Tyrosine kinase inhibitors for the treatment of Chronic Myeloid Leukaemia (CML)

Drug utilisation sub-committee (DUSC)

October 2019

Abstract

Purpose

To analyse the utilisation of PBS-listed tyrosine kinase inhibitors (TKIs), imatinib, dasatinib, nilotinib and ponatinib, for the treatment of chronic myeloid leukaemia (CML), as requested by DUSC at its June 2019 meeting.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

For CML:

- Imatinib: December 2001
- Dasatinib: August 2007
- Nilotinib: August 2008
- Ponatinib: November 2015

Data Source / methodology

Data were extracted from the PBS supplied prescription database from the date of first listing of imatinib for CML (1 December 2001) to 31 March 2019. Authority approvals were extracted from the PBS authority approval database from November 2003 (the earliest time point of the database) to March 2019.

Key Findings

- The number of prescriptions of imatinib, dasatinib, nilotinib and ponatinib supplied per year for CML had continued to grow since the previous analysis in 2014. Since the listing of imatinib in 2001, 6,179 patients initiated treatment for CML. In 2018, 437 patients initiated treatment, and 3,819 patients were treated.
- The number of treated patients is growing in a linear manner, similar to the number of supplied prescriptions. The majority of this use was for patients in the chronic phase of disease being treated with their first line medicine. The second highest group is patients in the chronic phase of disease being treated with their second line medicine.

- Imatinib was the most commonly used TKI for CML, however the use of nilotinib and dasatinib increased over the study period. Since 2016, the cost to government decreased due to price reductions.
- The use of ponatinib was small in the context of the CML market; 50 patients were treated with ponatinib in 2018.

Purpose of analysis

To analyse the utilisation of PBS-listed tyrosine kinase inhibitors (TKIs), imatinib, dasatinib, nilotinib and ponatinib, for the treatment of chronic myeloid leukaemia (CML), as requested by DUSC at its June 2019 meeting.

Background

Clinical situation

CML is a type of leukaemia in which an abnormal chromosome produces an enzyme that leads to uncontrolled growth of white blood cells.[1,2]

Under normal circumstances, white blood cells fight infection and maintain the body's immune system. In leukaemia, the uncontrolled growth of white blood cells means that the production of normal red blood cells (oxygen carrying cells), white blood cells (cells which fight infection), and platelets (cells which help blood to clot) is compromised. Therefore patients with leukaemia are at risk of developing serious anaemia, infections and bleeding. [3]

Pharmacology

TKIs block the signal that tells the body to produce abnormal white blood cells, thereby stopping the production of these cells.[4,5,6]

Therapeutic Goods Administration (TGA) approved indications

Imatinib (Glivec®) is indicated for the treatment of patients with CML.

Dasatinib (Sprycel®) is indicated for the treatment of adults aged 18 years or over with:

- newly diagnosed Philadelphia chromosome positive (Ph+) CML in the chronic phase; and
- adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy including imatinib.

Nilotinib (Tasigna®) is indicated for the treatment of:

- adult patients with newly diagnosed Ph+ CML in chronic phase; and

[1] Glivec (imatinib) Consumer Medicine Information. Accessed 18 July 2019. Available from https://www.ebs.tga.gov.au/
[2] Tasigna (nilotinib) Consumer Medicine Information. Accessed 18 July 2019. Available from https://www.ebs.tga.gov.au/
[3] Sprycel (dasatinib) Consumer Medicine Information. Accessed 18 July 2019. Available from https://www.ebs.tga.gov.au/
[4] Glivec (imatinib) Product Information. Accessed 18 July 2019. Available from https://www.ebs.tga.gov.au/
[5] Sprycel (dasatinib) Product Information. Accessed 18 July 2019. Available from https://www.ebs.tga.gov.au/
[6] Tasigna (nilotinib) Product Information. Accessed 18 July 2019. Available from https://www.ebs.tga.gov.au/

- adults with chronic phase and accelerated phase Ph+ CML resistant to or intolerant of prior therapy including imatinib.

Ponatinib (Iclusig®) is indicated for the treatment of:

- Chronic phase, accelerated phase, or blast phase CML whose disease is resistant to, or who are intolerant of at least two prior tyrosine kinase inhibitors; or where there is a T315I mutation.[7]

Imatinib, dasatinib and ponatinib are registered for indications other than CML. For more information, see the Product Information for details (http://tga.gov.au/hp/information-medicinespi.htm).

Dosage and administration

Table 1: Dosage and administration of TKIs for CML

Phase	Drug	Dose
Chronic phase	Imatinib[4]	Standard: 400 mg/day Increased dose: 600-800 mg/day
	Dasatinib[5]	100 mg/day Increased dose: 140 mg/day (lack of haematological or cytogenic response)
	Nilotinib[6]	Newly diagnosed:600 mg/day (300 mg twice daily) Resistant or intolerant to prior therapy: 800 mg (400 mg twice daily)
	Ponatinib[7]	45 mg/daily
Accelerated phase	Imatinib	Standard: 600 mg/day Increased dose: 400 mg twice daily
	Dasatinib	Standard dose: 140 mg/day Increased dose: 180 mg/day (lack of haematological or cytogenic response)
	Nilotinib	800 mg (400 mg twice daily)
	Ponatinib	45 mg/daily
Blast phase	Imatinib	600 mg/day Increased dose: 800 mg (400 mg twice daily)
	Dasatinib	Standard dose: 140 mg/day Increased dose: 180 mg/day (lack of haematological or cytogenic response)
	Nilotinib	-
	Ponatinib	45 mg/daily

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

[7] Iclusig (ponatinib) Product Information. Accessed 18 July 2019. Available from https://www.ebs.tga.gov.au/

PBS listing details (as at 1 July 2019)

Table 2: PBS listing of imatinib

Item	Name, form & strength, pack size	Max. quant. packs	Max. quant. units	Rpts	DPMQ	Brand name and manufacturer
10915L	imatinib 100 mg capsule, 60	1	60	5	$952.47	CIPLA IMATINIB ADULT, Cipla Australia Pty Ltd Glivanib, Juno Pharmaceuticals Pty Ltd IMATINIB AN, Juno Pharmaceuticals Pty Ltd IMATINIB-DRLA, Dr Reddy's Laboratories (Australia) Pty Ltd Imatinib GH, Generic Health Pty Ltd Imatinib-APOTEX, Apotex Pty Ltd
10920R	imatinib 100 mg capsule, 60	1	60	5	$952.47	
10916M	imatinib 400 mg capsule, 30	1	30	5	$1839.66	
10935M	imatinib 400 mg capsule, 30	1	30	5	$1839.66	
9113P	imatinib 100 mg capsule, 60	1	60	5	$952.47	Glivec, Alphapharm Pty Ltd IMATINIB RBX, Sun Pharma ANZ Pty Ltd Imatinib-Teva, Sandoz Pty Ltd
9115R	imatinib 100 mg capsule, 60	1	60	2	$952.47	
9114Q	imatinib 400 mg capsule, 30	1	30	5	$1839.66	
9116T	imatinib 400 mg capsule, 30	1	30	2	$1839.66	

Source: the PBS website.

Table 3: PBS listing of nilotinib

Item	Name, form & strength, pack size	Max. quant. packs	Max. quant. units	Rpts	DPMQ	Brand name and manufacturer
1309X	nilotinib 150 mg capsule, 120	1	120	5	$3847.01	Tasigna, Novartis Pharmaceuticals Australia Pty Limited
9171Q	nilotinib 200 mg capsule, 120	1	120	5	$5047.66	

Source: the PBS website.

Table 4: PBS listing of dasatinib

Item	Name, form & strength, pack size	Max. quant. packs	Max. quant. units	Rpts	DPMQ	Brand name and manufacturer
1354G	dasatinib 20 mg tablet, 60	1	60	5	$2673.60	Sprycel, Bristol-Myers Squibb Australia Pty Ltd
2478K	dasatinib 20 mg tablet, 60	1	60	5	$2673.60	
1381Q	dasatinib 50 mg tablet, 60	1	60	5	$4305.23	
2482P	dasatinib 50 mg tablet, 60	1	60	5	$4305.23	
1415L	dasatinib 70 mg tablet, 60	1	60	5	$5293.95	
2485T	dasatinib 70 mg tablet, 60	1	60	5	$5293.95	
1416M	dasatinib 100 mg tablet, 30	1	30	5	$4305.23	
9342Q	dasatinib 100 mg tablet, 30	1	30	5	$4305.23	

Source: the PBS website.

Table 5: PBS listing of ponatinib

Item	Name, form & strength, pack size	Max. quant. packs	Max. quant. units	Rpts	DPMQ	Brand name and manufacturer
10520Q	ponatinib 15 mg tablet, 60	1	60	5	$5760.73	Iclusig, Specialised Therapeutics Australia Pty Ltd
10530F	ponatinib 45 mg tablet, 30	1	30	5	$6480.17	

Source: the PBS website.

Restriction

The PBS restrictions for the TKIs for CML are complex and have evolved over time. The full restriction wording is available at pbs.gov.au. The TKIs are Authority Required General Schedule listings. The restriction history is summarised in Table 6.

For initial treatment, imatinib, dasatinib and nilotinib are listed for patients with CML in the chronic phase. Each restriction states that the patient must not have previously experienced a failure to respond to the PBS-subsidised first line treatment with this drug for this condition; or the patient must have experienced intolerance, not a failure to respond, to initial PBS-subsidised treatment with either of the other two drugs as a first line therapy for this condition.

The PBS restrictions state that the treatment must not exceed a total maximum of 18 months of therapy with a PBS-subsidised treatment with a tyrosine kinase inhibitor for this CML.

The PBS restriction for ponatinib states that the patient must have failed an adequate trial of dasatinib; or the patient must have developed intolerance to dasatinib of a severity necessitating permanent treatment withdrawal. The patient must have also either:

- failed an adequate trial of nilotinib; or
- developed intolerance to nilotinib of a severity necessitating permanent treatment withdrawal; or
- be eligible for PBS-subsidised treatment with nilotinib because the patient has a blast crisis.

Ponatinib is also listed for patients with CML that are expressing the T315I mutation, and have failed an adequate trial of either imatinib, dasatinib or nilotinib.

For initial and first continuing treatment, applications must be made in writing, and first continuing applications must include a pathology report demonstrating the patient has responded to the initial course of treatment. Subsequent continuing treatment applications may be made by telephone.

Patients are eligible for PBS-subsidised treatment with only one of imatinib, dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.

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

Date of listing on PBS

The four medicines were listed on the PBS for CML:

- Imatinib: December 2001
- Dasatinib: August 2007
- Nilotinib: August 2008
- Ponatinib: November 2015

Changes to listing

The restriction changes for the CML indications of the four drugs can be summarised as follows.

Table 6: Restriction changes to CML listings

Date	Restriction change
1 December 2001	Imatinib was listed (S85) for first line treatment of CML in the **accelerated** or **blast** phases.
1 November 2002	The listing of imatinib was extended to first line treatment in the **chronic** phase and the listing changed to S100, Special Authority Program.
1 August 2007	Dasatinib was listed (S85) for second line treatment (i.e. failed an adequate trial of imatinib) in **any** disease phase.
1 November 2007	All imatinib items were changed from S100 to S85 to be consistent with the dasatinib listings.
1 August 2008	Nilotinib was listed (S85) for second line treatment (i.e. failed an adequate trial of imatinib) in **chronic** or **accelerated** phases.
1 April 2012	Dasatinib and nilotinib restrictions were extended to first line treatment in **chronic** phase. Dasatinib retained the restriction for second line treatment (i.e. failed an adequate trial of imatinib or nilotinib) for **any** disease phase and nilotinib retained second line treatment (i.e. failed an adequate trial of imatinib or dasatinib) for **chronic** or **accelerated** phases.
1 April 2012	The wording of the first line restrictions were modified to include dose guidance. Patients should be commenced on a dose of imatinib mesylate 400 mg (base) daily, dasatinib of at least 100 mg (base) daily and nilotinib of 300 mg twice daily.
1 November 2015	Ponatinib was listed (S85) for treatment after failure or intolerance to dasatinib and nilotinib, or in patients expressing the T315I mutation who have failed either imatinib, nilotinib or dasatinib, in any disease phase.
1 October 2016 and 1 November 2016	New brands of imatinib were listed, triggering price reductions.
1 February 2017	The restrictions for second continuing and subsequent treatment applications for imatinib, dasatinib and nilotinib were changed from Authority Required (Written) to Authority Required (Telephone).

Current PBS listing details are available from the PBS website.

Previous reviews by the DUSC

DUSC reviewed imatinib utilisation for CML at its August 2003 meeting for the period December 2001 to April 2003. At that time, actual usage was slightly lower than that estimated in the submission. The DUSC considered that the trend indicated that the number of imatinib prescriptions could continue to increase and if so could result in slightly higher utilisation than estimated in the submission. Neither dasatinib nor nilotinib have been reviewed by DUSC previously.

DUSC reviewed utilisation of imatinib, dasatinib and nilotinib for CML at its February 2014 meeting. The report found:

- The number of patients on treatment, number of prescriptions and expenditure of TKIs for CML had increased steadily (i.e. linear tread) over a 12 year period from 2001 to 2013. This reflected the increasing prevalence of CML as mortality from CML declines and patients continue on treatment. Utilisation was expected to continue to increase in the future.
- The steadily increasing expenditure for TKIs in CML was explicable entirely on the basis of increased survival.

- The number of new patients commencing treatment had remained stable, which was consistent with incidence of CML reported by the AIHW.
- Listing of dasatinib and nilotinib for chronic phase CML after failure of imatinib, and subsequently as first line therapy, had not had a noticeable impact on the steady upward trend in prevalent patients, prescription utilisation and expenditure for CML drugs.

At the February 2014 meeting, DUSC requested a further analysis to assess the predicted equi-effective doses versus actual dosing of each of imatinib, dasatinib and nilotinib for first and second line treatment. DUSC considered an analysis to address this request at its October 2014 meeting. The calculated dose relativities of imatinib versus dasatinib and imatinib versus nilotinib in the first line treatment of newly diagnosed patients were found to be consistent with the values assumed by the PBAC when these drugs were recommended.

For details of the DUSC consideration of TKIs for CML refer to the Public Release Document from the February 2014 DUSC meeting.

Methods

PBS prescription data for the medicines included in this review that were dispensed from 1 December 2001 to 31 March 2019 were extracted from the PBS supplied prescriptions database managed by Services Australia. The PBS supplied prescriptions database includes data submitted to Services Australia for payment of a PBS or RPBS subsidy by the Government by all approved pharmacies in Australia. This dataset contains de-identified information that includes a unique patient identification number (PIN), dates and quantities of supply of all PBS listed drugs, prescriber and pharmacy information.

PBS prescription data were used to determine the number of prescriptions supplied, the number of incident and prevalent patients, the number of male and female patients, and the cost to government of these medicines. This report includes a predicted versus actual review of ponatinib for CML.

Where the result of an analysis was a small number of patients (≤5) the number has been replaced with "≤5" to confidentialise the data.

Medicine sequence

An analysis of medicine sequence was completed for all prescriptions from the listing of imatinib in 2001, and a second analysis was completed for patients who initiated on or after the listing of ponatinib on 1 November 2015.

Length of treatment

The length of treatment was estimated using the Kaplan Meier method. Two ways of measuring length of treatment were undertaken to account for patients stopping medicine for periods of time (called a 'break' in therapy). One analysis excluded the time of any

breaks in treatment (i.e. reports the total time a patient is actually receiving regular supplies of the medicine) and the other did not. A patient was deemed to have a break in treatment if the time between two of their supplied prescriptions was more than 3 times the median time to resupply (i.e. 3 x 31 days), which is an estimated break in treatment of at least two times the median time to resupply.

A censoring definition was applied in the length of treatment analysis, to account for the end of the data observation period where patients who might be continuing supply appear to stop treatment (because there is no further data for supplies). A patient was deemed to be continuing treatment at the end of the data period if their last prescription was supplied 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 (31 days) to resupply.

Analysis of Authority Approvals

The PBS authority approval database, managed by Services Australia, was used to determine the reason for each prescription. Authorities were extracted from the authority approval database from November 2003 (the earliest time point of the database) to March 2019. Of the prescriptions dispensed from 1 December 2001 to 31 March 2019, 99.07% were matched to an authority approval.

The prescriptions matched to the authority approval database were used to summarise the number of supplied prescriptions by disease phase (i.e. chronic, accelerated or blast), line of therapy and medicine. The phase was determined from the authority approval code and the line of therapy was determined by the number of medicines the patient had been supplied for CML.

Prescribed dose

The prescriptions matched to the authority approval database were used to analyse the prescribed dose of these medicines by disease phase. The actual prescribed dose is not recorded in the PBS prescription database. The prescribed dose was estimated from the PBS prescription data by calculating the total number of milligrams of the medicine that was supplied, and dividing this by the number of days each prescription was intended to treat for (in most cases 30 days). Where a patient received more than one prescription on a day, the total quantity dispensed was calculated.

The results are presented as being for line of treatment (determined from medicine sequence), disease phase and whether it was supplied for initial or continuing treatment (determined from authority approval codes).

Results

Analysis of drug utilisation

Overall utilisation

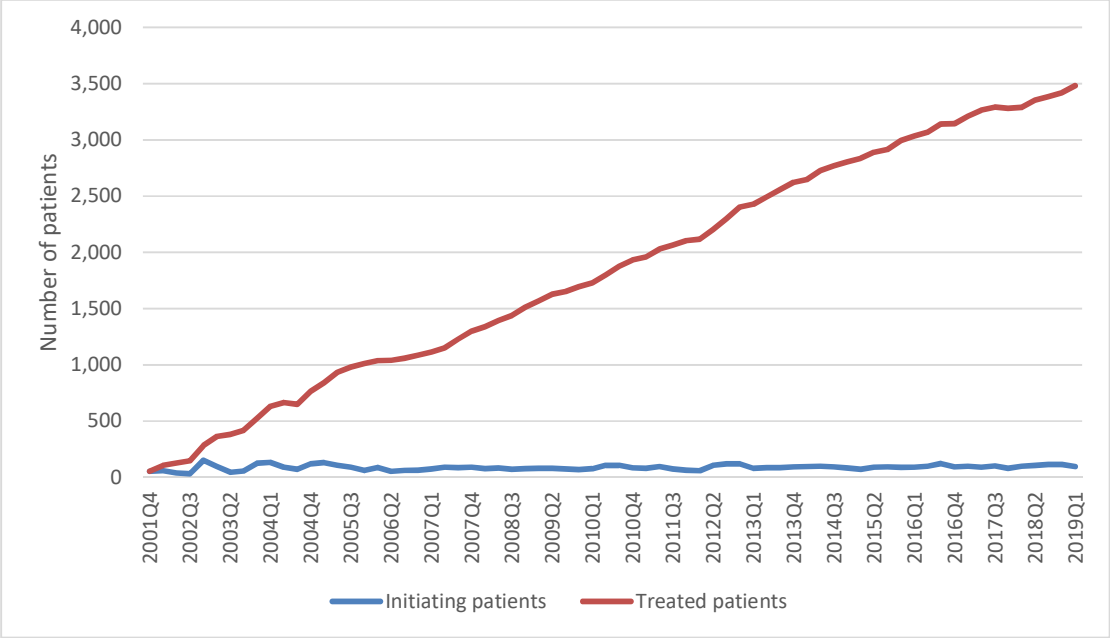

Figure 1: Patients supplied TKIs for CML by quarter

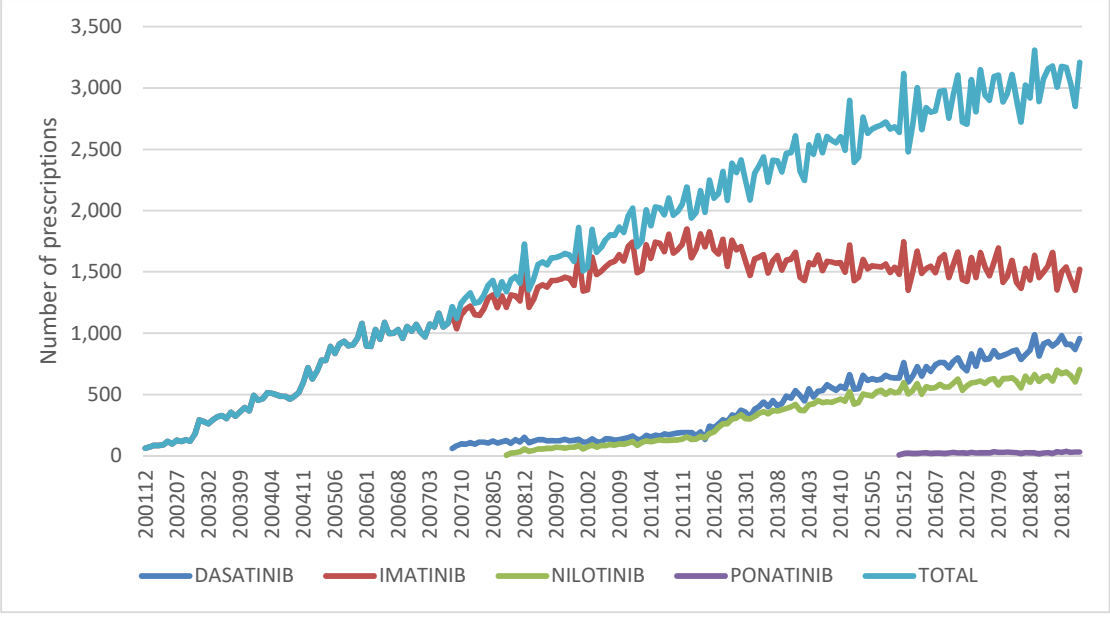

Figure 2: Supplied prescriptions for CML by medicine

The use of TKIs for CML is summarised from the first listing of imatinib for CML in December 2001. The use of these medicines is continuing to grow in a steady and linear manner. The addition of new medicines, including ponatinib in November 2015, does not appear to have affected the overall market trend of growing use of these medicines.

Patient level analysis

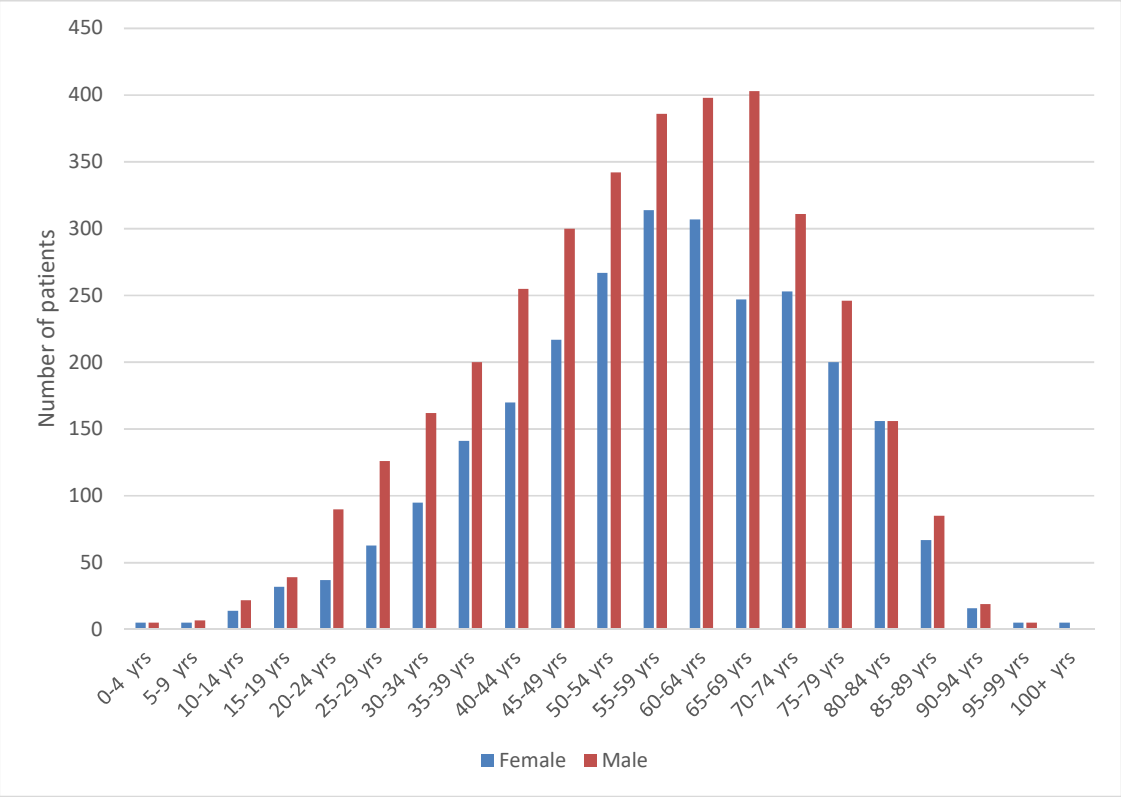

Figure 3: Age of patients at initiation
Note: Groups less than or equal to five have been adjusted to five.

The analysis of initiating CML patients by age and gender shows that a higher proportion of CML patients are male. The proportion of men and women was similar across most age groups, the only difference may be in the group aged 65 to 69 years old. Since 2001, 3,557 (58%) male patients initiated treatment for CML with one of these medicines, compared with 2,616 (42%) female patients. In 2018, 250 (57%) male patients initiated treatment for CML with one of these medicines, compared with 186 (43%) female patients.

Medicine sequence

The top ten medicine sequences for all prescriptions from December 2001 until March 2019, are shown in Table 4. The top ten medicine sequences for all medicines for patients who initiated on or after the listing of ponatinib in November 2015, are shown in Table 8. Table 7 includes several years of data when imatinib was the only medicine listed

for CML. Table 8 suggests more recently a lower proportion of patients have initiated on imatinib. Between November 2015 and March 2019, 589 patients have initiated on dasatinib, 544 on imatinib, and 235 on nilotinib. The number of patients who were supplied ponatinib prior to other TKIs was less than six. In total 1,371 patients were included in the analysis presented in Table 8. Of these, approximately 80% have been supplied one TKI for CML.

Table 7: Top ten medicine sequences since 2001

Sequence	Patient count
IMATINIB	3,040
DASATINIB	802
IMATINIB->DASATINIB	661
NILOTINIB	443
IMATINIB->NILOTINIB	326
IMATINIB->DASATINIB->NILOTINIB	186
DASATINIB->NILOTINIB	119
IMATINIB->NILOTINIB->DASATINIB	106
DASATINIB->IMATINIB	84
NILOTINIB->DASATINIB	61

Table 8: Top ten medicine sequences for patients who initiated after November 2015

Sequence	Patient count
DASATINIB	477
IMATINIB	408
NILOTINIB	192
IMATINIB->DASATINIB	68
DASATINIB->NILOTINIB	47
DASATINIB->IMATINIB	38
IMATINIB->NILOTINIB	32
NILOTINIB->DASATINIB	17
NILOTINIB->IMATINIB	12
IMATINIB->DASATINIB->NILOTINIB	11

Length of treatment

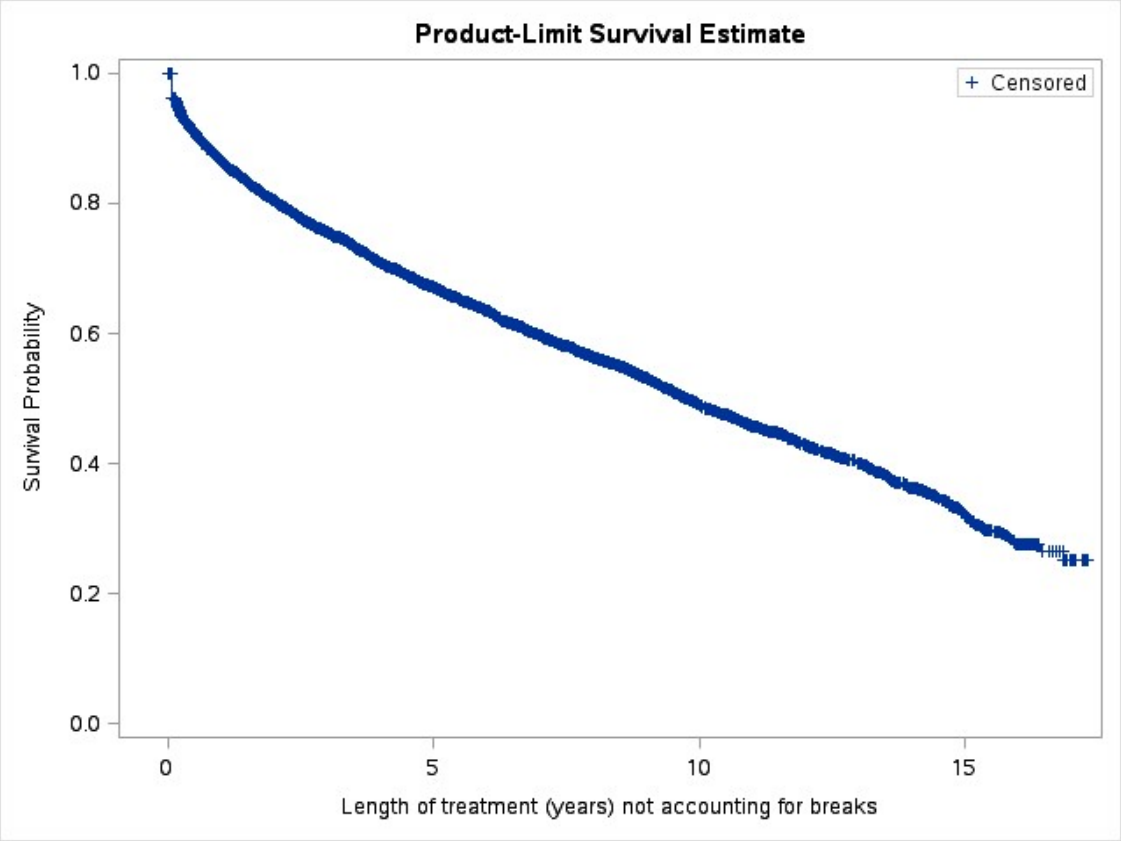

Figure 4: Length of treatment with TKIs for CML

The length of treatment for patients treated for CML without excluding breaks is shown in Figure 4. This analysis includes 6,179 patients who were treated for CML between December 2001 and March 2019 inclusive.

The drop off in treatment after initiation was small for CML medicines, 4% of the 6,179 patients treated received only one prescription.

Table 9: Kaplan Meier estimate of length of treatment

	Mean	Std Err	Median	Lower Limit	Upper Limit
Without excluding breaks					
Years	9.44	0.10	9.72	9.38	10.13
Excluding breaks					
Years	8.68	0.09	8.87	8.50	9.26

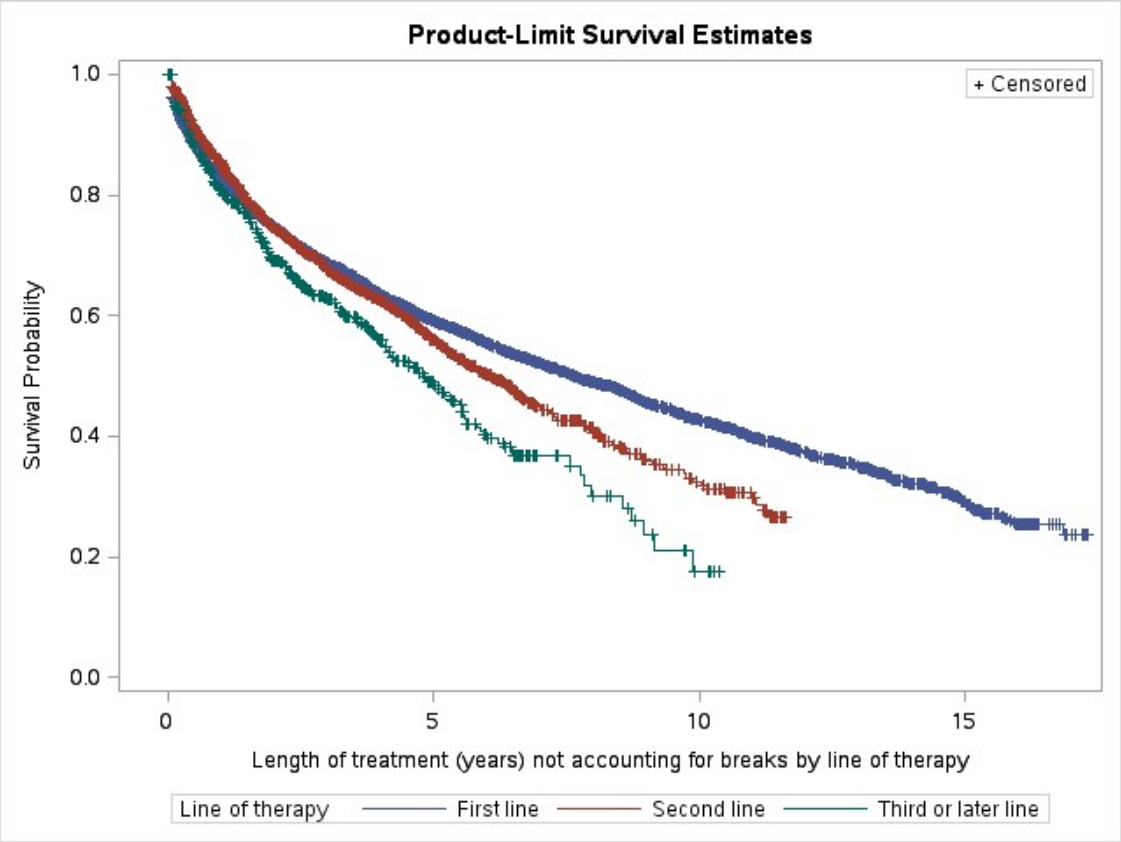

Figure 5: Length of treatment with TKIs for CML by line of therapy

The length of treatment for patients treated for CML by line of therapy is shown in Figure 5. First line includes all 6,179 patients in their first line of treatment. Most patients (around 70%) were not supplied a second medicine for CML, and relatively few patients (around 8%) received a third or later line medicine. The estimate of length of treatment in first line appears similar to the overall length of treatment, which may be because the majority of patients did not receive second line treatment, partly because imatinib was the only medicine listed for chronic CML for 11 years.

Table 10: Kaplan Meier estimate of length of treatment by line of therapy

	Mean	Std Err	Median	Lower Limit	Upper Limit
Without excluding breaks					
First line	8.49	0.10	7.65	7.16	8.19
Second line	6.22	0.13	6.08	5.45	6.52
Third or later line	5.06	0.21	4.79	4.04	5.52
Excluding breaks					
First line	7.89	0.10	7.08	6.49	7.57
Second line	5.90	0.14	5.31	4.79	5.95
Third or later line	4.45	0.19	4.01	3.33	5.00

Analysis of Authority Approvals

This section uses authority approvals to determine the number of supplied prescriptions for TKIs in CML by disease phase, line of therapy and drug. The majority of prescriptions in CML is chronic CML, the use of first line chronic CML is higher than second or later line chronic CML, although second or later line chronic CML may be growing. Figure 7 suggests the use of first line imatinib in chronic CML patients appears to be stable since 2012, when the restrictions of dasatinib and nilotinib were extended from second line treatment to first line treatment.

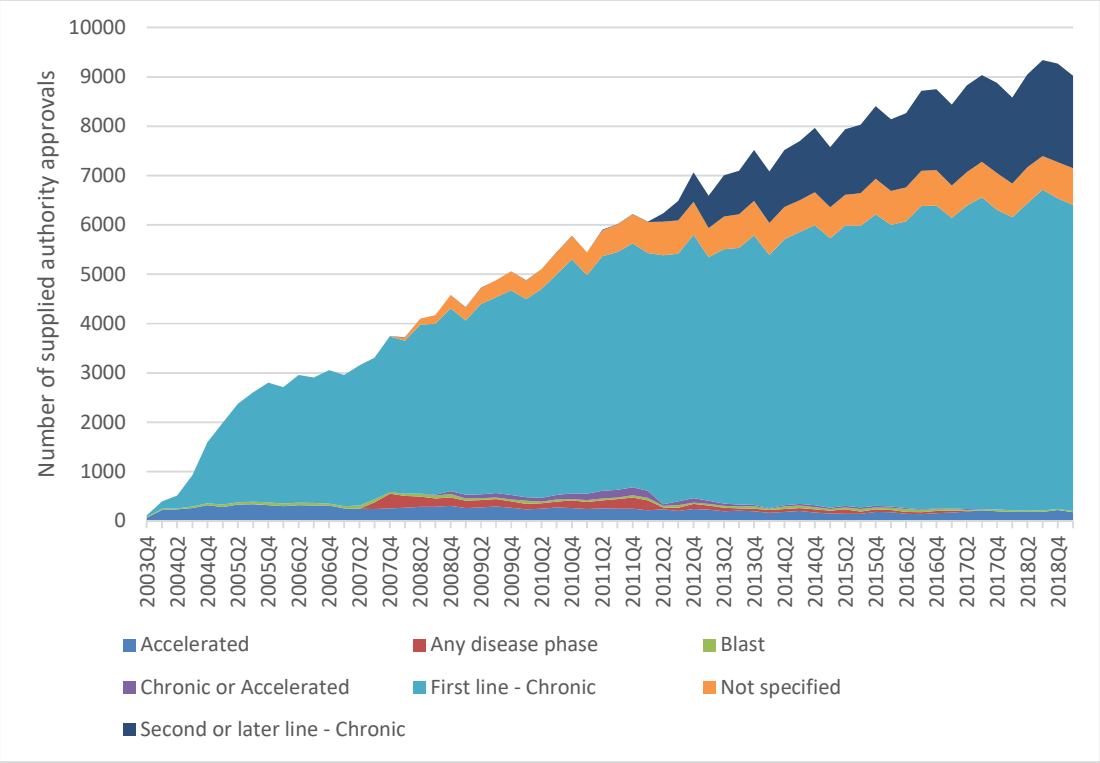

Figure 6: Authority approval reasons by time

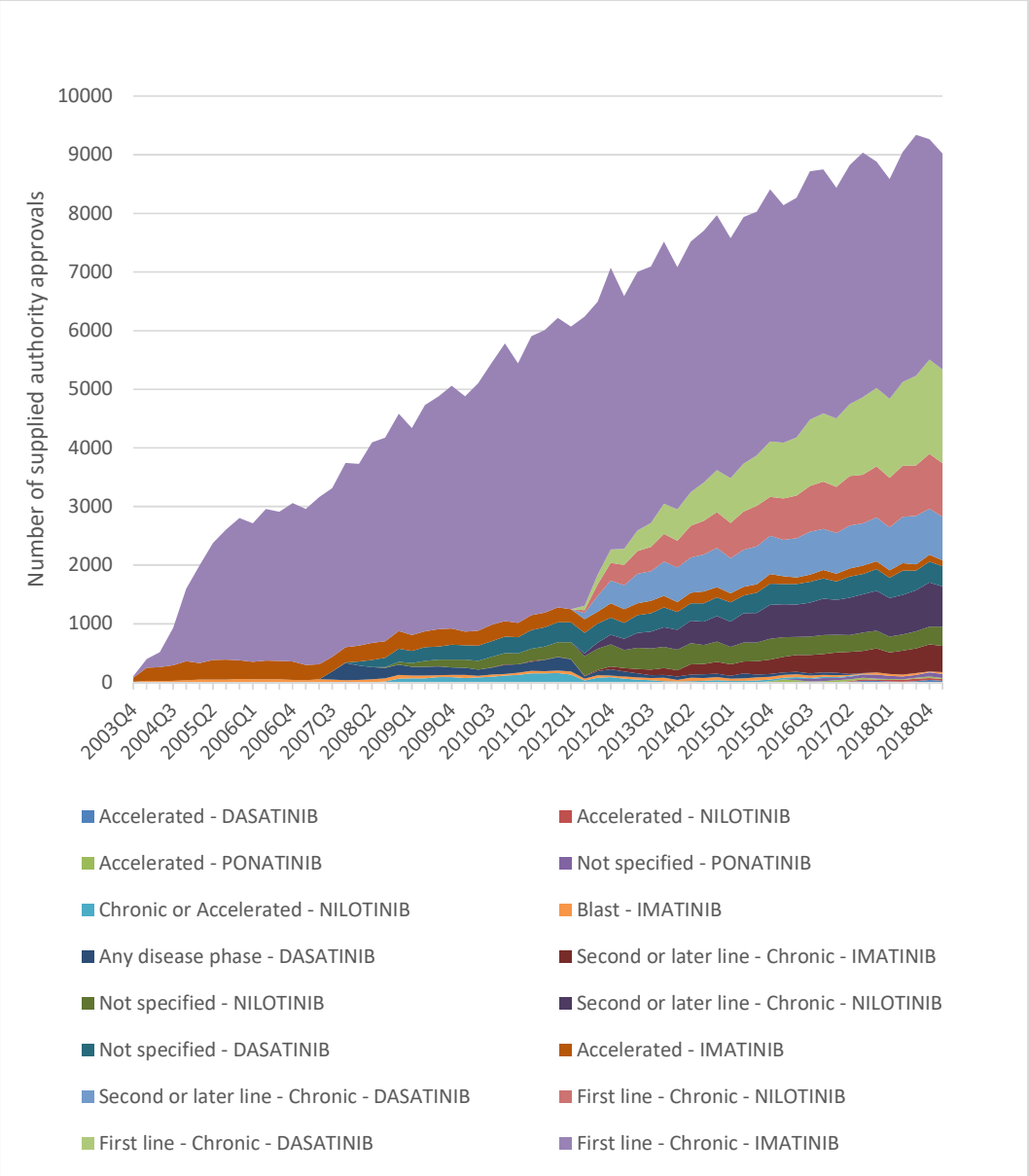

Figure 7: Authority approval reasons and medicine by time

Prescribed dose

The analysis of prescribed dose uses authority approvals to determine the number of supplied prescriptions for TKIs in CML by disease phase, line of therapy and drug.

Table 11: Estimated dose per day by reason for patients who initiated between April 2017 and March 2018

			Mean estimated mass amount per day				Number of prescriptions			
Line of treatment	**Phase**	**Initial or Continuing approval**	**Imatinib**	**Nilotinib**	**Dasatinib**	**Ponatinib**	**Imatinib**	**Nilotinib**	**Dasatinib**	**Ponatinib**
First line	Accelerated	Continuing	800				7			
		Initial	629	800			7	≤5		
	Accelerated Total		715	800			14	≤5		
	Blast	Continuing	600				≤5			
		Initial	600				6			
	Blast Total		600				6+			
	Chronic	Continuing	427	603	106		461	235	649	
		Initial	414	613	106		747	272	873	
	Chronic Total		419	608	106		1,208	507	1,522	
	Not specified	Continuing		914	140			7	9	
First line Total			424	614	106		1,228+	514+	1,531	
Second or later line	Accelerated	Continuing		800		45		≤5		≤5
		Initial		800		49		≤5		11
	Accelerated Total			800		48		≤10		11+
	Chronic	Continuing	411	636	110		38	67	83	
		Initial	422	610	115		36	62	84	
	Chronic Total		416	624	113		74	129	167	
	Not specified	Continuing		400		45		≤5		≤5
Second or later line Total			416	626	113	48	74	129+	167	11+

Note: using first 12 months of prescriptions

The doses for initiating patients in their first 12 months of treatment were similar to those reported previously for patients who initiated between April 2012 and March 2013 (DUSC October 2014). On 1 April 2012 the PBS restrictions of dasatinib and nilotinib were extended to first line treatment, and the first line restrictions were modified to include dose guidance. Despite this, the doses used in first line chronic treatment were almost identical to the previous analysis. The main difference between these analyses was that the doses of imatinib appeared to be higher for continuing patients in the accelerated phase of CML. Additionally, due to administrative changes in some listings, patients may have previously been recorded as treatment for an unknown phase where now the phase was clearer in the restriction.

The calculated average doses for imatinib and dasatinib in chronic first line patients were 419 mg and 106 mg respectively. This gives a dose relativity (imatinib:dasatinib) of 3.95:1 which was similar to the July 2011 PBAC[8] recommended assumed relativity of 395.77 mg:93.88 mg = 4.22:1. The average doses for imatinib and dasatinib were both higher than those assumed by the PBAC, but the relativity was approximately the same.

The recommended dosages for imatinib are 400 mg for chronic phase, and 600 mg for accelerated and blast phase. Patients supplied imatinib were using approximately 400 mg in the chronic phase, which matches the recommended dose for this indication. Patients were using mean doses of 600 mg in blast phase and 700 mg in accelerated phase. In the accelerated phase, continuing patients were using higher doses than patients in the initial phase. These matched the recommended doses of 400 mg in chronic phase, and 600 mg per day in accelerated and blast phases, with possible dose increases to 800 mg per day.

Nilotinib is recommended to be used as 600 mg per day in the chronic phase, with possible dose escalations to 800 mg per day. In the accelerated phase it is recommended to be used as 800 mg per day. It is not listed for patients in the blast phase. The estimated prescribed dose of nilotinib was approximately 600 mg in both initiating and continuing patients in the chronic phase, and 800 mg per day for patients in the accelerated phase.

Dasatinib is recommended to be used as 100 mg per day for patients in the chronic phase of treatment, with possible dose escalation to 140 mg per day due to a lack of haematological or cytogenic response. In the accelerated and blast phases patients are recommended to take 140 mg per day, with possible dose escalation to 180 mg per day. The prescribed doses in new and prevalent patients matched these dose recommendations.

The prescribed dose of ponatinib appeared to be similar to the recommended dose of 45 mg daily in all phases of treatment.

The prescribed dose in second line patients was generally lower than in first line patients.

[8] Public Summary Document, Dasatinib, July 2011. Accessed at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-07/pbac-psd-dasatinib-july11

Analysis of expenditure

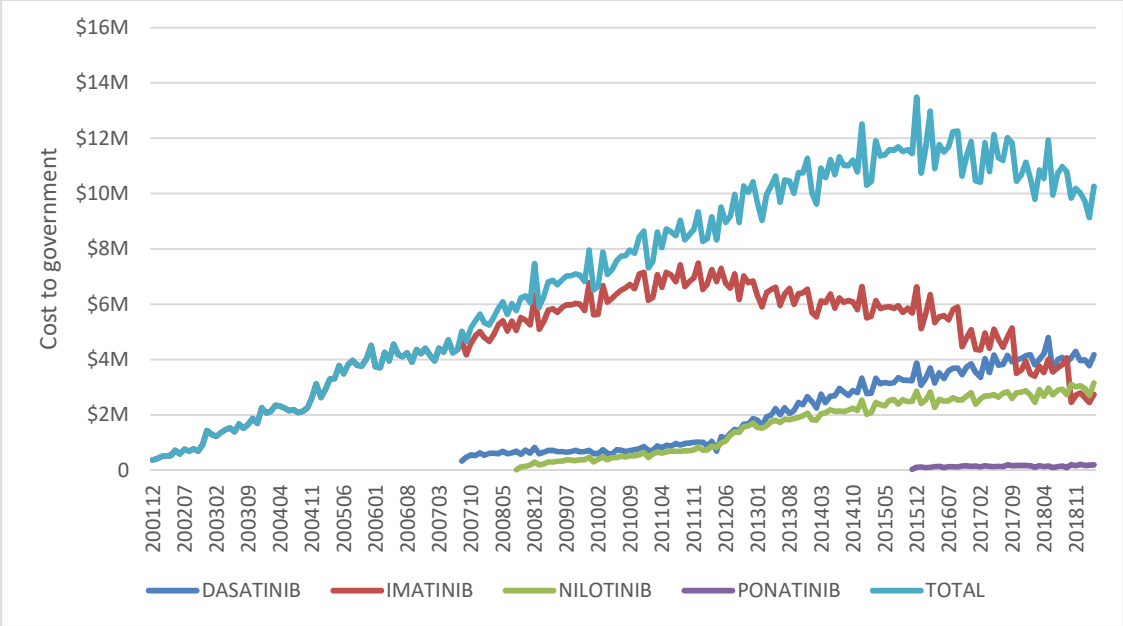

Figure 8: Cost to government for TKIs for CML since December 2001

Despite the growing use of TKIs for CML the net cost to government appeared to be decreasing. The decrease appeared to begin in 2016, and was due to several price reductions of imatinib in 2016, 2017 and 2018. A fifth price reduction was due to apply to imatinib on 1 October 2019.

Table 12: Price reductions applied to TKIs for CML

Date of Price Reduction Day	Medicine	Percentage Difference	Reason
01 April 2016	Imatinib	5%	Five Year Anniversary Price Reduction
01 April 2016	Nilotinib	5%	Five Year Anniversary Price Reduction
01 April 2016	Dasatinib	5%	Five Year Anniversary Price Reduction
01 October 2016	Imatinib	16%	First New Brand Price Reduction
01 October 2017	Imatinib	19.39%	Price Disclosure Reduction
01 June 2018	Dasatinib	10%	Ten Year Anniversary Price Reduction
01 October 2018	Imatinib	27.15%	Price Disclosure Reduction
01 April 2019	Nilotinib	10%	Ten Year Anniversary Price Reduction
01 October 2019	Imatinib	21.71%	Price Disclosure Reduction

Source: PBS Price Changes Section, Pricing and PBS Policy Branch, Technology Assessment and Access Division, Department of Health

Analysis of actual versus predicted utilisation

Approach taken to estimate utilisation of ponatinib

The submission used a mixed epidemiological and market share approach to estimate the utilisation and cost of the ponatinib. The submission used PBS prescription data published by the Department of Human Services to predict which first line therapy patients receive. The number of patients who failed previous lines of therapy, had the T315I mutation, and the number who were resistant or intolerant were estimated using published sources.

The estimates for ponatinib were presented in calendar years, so although it was PBS listed on 1 November 2015 the predicted versus actual review compares calendar years from 2016.

Actual versus predicted utilisation

Table 13: Predicted versus actual utilisation of ponatinib

		Year 1 (2016)	Year 2 (2017)	Year 3 (2018)
Treated patients	Predicted	116	115	123
	Actual	40	45	50
	Difference	-66%	-61%	-59%
Packs of 15 mg	Predicted	1,101	1,094	1,167
	Actual	175	209	212
	Difference	-84%	-81%	-82%
Packs of 45 mg	Predicted	213	212	226
	Actual	76	96	83
	Difference	-64%	-55%	-63%
Total packs/ prescriptions	Predicted	1,314	1,306	1,393
	Actual	251	305	295
	Difference	-81%	-77%	-79%
Net cost to government	Predicted	$6,535,235	$6,492,756	$6,928,446
	Actual	$1,555,002	$1,859,794	$1,807,857
	Difference	-76%	-71%	-74%

The number of patients treated with ponatinib, and the number of supplied prescriptions and the net cost to government, were all substantially lower than predicted. As the number of supplied prescriptions was overestimated more than the number of treated patients, it is possible some patients had trialled ponatinib and not continued.

It is interesting that the number of packs of 15 mg tablets were overestimated more than the number of packs on 45 mg tablets, because in the cohort of all treated patients, the estimated prescribed dose was lower than the recommended dose of 45 mg daily. However, in the first 12 months of treatment of patients who initiated between April 2017 and March 2018, the estimated prescribed dose was 48 mg overall for second line patients.

Discussion

The number of treated patients and the number of supplied prescriptions had continued to grow since the DUSC analysis in 2014. The total number of prescriptions per month appeared to be growing in a steady linear manner. The listings of dasatinib and nilotinib for chronic CML in 2012 had taken market share from imatinib, and had not affected the rate of growth. However, due to price reductions triggered by the PBS listing of generic brands of imatinib, the total cost to government had decreased and it appeared it was continuing to decrease.

The number of treated and initiating patients per quarter aligned with the analysis of the number of supplied authorities which showed that the majority of use of medicines for CML is for patients with chronic disease in their first line of treatment, and the second highest use was for patients with chronic disease in their second line of treatment. The use of TKIs for patients in the blast or accelerated phase of CML was much lower than the chronic phase. Together with the number of treated and initiating patients per quarter, this showed that the growing use of TKIs for CML was driven by continuing patients being treated for chronic disease.

The number of initiating patients per year may be slightly increasing over time, however had been between 300 and 450 per year since 2003. The reported incidence[9] appeared to be slowly increasing, although there was an increase between 2010 and 2012 which appeared to have since levelled off. The reported incidence of CML had been between 260 and 375 per year between 2001 and 2015, with the highest reported value in 2012. The age standardised incidence rate had been fairly stable between 1.3 and 1.6 between 2001 and 2015, which suggested that the slight increase in initiating patients may have been due to the ageing population.

Since 2001, 3,557 (58%) male patients have initiated treatment for CML with one of these medicines, compared with 2,616 (42%) female patients. The proportion of male and female patients in 2018 was similar to these proportions. The number of diagnosed patients reported by the AIHW[9] also matched these proportions. The AIHW reported that between 2001 and 2015 there were 2,656 (58%) incident male patients and 1,927 (42%) incident female patients.

DUSC consideration

DUSC noted the PBS restriction history reflects the addition of more TKIs and broadening of restrictions, followed by specific dosing guidance in 2012. DUSC noted that ponatinib was listed with a narrower restriction than imatinib, dasatinib and nilotinib.

[9] Australian Institute of Health and Welfare (AIHW) 2018 Cancer Data in Australia; Australian Cancer Incidence and Mortality (ACIM) books: chronic myeloid leukaemia Canberra: AIHW. <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/>.

DUSC noted that the report showed the number of treated patients is growing steadily and that the number of initiating patients is stable. DUSC commented that the addition of ponatinib had not impacted the overall trend of growth in the utilisation of TKIs for CML.

DUSC noted the report presented the top ten medicine sequences since the listing of imatinib in 2001, and since the listing of ponatinib in 2015. DUSC commented that the top ten medicine sequences showed that the majority of patients were treated with only one agent, which suggests patients tend to stay on the original TKI therapy they are initiated on, rather than switching to new therapies.

DUSC noted the overall length of time on PBS subsidised therapy was similar to the estimated length of treatment at the time of listing imatinib, dasatinib and nilotinib. DUSC commented that the time on therapy results indicated that the listing of TKIs for CML has been positive for patients.

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

Novartis Pharmaceuticals Australia Pty Limited: Novartis thanks the DUSC for the opportunity to comment on this report, and agrees with the findings which continue to support the effectiveness of TKIs for the treatment of CML.

Bristol-Myers Squibb Australia Pty Ltd, Specialised Therapeutics Australia Pty Ltd, Alphapharm Pty Ltd, Cipla Australia Pty Ltd, Juno Pharmaceuticals Pty Ltd, Dr Reddy's Laboratories (Australia) Pty Ltd, Generic Health Pty Ltd, Apotex Pty Ltd, Sun Pharma ANZ Pty Ltd, Sandoz 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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