comparative clinical benefit could not be quantified and the cost effectiveness and financial implications were underestimated and unacceptably high. In its consideration of the submission, DUSC advised of the following:

- The submission's incidence-based approach to derive the financial estimates did not account for the use of ibrutinib in patients diagnosed with CLL prior to 2012. DUSC considered that there would be a large prevalent group of CLL patients diagnosed prior to 2012 who may be treated with ibrutinib if it is listed on the PBS.
- The submission's estimate of treatment duration based on the mean treatment duration from the clinical trial was likely underestimated. Progression free survival had not been reached in the trial suggesting time on ibrutinib could be longer in practice.
- There was likely to be use beyond the restriction as the proposed restriction was narrower than the TGA approval for second-line treatment (i.e. further limiting to patients for whom fludarabine is considered inappropriate). In particular as earlier line therapy in patients who are able to use purine analogues.
- The uptake rates for ibrutinib were based on a small survey of haematologists with insufficient information provided in the submission to verify these assumptions. DUSC considered that the submission's estimate for the uptake of ibrutinib of [REDACTED] was too low for an efficacious oral treatment for patients with few other treatment options. DUSC considered that the uptake could reach [REDACTED] of the eligible population in the first 5 years of listing.

For further details, refer to the Public Summary Document from the July 2015 PBAC meeting.

A November 2015 minor re-submission for the second-line treatment of CLL and SLL was deferred. PBAC considered there was a high risk of leakage outside the proposed restriction to the other registered indications, including as first-line treatment for patients with 17p deletion, second-line CLL and SLL patients suitable for treatment with fludarabine and patients with mantle cell lymphoma. The PBAC recommended that a risk-sharing arrangement would be required, based on the DUSC estimates of the patient population representative of those included in the RESONATE trial.

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

In its advice for the November 2016 re-submission, the PBAC did not recommend the listing of ibrutinib for the treatment of relapsed or refractory CLL/SLL as the cost effectiveness of the treatment remained unacceptably high and uncertain. The incremental benefit of ibrutinib over its comparator of chlorambucil plus rituximab remained uncertain as the extent of benefit was highly influenced by the sponsor's approach for extrapolating data, particularly the time period over which survival curves converged. The PBAC noted that this uncertainty led to large differences in cost per QALY and the PBAC recommended a further reduction in the overall expenditure caps to allow for greater confidence in the cost effectiveness of ibrutinib.

The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of ibrutinib would be acceptable at the prices cited above and proposed in the sponsor's submission dated 23 January 2017, and if the measures cited above and in the sponsor's submission dated 23 January 2017 were implemented to contain risks associated with the cost of the drug to the PBS.

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

Approach taken to estimate utilisation

An epidemiological, incidence-based approach was used to estimate the expected utilisation and financial impact of listing ibrutinib on the PBS.

The incidence of CLL and SLL was sourced from the AIHW Australian Cancer Incidence and Mortality (ACIM) books. The incidence rates were applied to the projected general Australian population to estimate the number of incident CLL and SLL patients.

An initial pool of prevalent patients was expected to access ibrutinib. This was estimated based on a 10 year look back of incident patients and applying survival probabilities for CLL and SLL to each initiating year cohort based on AIHW relative survival data. Patients were assumed to be aged 70 years at diagnosis.

The time from first diagnosis to treatment was assumed to be two years. This lag in treatment uptake was applied to the estimates.

Based on a clinician survey, it was assumed that [REDACTED] of patients would commence treatment for CLL/SLL, and of these, [REDACTED] would be eligible for ibrutinib. The uptake of ibrutinib was assumed to be [REDACTED].

The mean treatment duration was estimated to be [REDACTED] months based on the RESONATE trial. Compliance to ibrutinib was assumed to be [REDACTED] percent based on the dose intensity administered in the RESONATE trial, with [REDACTED] supplied in the first year of therapy and [REDACTED] in the subsequent year.

Methods

Data from 1 December 2017 to 30 June 2020 were extracted from the PBS data maintained by Department of Health, processed by Services Australia on or before 10 August 2020 for the PBS item code 11213E which corresponds to the treatment of refractory or relapsed CLL/SLL.

PBS prescription data were used to determine the number of prescriptions supplied and the PBS expenditure. These data were also used to count the number of patients, both incident (new to treatment) and prevalent (number treated in each time period, i.e. year or quarter).

PBS prescription data also contains age and gender information. This information was used to perform a breakdown of incident patients by age and gender from date of 1 December 2017 until 30 June 2020.

The Kaplan Meier method was used to determine the length of treatment for patients on ibrutinib. A break in treatment was defined as a gap of more than three times the median time between supplies. A patient was deemed to be continuing treatment (classified as censored in the Kaplan Meier analysis) at the end of the data period (i.e. the end of June 2020) if their last prescription was within three times the median time to resupply of this end date. Otherwise the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply. If a patient's supply was after a gap of more than three times the median time to resupply, then the patient was deemed to have been re-treated.

The PBS restriction for ibrutinib states that it is to be used for relapsed or refractory CLL/SLL and not as first line therapy. To determine if patients were accessing ibrutinib in the first line setting, a list of possible alternate treatments was collated using eviQ and included rituximab, fludarabine, cyclophosphamide, idelalisib, venetoclax, mitozantrone, ofatumumab, chlorambucil and obinutuzumab. Patients initiating onto ibrutinib were then also assessed for prior use of these medications since 1 January 2006 until 30 June 2020. A time between therapies was also established by comparing the difference between the starting date of ibrutinib therapy and the last dispensing date of their prior episode of treatment.

The PBS restriction for ibrutinib in relapsed or refractory ibrutinib states that a "Patient must be considered unsuitable for treatment or retreatment with a purine analogue". Fludarabine is the purine analogue of choice in CLL/SLL therapy and patients initiating on to ibrutinib were also assessed for their prior use of fludarabine since 1 January 2006 until 30 June 2020.

A sequence analysis was also done on patients who had started treatment on ibrutinib since December 2017. This analysis involved observing the sequence of dispensing of the common medications used in the treatment of CLL/SLL as listed previously in those incident patients.

The estimates model used to present the estimated cost to the PBS/RPBS was a model that was agreed upon by both the Department of Health and the Sponsor. Refer to the 'Approach to estimate utilisation' section for further details on the development of the financial estimates.

Results

Analysis of drug utilisation

Overall utilisation

Table 2: Summary of overall utilisation of ibrutinib since listing on the PBS on 1 December 2017 for relapsed or refractory CLL/SLL.

Year	Prevalent Patients	Incident Patients	Dispensings
2017 ^a	591	591	695
2018	1,435	860	10,986
2019	1,629	463	12,963
2020 ^b	1,504	229	6,743

^a Part-year data for the month of December.

^b Part-year data for the period 1 January 2020 to 30 June 2020.

Ibrutinib was listed on the PBS on 1 December 2017 for relapsed or refractory CLL/SLL with an average of approximately 1,500 prevalent patients per year in 2018 and 2019 (Table 2). Since its listing, the utilisation of ibrutinib has increased steadily with approximately 40 first initiating (incident) patients on ibrutinib per month (Figure 1).

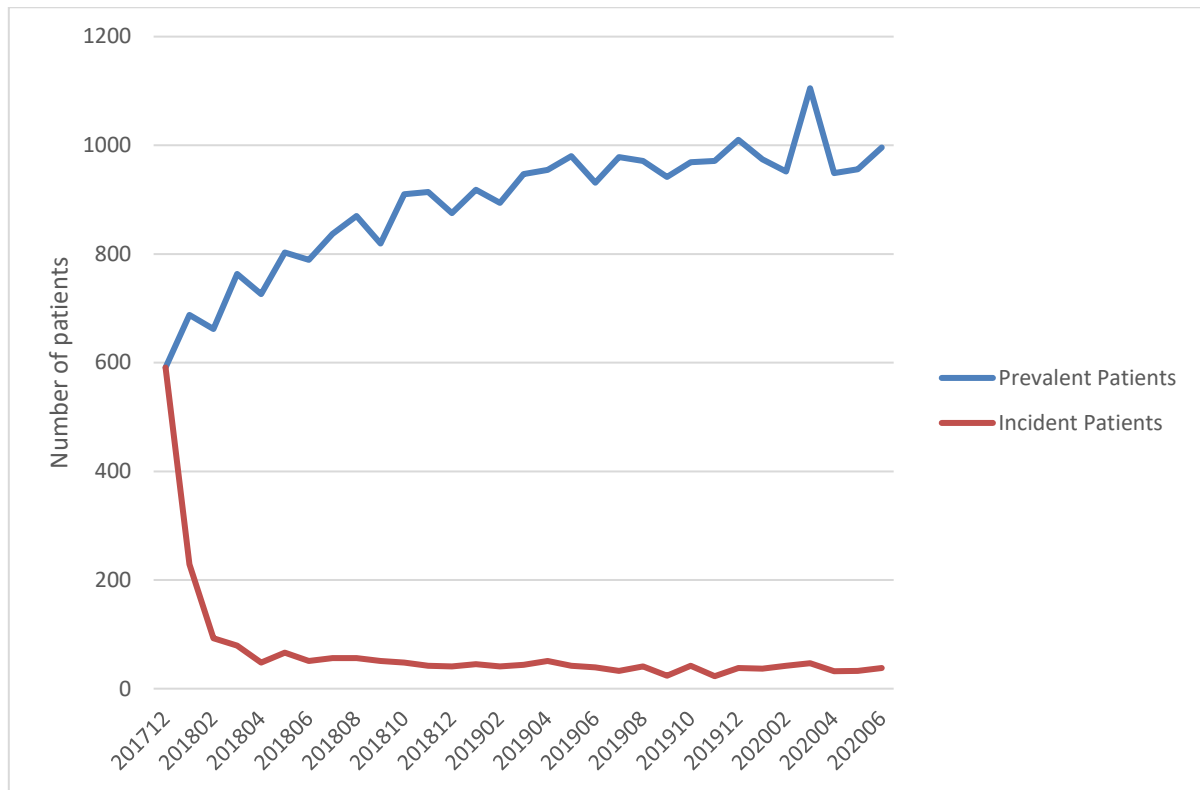


Figure 1: Ibrutinib utilization since listing on the PBS in December 2017

Idelalisib and Venetoclax are two other oral medications used in relapsed or refractory CLL/SLL. Figure 2 presents the prevalent patients for idelalisib and venetoclax alongside ibrutinib. The listing of venetoclax on the PBS in March 2019 and its subsequent steady growth may be the cause of ibrutinib appearing to plateau at approximately 1,000 prevalent patients.

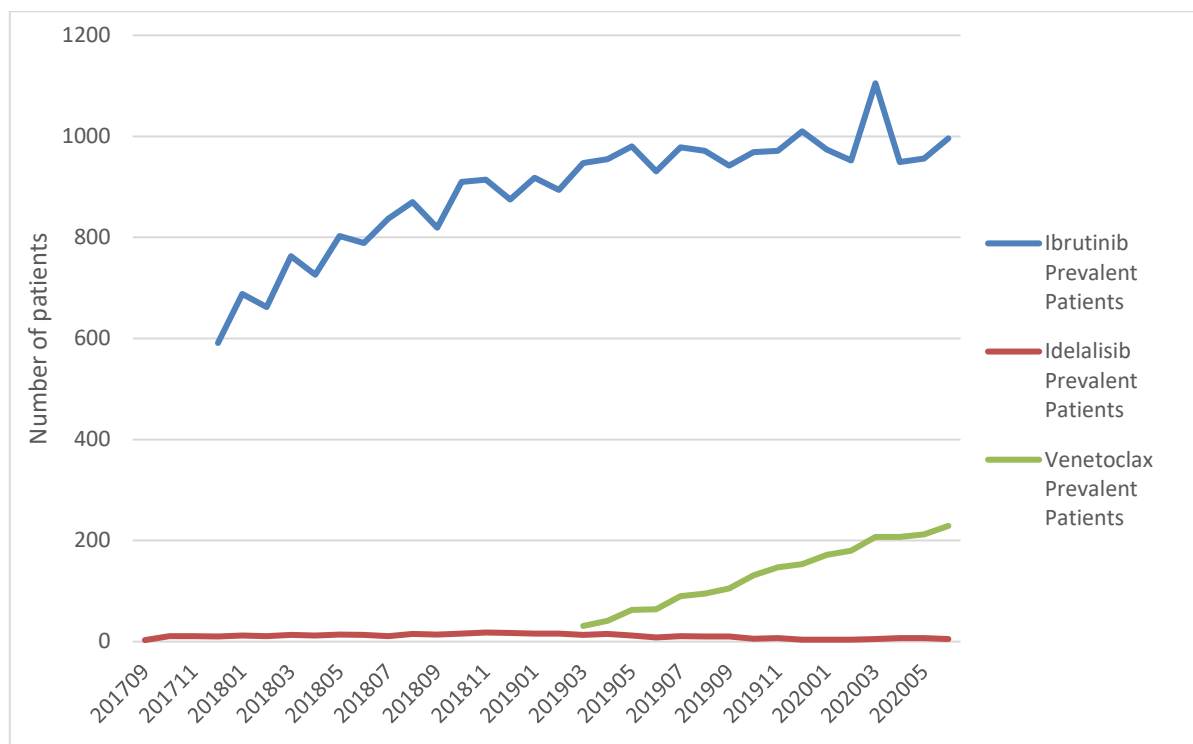


Figure 2: Prevalent patients for alternate oral medications used in refractory or relapsed CLL/SLL

Patient level analyses

Time on treatment

A Kaplan-Meier analysis was done to estimate time on treatment for patients utilising ibrutinib. Median time on treatment was not reached (Figure 3) however the mean time on treatment was 609 ± 7 days (~21.75 months). The Kaplan-Meier analysis of patients utilising ibrutinib until a treatment break occurs (Figure 4) shows that the median time for first treatment episode was 508 days (95% CI: 455-557 days) and the mean time for first treatment was 482.6 ± 7.8 days (~17 months).

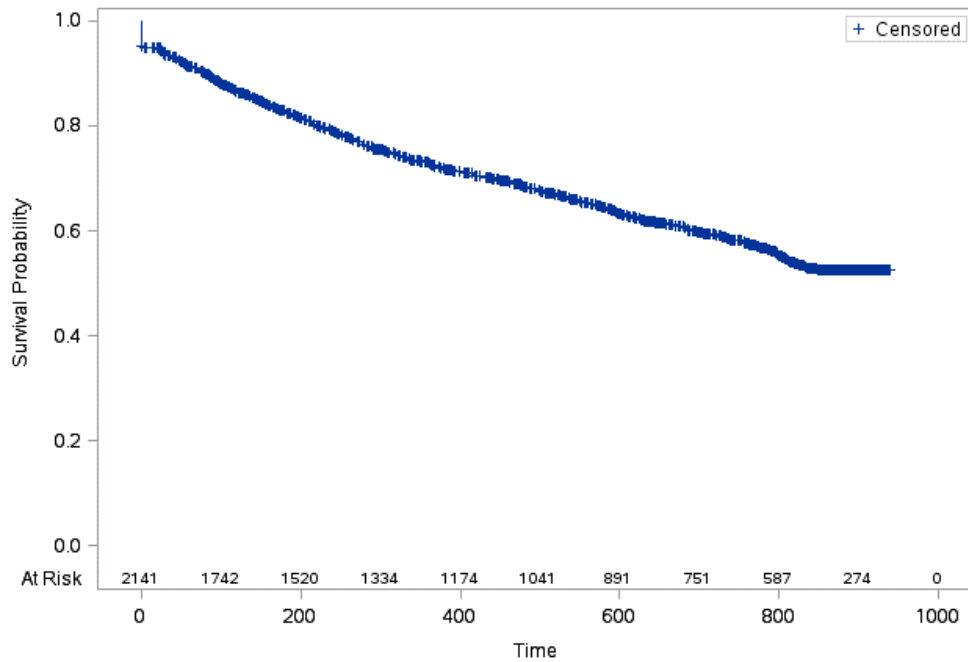


Figure 3: Kaplan-Meier analysis of the number of days patients were supplied ibrutinib, including treatment breaks.

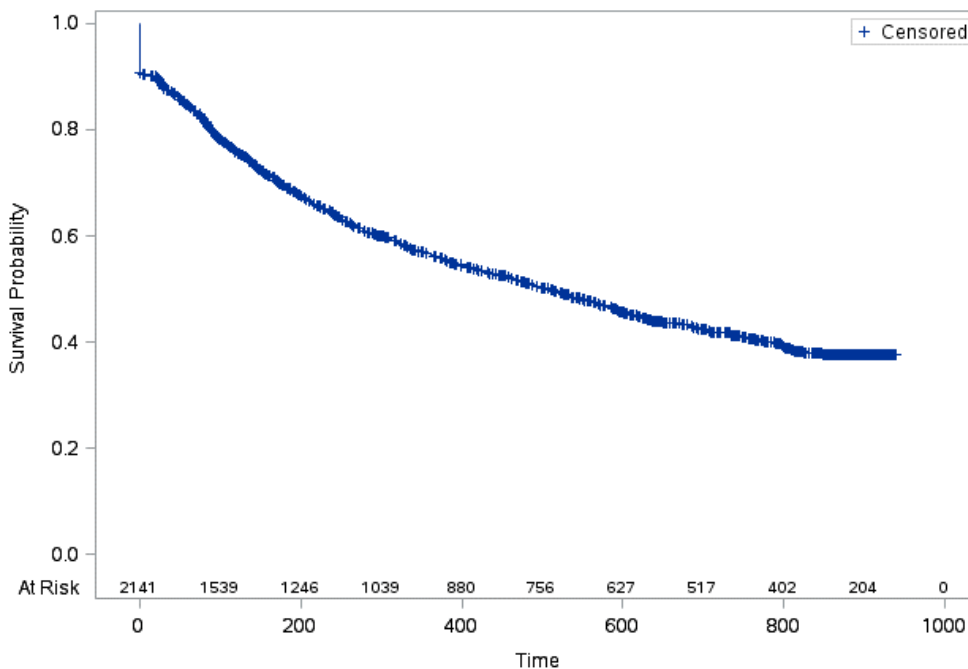


Figure 4: Kaplan-Meier analysis of patients supplied ibrutinib as a first episode of therapy (excluding treatment breaks)

The breakdown of ibrutinib first initiators from the 1 December 2017 (date of listing on the PBS) until 30 June 2020 by gender and age (Figure 5) indicates that the majority of patients utilising ibrutinib are male and initiate on to ibrutinib over 50 years of age. There are also around double the amount of males than females initiating on ibrutinib at each age group until 70-74 years old. The disparity between genders decreases as the age of initiation on to ibrutinib increases.

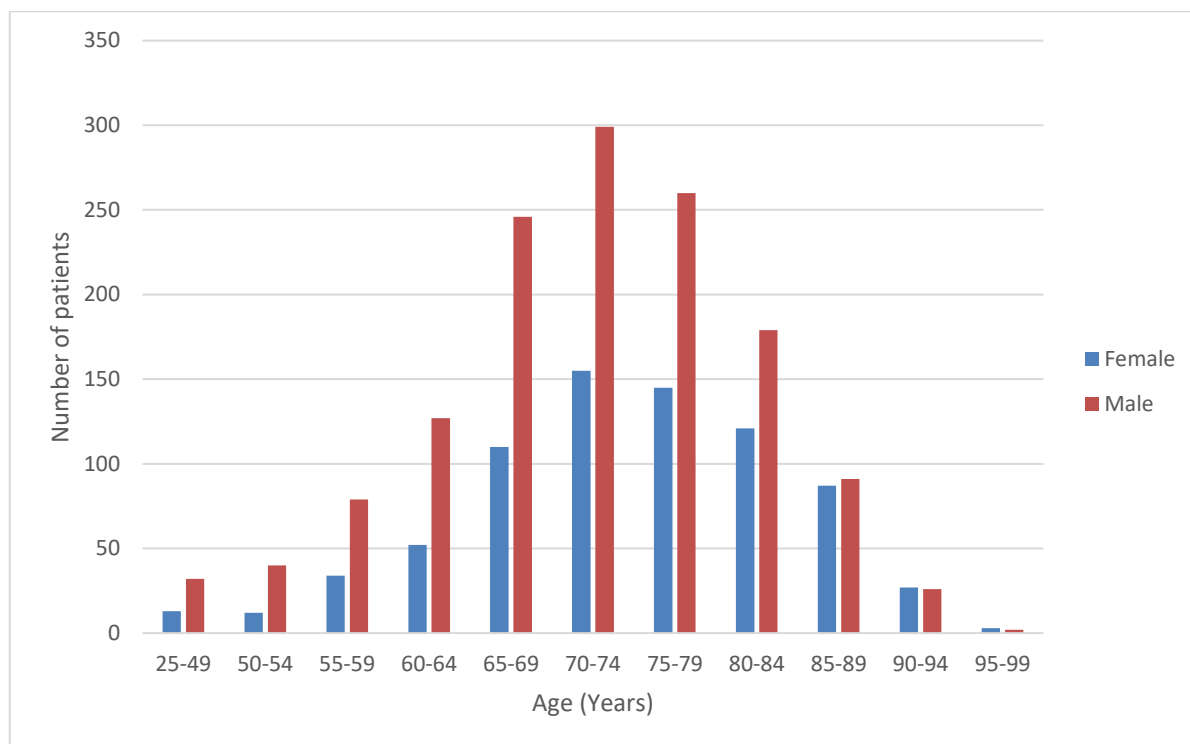


Figure 5: Breakdown of ibrutinib utilisation by Age and Gender from 1 December 2017 (Date of PBS listing) to 30 June 2020

The number of patients initiating treatment on to ibrutinib with a history of previous fludarabine use (the purine analogue of choice in treating CLL/SLL) is approximately 38% in people aged less than 70 (Figure 6). In patients aged 70 or older this number decreases to approximately 23% (Figure 6).

The difference in time between when a patient ceased their first episode of treatment which was assumed to be first line treatment for CLL/SLL and when they began ibrutinib as subsequent treatment was also examined (Figure 7). The results from this analysis indicate that a large portion of patients (19%) move on to treatment with ibrutinib within six months of ceasing their previous line medications and 68% within 42 months.

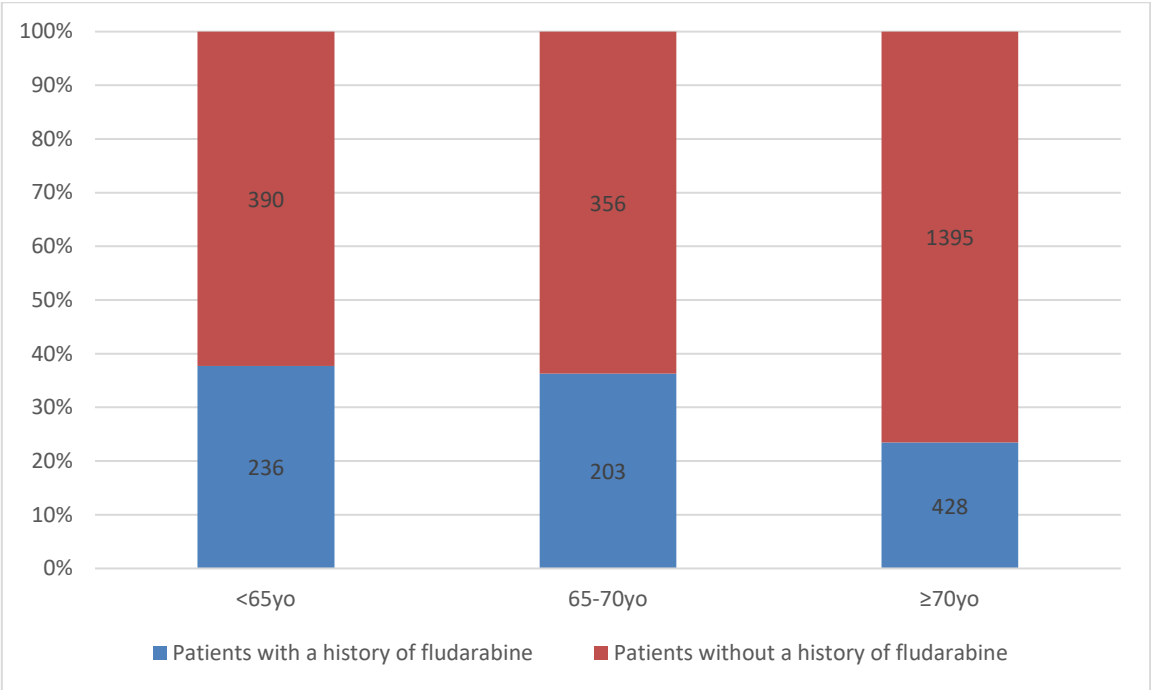


Figure 6: History of purine analogue (fludarabine) use in patients initiating on to ibrutinib.

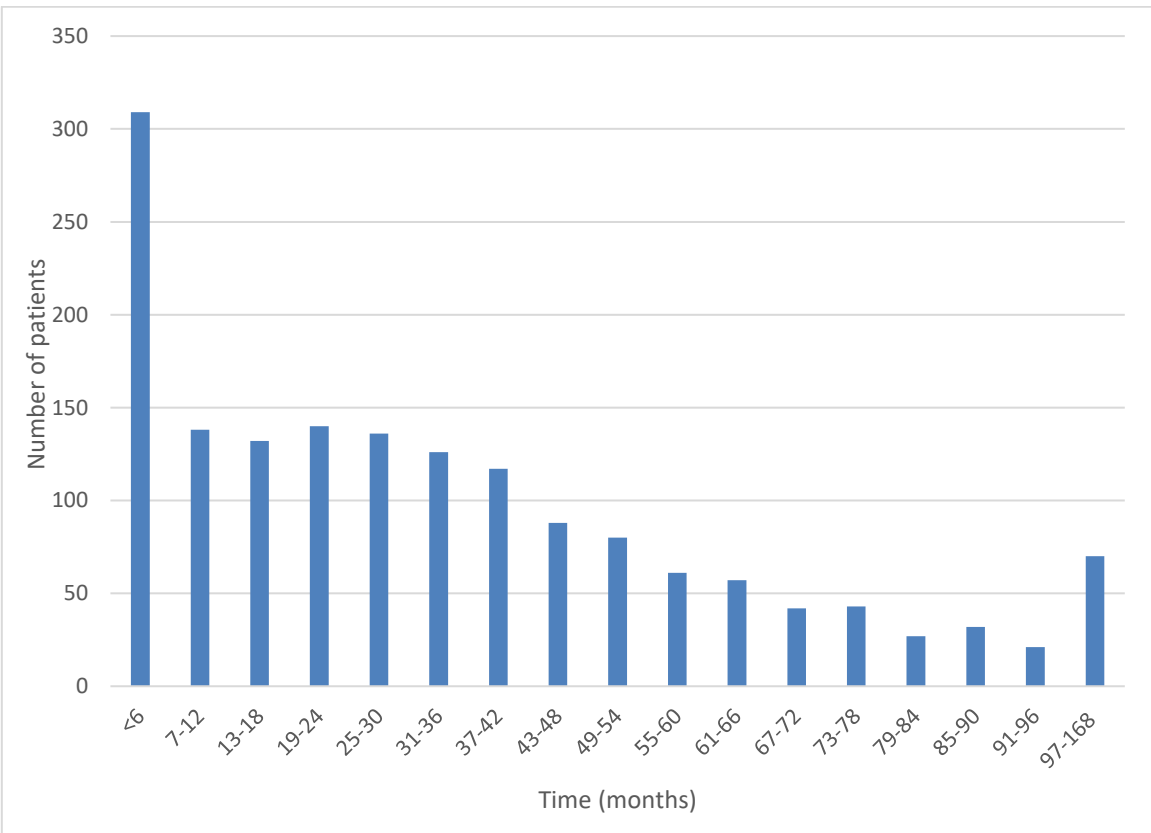


Figure 7: Time between previous line of therapy and initiating on ibrutinib

Concomitant use

A sequence of medications was generated for patients initiating on to ibrutinib. Since the listing of ibrutinib on the PBS approximately 51 patients appeared to be switching between rituximab and ibrutinib and approximately 10 patients appeared to switch between venetoclax and ibrutinib.

Analysis of actual versus predicted utilisation

In the first year of listing ibrutinib had 1,435 initiating patients. This is similar to the predicted number of patients (██████). There is a ██████ decrease in initiating patients in 2019 compared to Year 2 of the estimates model. Initiating patients are used in the estimates model as it was assumed that patients would likely be on ibrutinib therapy for approximately ██████. The estimated number of packs per patient in their first year of treatment is ██████ and the remainder in their second year.

Table 3: Actual versus predicted cost to PBS/RPBS

	2018 (Year 1)			2019 (Year 2)		
Parameter	Actual	Predicted	Difference	Actual	Predicted	Difference
Patients	1,435	██████	██████	463	██████	██████
Estimated Packs	16,503	██████	██████	19,393	██████	██████
Total cost	██████	██████		██████	██████	
Co-pays	██████	██████		██████	██████	
Net cost	██████	██████	██████	██████	██████	██████

DUSC consideration

The actual utilisation in its first year of listing was similar to predicted. However the uptake of ibrutinib in the second year of listing appears was overestimated resulting in a difference of -53% in initiating patients. The entrance of venetoclax in April 2019 to the PBS may be responsible for the overestimation as the combined number of prevalent patients in June 2020 of approximately 1200 is closer to what was predicted. DUSC noted that the revision of eligible population provided by DUSC in 2015 was appropriate and provided an accurate estimation of utilisation in the first year of listing.

In its previous advice on ibrutinib DUSC considered 'due to the long duration of the disease, the prevalent number of patients treated with ibrutinib should plateau, however, the plateau may not occur within the first five year estimates, and the market is likely to keep growing beyond the first five years.' The Kaplan-Meier analysis supports this idea as the median survival was not reached in the 942 days (~31 months) of data. DUSC agreed with the sponsor that patients are continuing on ibrutinib longer than expected and likely will lead to an increase in expenditure in year 3-5. In the July 2015 PBAC submission it was

estimated that mean time on treatment would be [REDACTED] with the expectation that this could be longer. In the six year follow up data from the RESONATE clinical trial, median time on treatment was 41 months, reflective of the long time on treatment in the PBS population.

The restriction for ibrutinib involves being refractory or unsuitable to previous treatment for CLL/SLL. An analysis was done on the prior therapy of those patients initiating ibrutinib to observe if there was any leakage from the restriction where patients had accessed ibrutinib as first line therapy rather than in the relapsed or refractory setting. There were negligible cases detected of ibrutinib use as first line therapy. DUSC noted that the PBAC did not recommend ibrutinib for first line use in November 2017 and that there has not been any appreciable leakage into this setting.

The PBS restriction for ibrutinib in relapsed or refractory ibrutinib states that a "Patient must be considered unsuitable for treatment or retreatment with a purine analogue". The average proportion of incident patients utilising ibrutinib without a history of fludarabine is 68%. In its submission the sponsor estimated the proportion of patients who were unsuitable for treatment or retreatment with a purine analogue to be [REDACTED] whereas this analysis indicates that 68% of patients were considered untreatable with a purine analogue. It should be noted however that the data does not include those patients who could be considered refractory and therefore not suitable for retreatment with a purine analogue. It may be that in practice a larger proportion than 68% would be utilising this restriction clause to access ibrutinib. [REDACTED]

The concomitant use of other medications with ibrutinib which have the potential for treating CLL/SLL was examined. It was found that since listing there were approximately 50 patients who appeared to receive concurrent rituximab with ibrutinib, and there was also potential use of ibrutinib and venetoclax in combination. The Food and Drug Administration (FDA) has recently expanded the indication of ibrutinib to include its combination with rituximab as first line treatment for CLL/SLL in April 2020. Venetoclax and ibrutinib also appears to be an emerging first line treatment option for CLL/SLL. Further analysis could be considered to more accurately estimate the number of patients utilising these treatment options. DUSC noted that monitoring may need to be done to observe if the number of patients receiving both ibrutinib and rituximab is growing.

There was a large portion of patients (19%) initiating on ibrutinib within six months of ceasing their previous line treatment. This may indicate that these patients are refractory to their prior therapy. DUSC noted it may be interesting to observe the time on ibrutinib treatment in those patients who were refractory to prior treatment as more data becomes available.

DUSC actions

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

Context for analysis

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

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

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

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

Sponsors' comments

Janssen-Cilag Pty Ltd : 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 (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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