Ruxolitinib for the treatment of myelofibrosis: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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## Abstract

### Purpose

### To compare the predicted and actual utilisation of ruxolitinib for myelofibrosis in the first 24 months of Pharmaceutical Benefits Scheme (PBS) listing.

### Restriction (abridged)

### Ruxolitinib was PBS listed for myelofibrosis on 1 February 2016.

It is restricted for use in high risk and intermediate-2 (Int-2) risk myelofibrosis, or intermediate-1 (Int-1) risk myelofibrosis. The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Int-1 risk myelofibrosis patients have the additional clinical criterion that they must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy.

### Data Source

The analyses use data from the Department of Human Services (DHS) prescriptions database and the DHS Authority approvals database from February 2016 to the end of April 2018.

### Key Findings

* In the first and second years of PBS listing, 861 and 1,082 patients received treatment with ruxolitinib, respectively. This was xxx more patients than predicted in both years.
* Despite more patients receiving treatment, there were fewer prescriptions dispensed than expected. This may be due to new patients commencing throughout a listing year and lower adherence in clinical practice than in the clinical trial setting. Insufficient data are available at this stage to establish the median time on therapy.
* The average dose used in practice was similar to that predicted from the clinical trial setting. The average predicted daily dose was xxxx mg per day and the actual average daily dose was 27.1 mg.
* The proportion of patients with Int‑1 risk myelofibrosis treated with ruxolitinib was 14% and 23% in Years 1 and 2 respectively.
* Approximately half of Int-1 patients had PBS hydroxyurea in the 2 years prior to commencing treatment with ruxolitinib.

# Purpose of analysis

To compare the predicted and actual utilisation of ruxolitinib for high, Int-2 and Int-1 risk myelofibrosis in the first 24 months of PBS listing.

# Background

Myelofibrosis is a disorder of the bone marrow, in which the marrow is replaced by scar tissue. The abnormal marrow can no longer produce enough normal blood cells and results in a significantly enlarged spleen.[[1]](#footnote-1)

Myelofibrosis can produce a variety of symptoms such as fever, night sweats, bone pain, itch, lethargy and weight loss. Myelofibrosis can occur at any age but is usually diagnosed later in life, between the ages of 60 and 70 years. It is diagnosed using a combination of a physical examination showing the presence of an enlarged spleen, blood tests and a bone marrow examination.[[2]](#footnote-2)

The current prognostic models used for myelofibrosis include the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS), and DIPSS-plus.[[3]](#footnote-3) The scoring systems include the variables age, white blood cell count, haemoglobin, peripheral blood blast and constitutional symptoms. The IPSS is applicable at the time of initial diagnosis and the DIPSS can be applied at any time during follow-up. The DIPSS contains two separate models, one that incorporates all patients (DIPSS) and one for patients below the age of 65 (age-adjusted DIPSS).[[4]](#footnote-4) Eligibility for PBS subsidised ruxolitinib is based on the IPSS, DIPSS or age-adjusted DIPSS. Another model, the DIPSS-plus, incorporates eight risk factors; the five risk factors from IPSS, in addition to a further three risk factors. Patients are categorised as low, Int‑1, Int‑2, or high risk depending on how many risk factors they present with.3

Drug therapy for myelofibrosis aims to relieve symptoms and reduce the risk of complications. Therapies may include ruxolitinib, hydroxyurea and interferons.[[5]](#footnote-5) Low or Int‑1 risk asymptomatic patients are usually observed without intervention. Higher risk patients may be considered for allogeneic stem cell transplantation (ASCT) or investigational treatments. The only treatment that has shown to have an impact on disease progression is allogeneic stem cell transplantation (ASCT), although it is not a suitable option for most people.3

## Pharmacology

Ruxolitinib is an inhibitor of janus kinase (JAK)1 and JAK2 with nanomolar potency. JAKs mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. JAK signalling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation, and subsequent localisation of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells. Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies.[[6]](#footnote-6)

## Therapeutic Goods Administration (TGA) approved indications

Ruxolitinib (Jakavi®) is indicated for the treatment of

* Disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.
* Adult patients with polycythemia vera who are resistant or intolerant of hydroxyurea.

## Dosage and administration6

A blood cell count must be performed before initiating therapy with ruxolitinib. Complete blood counts should be monitored every 2 to 4 weeks until doses are stabilised, and then as clinically indicated. Ruxolitinib is given orally twice daily with or without food in myelofibrosis. The recommended starting dose is based on platelet count as shown in Table 1.

Table 1: Recommended starting dose of ruxolitinib

| Platelet Count | Starting dose and frequency of administration |
| --- | --- |
| 50-100 x 109/L | oral 5 mg twice daily |
| 100-200 x 109/L | oral 15 mg twice daily |
| >200 x 109/L | oral 20 mg twice daily |

Source: [Product Information](https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01918-1&d=2018062816114622483)6

The dose is then titrated based on efficacy and safety. The maximum dose is 25 mg twice daily.

The dose is reduced or treatment interrupted if the platelet count decreases below certain levels. Dose adjustment is also needed with concomitant strong CYP34A inhibitors or fluconazole, in patients with moderate or severe renal impairment, and in patients with hepatic impairment. See the [Product Information](https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01918-1)6 for full details.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA (Product Information)](http://tga.gov.au/hp/information-medicines-pi.htm) and [the TGA (Consumer Medicines Information)](http://www.tga.gov.au/consumers/information-medicines-cmi.htm).

## PBS listing details (as at July 2018)

### Date of listing on PBS

The 5 mg, 15 mg and 20 mg strengths of ruxolitinib were PBS listed on 1 February 2016 and the 10 mg strength on 1 November 2016. The PBS item codes are shown in Table 2.

Table 2: PBS listing of ruxolitinib

| Item | Name, form & strength, pack size | Treatment Phase | Max. quant. (tablets) | Rpts | DPMQ\* | Brand name and manufacturer |
| --- | --- | --- | --- | --- | --- | --- |
| 10614P | Ruxolitinib 5 mg tablet, 56 | Initial | 112 | 0 | $5151.04 | Jakavi®  NOVARTIS Pharmaceuticals Australia Pty Limited |
| 10616R | Ruxolitinib 5 mg tablet, 56 | Continuing | 112 | 5 | $5151.04 |
| 10913J | Ruxolitinib 10 mg tablet, 56 | Initial | 56 | 0 | $5151.04 |
| 10927D | Ruxolitinib 10 mg tablet, 56 | Continuing | 56 | 5 | $5151.04 |
| 10619X | Ruxolitinib 15 mg tablet, 56 | Initial | 56 | 0 | $5151.04 |
| 10615Q | Ruxolitinib 15 mg tablet, 56 | Continuing | 56 | 5 | $5151.04 |
| 10618W | Ruxolitinib 20 mg tablet, 56 | Initial | 56 | 0 | $5151.04 |
| 10617T | Ruxolitinib 20 mg tablet, 56 | Continuing | 56 | 5 | $5151.04 |

Source: the [PBS website](http://www.pbs.gov.au/pbs/home). \*Special Pricing Arrangements apply to these items.

### Restriction

High risk and intermediate-2 risk myelofibrosis

The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Note: Risk of myelofibrosis is defined in accordance with the Myelofibrosis International Prognostic Scoring System (IPSS) OR the Dynamic International Prognostic Scoring System (DIPSS) OR the Age-Adjusted DIPSS.

Note: The initial authority application must be made in writing and must include:

1. A completed authority prescription form; and
2. A completed Myelofibrosis Authority Application Supporting Information Form, which includes all of the following:
3. A copy of the bone marrow biopsy report confirming diagnosis of myelofibrosis; and
4. A classification of risk of myelofibrosis according to the IPSS, DIPSS, or the Age-Adjusted DIPSS.

Intermediate-1 risk myelofibrosis

The condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, and patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy.

Note: The initial authority application must be made in writing and must include:

1. A completed authority prescription form; and
2. A completed Myelofibrosis Authority Application Supporting Information Form, which includes all of the following:
3. A copy of the bone marrow biopsy report confirming diagnosis of myelofibrosis; and
4. A classification of risk of myelofibrosis according to the IPSS, DIPSS, or the Age-Adjusted DIPSS
5. A confirmation that the patient’s disease related symptoms are resistant, refractory or intolerant to available therapy.

Note: No increase in the maximum quantity may be authorised for the 15 mg and 20 mg dose strengths. For details of the current PBS listing refer to the [PBS website](file:///\\central.health\DFSGroupData\Sites\CO1\CO\PBD\PEB\EVAL\DUSC\DUSC%20Documents\Predicted%20vs%20actual%20usage\pbs.gov.au).

Authority approval applications for continuing treatment for both of the above restrictions can be made by phone.

From February to October 2016 inclusive there was also a grandfathering restriction for high risk, Int‑2 risk and Int‑1 risk myelofibrosis. This stated that the condition must be primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, and the patient must have previously received non-PBS-subsidised treatment with this drug for this condition before 1 February 2016.

Current PBS listing details are available from the [PBS website](file:///\\central.health\DFSGroupData\Sites\CO1\CO\PBD\PEB\EVAL\DUSC\DUSC%20Documents\Predicted%20vs%20actual%20usage\pbs.gov.au).

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

The first submission for ruxolitinib, considered at the July 2013 PBAC meeting, requested listing as first line treatment for intermediate risk or high risk primary myelofibrosis, post‑polycythemia or post-essential thrombocythemia myelofibrosis. The PBAC noted that the pivotal clinical trials included only high-risk and Int‑2 risk patients and the restriction would allow access to Int­1 patients. It is unknown whether this population would derive the same benefit from treatment as the study population, or whether Int‑1 patients with mild symptoms would gain any benefit. However, the PBAC also recognised that some patients with severe symptoms refractory to best available therapies, but with a more favourable prognosis, could benefit from treatment with ruxolitinib through symptom relief, and that exclusion of these patients from PBS-subsidy would be problematic. The PBAC therefore considered that the cost-effectiveness of ruxolitinib can only be determined with acceptable accuracy once the population for PBS subsidy is further refined.

For further details refer to the [Public Summary Document](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/ruxolitinib-psd-march-2015.pdf) from the July 2013 PBAC meeting.

A subsequent resubmission, considered at the July 2014 meeting, requested second line treatment for patients with Int‑2 risk or high-risk myelofibrosis who are resistant, refractory, intolerant, or not a candidate for available therapy. The PBAC deferred making a recommendation due to a lack of clarity around the appropriate clinical place of ruxolitinib in Australian clinical practice, concerns regarding the proposed restriction, and an unacceptably high price. Each of these matters precluded the Committee from reaching a conclusion that ruxolitinib was cost-effective.

The PBAC noted the sponsor’s request to limit the restriction to Int‑2 and high risk patients, so as to ensure the restriction was consistent with the current available clinical evidence. The Committee considered this inappropriate as it would exclude lower risk patients who still demonstrated a clear clinical need. The PBAC considered there is a clinical need for ruxolitinib in the treatment of myelofibrosis and that there are patients who may benefit from treatment across the risk groups.

The PBAC recommended a stakeholder meeting be held between the sponsor, the Department, clinicians from applicable professional bodies, consumer representatives and PBAC members to provide clarity around the clinical place for ruxolitinib and to consider an appropriate restriction. This in turn would inform the cost-effectiveness analyses.

For further details refer to the [Public Summary Document](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/ruxolitinib-psd-07-2014) from the July 2014 PBAC meeting.

The stakeholder meeting was convened in September 2014. Stakeholders discussed the clinical place for ruxolitinib including the patient groups for whom treatment with ruxolitinib is appropriate and not appropriate, the various scoring systems for classifying according to risk status, the proposed PBS restriction including whether the restriction should require measurement of spleen size or continuation criteria, and quantities of tablets necessary for dose titration.

For further details see the [Outcome Statement](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/ruxolitinib-stakeholder-meeting-outcome-statement-sep-2014.pdf) for the ruxolitinib stakeholder meeting.

At the March 2015 meeting, the PBAC recommended ruxolitinib for PBS listing. The recommendation was for Int‑1-risk, Int‑2 and high risk patients with the listing for Int‑1 patients restricted to those patients with severe disease‑related symptoms that are resistant, refractory or intolerant to available therapy.

The PBAC was satisfied that ruxolitinib provides a major advance in care for patients with poor prognosis and/or with symptoms refractory to current care.

The PBAC accepted the clinical place for ruxolitinib, noting advice from expert clinicians at the PBAC stakeholder meeting for ruxolitinib. The PBAC agreed that Int‑1 patients with a high symptom burden should be included in the requested population, noting that no randomised controlled trials of ruxolitinib have included Int‑1 patients.

The PBAC considered the extent of survival benefit remains uncertain but cannot be resolved.

The PBAC accepted that in the absence of comparative evidence for the Int‑1 population, it would be reasonable to assume that the effectiveness of ruxolitinib for Int‑1 patients would be the same as for Int‑2 for the purpose of determining cost effectiveness, noting the difference in baseline mortality risk.

The PBAC considered that ruxolitinib could potentially be used outside of the eligible population in myelofibrosis with lower symptom burden or in other chronic myeloid neoplasms. The PBAC recommended a written Authority Required restriction for initial use, with continuation by telephone authority approval to mitigate this risk.

For further details refer to the [Public Summary Document](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/ruxolitinib-psd-march-2015.pdf) from the March 2015 PBAC meeting.

## Approach taken to estimate utilisation

The submission used an epidemiological approach to estimate the number of patients eligible for ruxolitinib.

Published literature was used to estimate annual incidence and prevalence of myelofibrosis. The assumptions of risk stratification and mortality rate prior to ruxolitinib access were based on published literature. Mortality rate following availability of ruxolitinib was based on trial data from COMFORT I study. Uptake rates were based on clinical advice.

Table 3: Data sources and assumptions used for financial estimates

|  | **Assumption** | **Source/Comments** |
| --- | --- | --- |
| Incidence (rate/100,000) | 1.2 | Mehta 2013 [[7]](#footnote-7)  Prevalence is applied in the first year estimates and incidence thereafter. |
| Prevalence  (rate/100,000) | 3.8 |
| Distribution of risk categories | | Low risk | 22% | | --- | --- | | Int-1 risk | 29% | | Int-2 risk | 28% | | High risk | 21% | | Cervantes 2009[[8]](#footnote-8)  Based IPSS. on risk categories at diagnosis using the |
| 5 year survival (proportion) | | Low risk | 90% | | --- | --- | | Int-1 risk | 75% | | Int-2 risk | 46% | | High risk | 18% | | Cervantes 20098 |
| Survival benefits | Mortality rates   |  | Pre-RUX | Post-RUX | | --- | --- | --- | | Int-1 | xxxx | xxxx | | Int-2/HR | xxxxx | xxxx | | Assumed survival benefits from ruxolitinib use sourced from COMFORT-I (annual mortality rates listed below). |
| Progression rate | Low to int-1: x%; Int-1 to Int-2/HR: xx% | Sponsor assumption. |
| Proportion eligible for treatment | Int-1: xx%; Int-2/HR: xx% | PBAC stakeholder meeting and sponsor sourced clinician input. |
| Uptake rate | Int-1 (second line): xxx% year 1 to year 5  Int-2/HR: xx% year 1, up to xx% in year 5 | Sponsor assumption based on clinician advice. |
| Dosage used | | 5 mg bid (2 x 5mg) | xxxxx% | | --- | --- | | 10 mg bid (4 x 5mg) | xxxxx% | | 15 mg bid (2 x 15mg) | xxxxx% | | 20 mg bid (2 x 20mg) | xxxxx% | | 25 mg bid ((2 x 20mg) + (2 x 5mg) | xxxxx% | | Dose distribution across 144 weeks of COMFORT-I |
| Average number of days of exposure per patient treated | xx%\* | Proportion of days of exposure relative to the number of potential days on treatment (until death or discontinuation of treatment) from COMFORT 1 trial |

Source: Adapted from the PEB Addendum to the ESC Advice and the Sponsor pre-PBAC response to the March 2015 PBAC meeting.

\*The approach for estimating prescriptions was implemented by assuming that xx% of prevalent patients will be on treatment for the whole year (xx prescriptions) and x% of patients discontinue during the year and receive on average x scripts. This was referred to as the half cycle correction and resulted in the average number of prescriptions per year of xxxx. In addition, for the xx% of patients expected to be prescribed the 25mg dose two prescriptions (5mg and 20mg) are required, increasing the average number of prescriptions/patient/year to xxxx.

# Methods

PBS prescription data for ruxolitinib dispensed from 1 February 2016 to 30 April 2018 were extracted from the DHS PBS prescription database.[[9]](#footnote-9) PBS prescription data were used to determine the number of prescriptions supplied and the number of incident and prevalent patients for the predicted vs actual analysis. They were also used for the patient demographics, length of treatment, indication sequence, medicines taken prior to initiating ruxolitinib and dose analyses. Prescription indications (i.e. Int‑1 risk myelofibrosis, Int‑2 and high risk myelofibrosis and grandfathered patients) were determined using additional information in the DHS Authority Approvals database. This database records the restriction code for written and telephone authorities. There were 0.29% of prescriptions where the indication of the prescription was unknown after matching with DHS Authority Approvals database. These prescriptions were assumed to be for Int‑2 and high risk myelofibrosis, as this was the most common indication (72% of all prescriptions).

### Length of treatment

The duration of treatment analysis used the Kaplan Meier (aka Product-Limit) method to determine the length of treatment for patients on ruxolitinib. Two ways of measuring length of treatment were undertaken. One excluded any breaks in treatment and the other did not. A break in treatment was defined as a gap of more than 3 times the median time to resupply between supplies, which was an estimated break in treatment of at least 2 times the median time to resupply. A patient was deemed to be continuing treatment (classified as censored in the Product-Limit method) at the end of the data period (i.e. the end of April 2018) if their last prescription was within 3 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 or the end of the data period, whichever was later.

Only patients initiating from February 2016 (date of PBS listing) to the end of January 2018 (i.e. 24 months) were included in the analysis. Prescriptions for these patients were followed up to the end of April 2018 (i.e. follow up from 3 to 27 months). Patients initiating from February to the end of April 2018 were excluded as they were considered to have insufficient follow up.

### Dose distribution

The patient average dose distribution analysis relied on the results of the length of treatment (excluding breaks) analysis. A patient average dose across time was calculated as the total mass of drug supplied divided by the number of days on treatment (excluding breaks). Only patients included in the length of treatment analysis were included in the average dose distribution analysis.

This measure of dose (i.e. the average across the patients estimated time on treatment) is conceptually very similar to the measure of dose in the estimates which was based on days of exposure at each dose across the whole 144 weeks of the COMFORT I trial.

# Results

## Analysis of drug utilisation

### Number of patients treated

Figure 1: Patients initiating (by indication) and prevalent to PBS ruxolitinibSources: DHS prescription database (accessed 2 July 2018) and DHS authority approvals database.

Note: where the patient count is between 1 and 5 (inclusive), the data point has been set to 5 to protect confidentiality. Indications are that of the first prescription for a patient.

In the first few months after listing 315 grandfathered patients initiated PBS treatment as patients transitioned from the Sponsors’ compassionate use program. It is reasonable to assume that most grandfathered patients have Int-2 or high risk myelofibrosis as the Sponsor’s compassionate use program enrolled patients in accordance with the COMFORT‑2 trial eligibility criteria.[[10]](#footnote-10) The number of new Int‑2 or high risk patients commencing treatment with ruxolitinib stabilised to about 67 patients per quarter within 6 months of listing. The number of Int‑1 risk patients initiating ruxolitinib was approximately half that of Int‑2 and high risk patients.

### Number of prescriptions

Figure 2 shows the utilisation of PBS prescriptions for ruxolitinib.

Figure 2: PBS prescriptions for ruxolitinib

Source: DHS prescription database (accessed 2 July 2018). Note: ruxolitinib was listed on 1 February 2016 so 2016 Q1 only contains two months of data.

Figure 2 shows that prescription utilisation increased at a steady linear rate from mid-2016 to the end of 2017. The slight decrease in 2017 Q1 and the levelling off in 2018 Q1 may be due to Safety Net seasonality.

Figure 3: PBS prescriptions for ruxolitinib by itemSources: DHS prescription database (accessed 2 July 2018).

The 10 mg tablet was listed after the other strengths, in November 2016. Figure 3 shows that the 5 mg tablet was substituted by the 10 mg tablet after it was listed. The number of prescriptions overall would not have changed as the 5 mg strength is supplied as double the quantity (112 tablets) compared with the 10 mg strength (56 tablets). The 20 mg tablet is most commonly prescribed. This is consistent with the predicted dose distribution in Table 3. An analysis the average daily dose is provided in the “Dose analysis” section later in this report.

Figure 4: PBS prescriptions for ruxolitinib by indicationSources: DHS prescription database (accessed 2 July 2018) and DHS authority approvals database.  
Note: Where the number of prescriptions was between 1 and 5 (inclusive), the data point has been set to 5 to protect confidentiality.

The grandfathering restriction ceased at the end of October 2016. The small volume of grandfathering prescriptions supplied in 2017 are most likely repeats and take the indication assigned at the authority approval prior to the supply of the original prescription.

Utilisation by Int-1 risk patients was approximately one third of that of Int-2 patients in 2018 Q1 (631/2012 = 31%). This is in line with the estimates which predicted Int-1 prescriptions would be xx% of Int-2 prescriptions in Year 2 after listing (see Predicted vs Actual analysis section for more details).

## Predicted vs Actual analysis

Table 4: Predicted vs Actual analysis – ruxolitinib for myelofibrosis

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Year1** | **Year 2** |
| **Feb 16 to Jan 17** | **Feb 17 to Jan 18** |
| Treated patients (PBS & RPBS) | Predicted (P) | xxx | xxx |
| Actual (A) | 861 | 1,082 |
| % Difference (A-P)/P | xxxx | xxxx |
| Prescriptions | Predicted (P) | xxxxx | xxxxxx |
| Actual (A) | 7,223 | 9,662 |
| % Difference (A-P)/P | xxxx | xxxx |
| Prescriptions per patient | Predicted (P) | xxxx | xxxx |
| Actual (A) | 8.4 | 8.9 |
| % Difference (A-P)/P | xxxx | xxxx |

Source: Final agreed estimates between the Department of Health and sponsor (PBS Ruxolitinib vI 20151201.xlsx) with 2016 as the first year of listing.

Table 4 shows that the number of patients treated in both Year 1 and 2 was approximately xx% more than expected. However the number of prescriptions supplied was slightly less than expected (xxx% and xxx% in Years 1 and 2 respectively). A contributing factor to the lower number of prescriptions may be the assumption of a full year of treatment for patients new to ruxolitinib, whereas commencement is spread throughout the year (see Figure 1). For patients discontinuing treatment throughout the year patients were assumed to receive fewer prescriptions. A further contributing factor to the lower number of prescriptions is likely to be lower rates of adherence in practice compared to the clinical trial setting upon which the estimates were based. A supplementary analysis, examining the number of prescriptions in the first 12 months after initiation for each patient that had a full 12 months follow up (i.e. initiators from February 2016 to the end of April 2017) from the PBS data found a median of 12 and a mean of 10.8 prescriptions.

The PBAC considered that for the purpose of the RSA the maximum number of Int‑1 patients should not exceed the number of Int‑1 patients in the pre-PBAC response. Table 5 compares the predicted and actual patient numbers by indication.

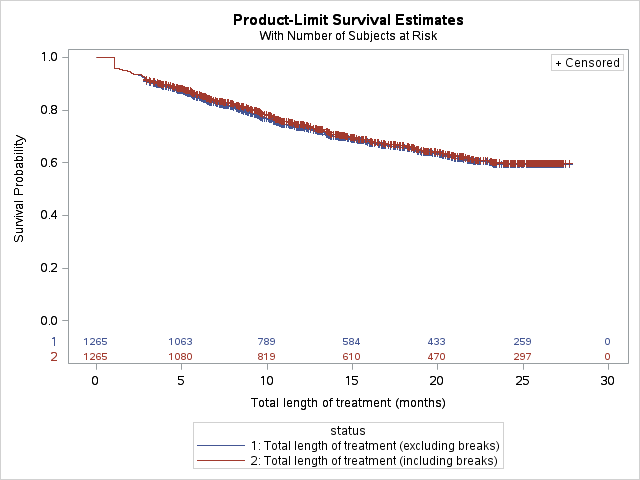
Table 5: Predicted vs Actual analysis by indication

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Year1** | **Year 2** |
| **Feb 16 to Jan 17** | **Feb 17 to Jan 18** |
| Treated Int-1 patients | Predicted (P) | xxx | xxx |
| Actual (A) | 124 | 253 |
| % Difference (A-P)/P | xxxx | xxx |
| Treated Int-2 & High Risk patients (including Grandfathered & Unknown) | Predicted (P) | xxx | xxx |
| Actual (A) | 737 | 829 |
| % Difference (A-P)/P | xxx | xxx |
| Prescriptions for Int-1 patients | Predicted (P) | xxxxx | xxxxx |
| Actual (A) | 616 | 2,078 |
| % Difference (A-P)/P | xxxx | xxxx |
| Prescriptions for Int-2 & High Risk patients (including Grandfathered & Unknown) | Predicted (P) | xxxxx | xxxxx |
| Actual (A) | 6,575 | 7,557 |
| % Difference (A-P)/P | xx | xxxx |
| Prescriptions per Int-1 patient | Predicted (P) | xxxx | xxxx |
| Actual (A) | 5.0 | 8.2 |
| % Difference (A-P)/P | xxxx | xxxx |
| Prescriptions per Int-2 & High Risk patient (including Grandfathered & Unknown) | Predicted (P) | xxxx | xxxx |
| Actual (A) | 8.9 | 9.1 |
| % Difference (A-P)/P | xxxx | xxxx |

Note: indications are that of the first prescription for a patient in the period.

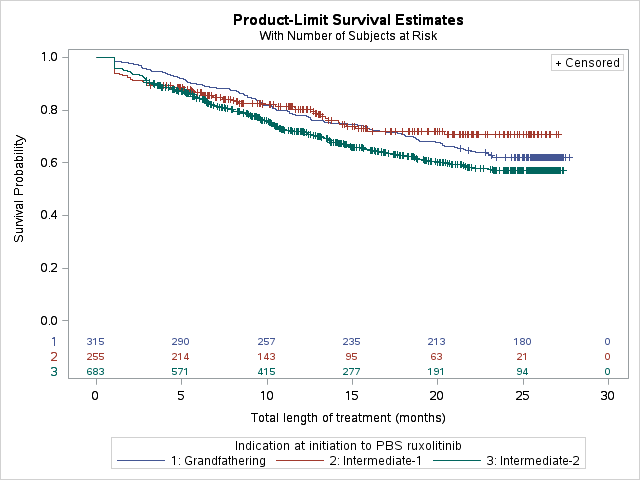
Table 5 shows that the number of Int-1 patients was less than predicted in Year 1 and more than predicted in Year 2. Figure 1 showed gradual uptake in the Int-1 population compared with the Int-2 population where there was initially higher uptake that then stabilised. The higher than predicted number of Int-1 patients in Year 2 (xxx%) consumed xx% less than predicted prescriptions. Thus even though the number of Int-1 patients exceeded the PBAC threshold, the number of prescriptions and therefore cost for these patients did not.

Length of Treatment

Figure 5: Length of treatment, including and excluding breaks.

Note: Includes initiations from listing in February 2016 to the end of January 2018 (i.e. 24 months). Follow up to the end of April 2018 (i.e. follow up from 3 to 27 months).

Figure 5 shows there is minimal difference in the length of treatment including or excluding breaks. The estimated median length of treatment (Survival Probability = 0.5) has not yet been reached. The 0.25 Survival Probability (i.e. probability of stopping treatment) occurs at 10.8 months if breaks are excluded and 11.5 months if breaks are included, a difference of 0.7 months.

Figure 6: Length of treatment including breaks by indication at initiation to PBS Ruxolitinib.

Int-2 & High risk

Note: Includes initiations from listing in February 2016 to the end of January 2018 (i.e. 24 months). Follow up to the end of April 2018 (i.e. follow up from 3 to 27 months).

The estimated median length of treatment has not yet been reached for any indication. The 0.25 Survival Probability occurs at 10.3, 14.2 and 13.7 months for Int-2 & High risk, Int-1 and grandfathered patients respectively.

It can be seen that the grandfathered patients do not have significant discontinuation after their first PBS prescription as it is not their first ruxolitinib treatment.

### Dose analysis

Figure 7 shows the distribution of average daily dose for patients included in the length of treatment analysis. A patient average dose across time was calculated as the total mass of drug supplied divided by the number of days on treatment (excluding breaks). Only patients included in the length of treatment analysis were included in the average dose distribution analysis. See Methods section for details.

Figure 7: Percent distribution of average daily dose (mg) by indication at initiation to PBS ruxolitinib.

Note: initiations from February 2016 to the end of January 2018 (i.e. 24 months). Follow up to the end of April 2018 (i.e. follow up from 3 to 27 months).

Figure 7 shows that the 30 mg dose (15 mg bid) is the most common. The median doses are 29, 30, 26 and 28 mg per day for Grandfathering, Int-1, Int-2 & High risk and Total patients respectively. Thus the doses are fairly consistent across the indications.

Table 6 compares the above distribution of doses with that predicted in the submission.

Table 6: Predicted vs Actual average daily doses of PBS ruxolitinib

| Dose (bid) | Tablets | % of patients in COMFORT I trial | Actual dose range | % of all PBS patients | % of Int-2 and high risk PBS patients |
| --- | --- | --- | --- | --- | --- |
| 5 mg | 2 x 5mg = 10mg | xxx | 5 to 14 mg | 15% | 18% |
| 10 mg | 4 x 5mg = 20mg | xxx | 15 to 24 mg | 27% | 28% |
| 15 mg | 2 x 15mg = 30mg | xxx | 25 to 34 mg | 29% | 29% |
| 20 mg | 2 x 20mg = 40mg | xxx | 35 to 44 mg | 25% | 24% |
| 25 mg | 2 x 20mg + 2 x 5mg = 50mg | xxx | >= 45 | 4% | 2% |

Note: In this analysis Int-2 and high risk does not include grandfathered patients

For all patients, Table 6 shows that there is good agreement between predicted and actual for the two lower doses. Actuals were greater than predicted for the middle dose (30 mg per day) and less than predicted for the higher doses. The mean predicted dose was xxxx mg per day and the mean actual dose was 27.1 mg per day.

As the COMFORT I trial was only for Int-2 and high risk patients the distribution for these patients is also shown in Table 6. It can be seen that the distribution is similar to that for all PBS patients.

Patient demographics

Figure 8: Number of patients initiating ruxolitinib by age and gender\*\* age and gender are those recorded on a patient’s first script. Note: includes all patients since listing to the end of April 2018, except grandfathered patients (i.e. patients whose first script was grandfathering).

Figure 8 shows that there are more males than females that have initiated ruxolitinib. The median age to initiate treatment for both genders is 70-74 years.

The gender distribution of patients in the COMFORT I trial was 46% female and 54% male. In Figure 8 the gender distribution is 41% female and 59% male.

Figure 9: Number of patients initiating PBS ruxolitinib by indication and ageNote: indication and age are those at the patient’s first script. Where the patient count is between 1 and 5 (inclusive), the data point has been set to 5 to protect confidentiality.

The median age of patients when they received their first PBS prescription for ruxolitinib in Figure 9 is lower for Int-1 risk patients (65-69 years) compared to Int-2 and grandfathered patients (both 70-74 years). Age is a prognostic variable for myelofibrosis.

In the COMFORT I trial (Int-2 and high risk patients) the median age of patients at baseline was 68 years. This was slightly younger than the PBS initiation age for Int-2 and high risk.

### Medicines taken prior to initiating ruxolitinib

The PBS restriction for Int-1 risk myelofibrosis includes the criterion that the “patient must have severe disease-related symptoms that are resistant, refractory or intolerant to available therapy.”

To determine what available PBS therapy patients used prior to initiation of ruxolitinib, all prescription data were extracted for each patient (n= 1,367) in the 2 years prior to starting ruxolitinib. The main medicine of interest is hydroxyurea (hydroxycarbamide). Busulfan and thalidomide were also included as they have been reported as being used for symptoms associated with myeloproliferative neoplasms. Busulfan may be used as a conditioning agent prior to ASCT, so supply may indicate that the patient was a candidate for ASCT.5 Peginterferon alfa-2a was recommended by the PBAC in November 2017 as an unrestricted listing thereby allowing access for patients with myeloproliferative neoplasms. It is too early to assess the impact of this listing.

Table 7: Drug sequence in the 2 years prior to initiation of PBS ruxolitinib for the drugs hydroxyurea, busulfan and thalidomide by indication at ruxolitinib initiation.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Indication at ruxolitinib initiation | | | | | | |  |
| Patients | Int-2 & High risk | GF | | Int-1 | | Total | | Rank |
| ruxolitinib | 431 | 194 | | 133 | | 758 | | 1 |
| hydroxyurea -> ruxolitinib | 318 | 115 | | 148 | | 581 | | 2 |
| hydroxyurea -> busulfan -> ruxolitinib | <=5 | <=5 | | <=5 | | 10 | | 3 |
| busulfan -> ruxolitinib | <=5 | <=5 | | <=5 | | 9 | | 4 |
| hydroxyurea -> ruxolitinib(sd) | <=5 | <=5 | | <=5 | | 7 | | 5 |
| Other | <=5 | <=5 | | <=5 | | <=5 | |  |
| Total | 760 | 315 | | 292 | | 1,367 | |  |
| % Patients | Int-2 & High risk | GF | Int-1 | | Total | | Rank | | |
| ruxolitinib | 56.7% | 61.6% | 45.5% | | 55.4% | | 1 | | |
| hydroxyurea -> ruxolitinib | 41.8% | 36.5% | 50.7% | | 42.5% | | 2 | | |
| hydroxyurea -> busulfan -> ruxolitinib | <=0.6% | <=1.6% | <=1.7% | | 0.7% | | 3 | | |
| busulfan -> ruxolitinib | <=0.6% | <=1.6% | <=1.7% | | 0.7% | | 4 | | |
| hydroxyurea -> ruxolitinib(sd) | <=0.6% | <=1.6% | <=1.7% | | 0.5% | | 5 | | |
| Other | <=0.6% | <=1.6% | <=1.7% | | <=0.4% | |  | | |
| Total | 100% | 100% | 100% | | 100% | |  | | |

Note: GF = grandfathering.   
(sd) = the patient initiated this medicine group and the prior one on the same day.  
Patient counts and percentages may be slightly perturbed to protect confidentiality.

Almost half of Int-1 risk patients had not had PBS hydroxyurea in the two years prior to commencing ruxolitinib. More than one third of int-2, high risk and grandfathered patients had hydroxyurea in the previous two years likely reflecting disease severity and the available therapies.

# DUSC consideration

DUSC noted that:

* Myelofibrosis is a heterogeneous condition that is an end point for a range of other conditions. This made it difficult to predict the number of patients accurately.
* The Sponsor claimed in their Pre-Sub Committee Response (PSCR) that the greater than predicted number of patients may have been due to “a decrease in use of bone marrow biopsies prior to the listing of ruxolitinib that may have skewed data to provide an underestimate on incident cases as there may have been a lower number recorded due to the absence of a confirmatory diagnosis.”

Almost half (i.e. 45.5%) of Int-1 risk patients had not had PBS hydroxyurea in the two years prior to commencing ruxolitinib. DUSC considered that this was lower than expected in this group of patients that were required by the restriction to be “resistant, refractory or intolerant to available therapy”. DUSC noted that a risk-sharing arrangement was in place which may manage any additional cost from this practice. DUSC advised that the PBAC may wish to consider whether or not this lower rate of prior treatment with hydroxyurea is consistent with the current treatment algorithm. As part of this consideration, DUSC noted that the advice within the PSCR about the variety of drugs that myelofibrosis patients may be treated with may be relevant.

# DUSC actions

The report, Sponsor responses and DUSC minutes were referred to the PBAC.

# 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 (Jakavi®): 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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9. The date of processing of a PBS prescription may differ from the date of dispensing. Consequently there may be differences in data reported by date of dispensing or processing (such as that available publicly available from [DHS Medicare website](https://www.humanservices.gov.au/corporate/statistical-information-and-data/medicare-statistics#a2)). [↑](#footnote-ref-9)
10. [March 2015 PBAC Public Summary Document – ruxolitinib (Jakavi®)](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/ruxolitinib-jakavi-psd-03-2015) [↑](#footnote-ref-10)