PBAC STAKEHOLDER MEETING OUTCOME STATEMENT

RUXOLITINIB FOR MYELOFIBROSIS

22 September 2014

The Sheraton Hotel, Melbourne

Attendees

Members of the Pharmaceutical Benefits Advisory Committee (PBAC), the consumer representative member of the PBAC's Drug Utilisation Sub Committee (DUSC), representatives of The Haematological Society of Australia and New Zealand (HSANZ), The Leukaemia Foundation, Novartis Pharmaceuticals Pty Ltd and the Department of Health were in attendance.
A representative of CanSpeak was not in attendance but available for advice.

Purpose of stakeholder meeting

To provide clarity on the clinical place of ruxolitinib in the treatment of myelofibrosis and subsequently to consider an appropriate Pharmaceutical Benefits Scheme (PBS) restriction. This in turn will inform a submission to the PBAC to consider cost effectiveness.

Background

The PBAC has considered submissions for the PBS listing of ruxolitinib for myelofibrosis on two occasions; July 2014 and July 2013.

At its July 2014 meeting the PBAC deferred the proposed Authority Required listing for ruxolitinib for second line management of myelofibrosis in patients satisfying certain clinical criteria due to a lack of clarity around the appropriate clinical place of ruxolitinib in Australian 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 intermediate-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.

A Public Summary Document on the PBAC's consideration of ruxolitinib for myelofibrosis at its July 2014 meeting will be published on the PBS website on 14 November 2014.

The Guidelines for Initiation of PBAC Stakeholder Meetings are available on the PBS website at http://www.pbs.gov.au/info/industry/listing/elements/initiation-of-stakeholder-meetings.

At its July 2013 meeting, the PBAC rejected the submission requesting PBS listing of ruxolitinib for the treatment of myelofibrosis on the basis of a high and unacceptable incremental cost effectiveness ratio (ICER).

The PBAC acknowledged that a high clinical need exists for an effective treatment for some patients with myelofibrosis. The PBAC considered ruxolitinib to be an advance in therapy for patients with a poor prognosis and/or with symptoms refractory to current care, through improved quality of life. However, the PBAC considered that a substantial price reduction would be required to achieve acceptable cost-effectiveness.

A Public Summary Document on the PBAC's consideration of ruxolitinib for myelofibrosis at its July 2013 meeting is published on the PBS website at http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/ruxolitinib.

Discussion and outcomes

Clinical place of ruxolitinib

The PBAC has accepted, based on the evidence presented in the submissions to the PBAC[1,2] that ruxolitinib has an advantage over placebo or best available therapy in patients with a poorer prognosis and/ or those with symptoms refractory to current care as included in these pivotal clinical trials. These patients were defined in the clinical trials as high risk and intermediate-2 (int-2) risk using the International Prognostic Scoring System (IPSS).

The sponsor noted that evidence available on the clinical efficacy of ruxolitinib is limited to these more severe patient groups and this was acknowledged by those in attendance at the stakeholder meeting.

It was noted that when evaluating the submissions for ruxolitinib for myelofibrosis, the PBAC considered that ruxolitinib may have benefit for a wider group of patients, including some with a lower risk categorisation than int-2. However, it was not clear which patients would be most likely to derive benefit from treatment. The PBAC considered that the benefit in a patient population beyond high risk/ int-2 was most likely to be in terms of symptom relief leading to an improved quality of life. The clinical experts at the Stakeholder Meeting considered a broader population with a high symptom burden could be assumed to show no less benefit in symptom relief and the same duration of response to treatment with ruxolitinib as that shown for the high risk/ int-2 patient population. The PBAC considered that the effect of ruxolitinib on overall survival in a patient group wider than high/ int-2 risk is unknown.

[1] Harrison C, Kiladjian J, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V et. Al. JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis. N Engl J Med 2012; 366:787-798.
[2] Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et. Al. A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis. N Engl J Med 2012; 366:799-807.

Clinical experts present at the Stakeholder Meeting were asked for advice on which patients with myelofibrosis they were currently treating with ruxolitinib, and which patients they considered are appropriate for treatment with ruxolitinib.

Patient groups for whom treatment with ruxolitinib is appropriate:

In each of the following patient groups myelofibrosis has been diagnosed. It was considered that IPSS high risk and int-2 risk patients, consistent with the clinical trial population are appropriate for treatment with ruxolitinib. It was noted that a number of patients in this category are currently being treated through the sponsor's compassionate access program. In addition;

- Patients with a high symptom burden. In particular those experiencing substantial weight loss, night sweats (constitutional symptoms included in the IPSS rating criteria), fatigue, itchiness, or discomfort due to spleen enlargement (other symptoms, not included in the IPSS criteria);
- Younger patients whose risk would be categorised as IPSS int-2, except that they are younger than 65 years of age (as age greater than 65 years is one of the criteria to be classified as int-2 risk).

Patient groups for whom treatment with ruxolitinib was considered NOT appropriate:

- Patients with an enlarged spleen who have a low symptom burden;
- Those with a low symptom burden who do not currently require medicines to manage their MF;
- Bone marrow function stable, and a low symptom burden.

The risk status of the above patients groups in relation to the IPSS, the Dynamic International Prognostic Scoring System (DIPSS) and the age-adjusted DIPSS was discussed. The IPSS was used in the clinical trials of ruxolitinib in the submissions to the PBAC.[1,2] It was noted that a number of the patients identified above would be classified as intermediate-1 (int-1) on the IPSS, such as some patients with a high symptom burden who are under 65 years of age.

As the IPSS was developed and validated for prognostication of MF using data from the time of diagnosis, it was noted that requiring confirmation of the patient's IPSS for PBS subsidy of ruxolitinib may cause access issues if the prescriber needed to refer to medical notes from a clinician previously treating the patient or from some years prior when the patient was diagnosed. The clinicians present at the stakeholder meeting agreed that for some patients the DIPSS would be a more appropriate scoring system as the DIPSS takes into account the effect of MF risk factors at a point in time. Clinicians noted that both the IPSS and the DIPSS have the criteria of age greater than 65 years in their scoring systems and hence considered that the age-adjusted DIPSS would be an additional suitable scoring system to assist assessing patients appropriate for treatment with ruxolitinib.

PBS Restriction

Following identification of the patient population with MF considered appropriate for treatment with ruxolitinib, the potential PBS restriction was discussed.

The restrictions proposed by the sponsor in the July 2013 and July 2014 submissions to the PBAC are available in the Public Summary Documents.

The following PBS restriction was proposed taking into account the identified patient population, MF prognosis scoring systems and other clinical criteria. It is noted that this restriction is indicative only based on the clinical advice and discussions at this stakeholder meeting. A restriction would be finalised following a positive recommendation by the PBAC.

Condition	Myelofibrosis
Severity	High risk or Intermediate-2 risk
Restriction	Authority Required
Clinical criteria	Patient must have an indication for treatment
Administrative Advice	Risk of myelofibrosis is defined in accordance with the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS) or the age-adjusted DIPSS.

Condition	Myelofibrosis
Severity	Intermediate-1 risk
Restriction	Authority Required
Clinical criteria	Patient must have severe disease related symptoms that are resistant, refractory or intolerant to available therapy.
Administrative Advice	Risk of myelofibrosis is defined in accordance with the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS) or the age-adjusted DIPSS.

It was noted that the proposed restriction:

- Does not include a measurement of spleen size. Clinicians considered that patients should not be treated with ruxolitinib for MF based on splenomegaly alone. That is, patients may be a candidate for treatment with ruxolitinib if an enlarged spleen was causing symptoms of a severity warranting treatment, however not if the patient with splenomegaly was asymptomatic or had a low symptom burden. Additionally, clinicians considered that spleen size could not be accurately measured by palpation.
- Does not include continuation criteria. The clinicians considered that there are no suitable objective measures available to use as stopping criteria. Measurement of symptoms as part of a stopping rule/ continuation criteria would be subjective.

The dosage regimen recommended in the approved Product Information for ruxolitinib was noted in relation to the quantity of 5 mg tablets that may be required for titration purposes. The ruxolitinib Product Information recommends initiating at a dose of 5, 15 or 20 mg twice

daily based on the patient's platelet count at the time of initiation. Should platelet and neutrophil counts be adequate, the dose may be increased in increments of 5 mg twice daily to a maximum of 25 mg twice daily. It was noted that 112 tablets may not be a sufficient quantity for some patients for titration purposes. Clinicians present considered that dose titration with ruxolitinib would usually be stabilised within three months of initiation of treatment.

The Product Information for ruxolitinib is available from the Therapeutic Goods Administration's website at https://www.ebs.tga.gov.au/.

Conclusion

The PBAC is required to consider the cost effectiveness of a medicine before a recommendation can be made to the Minister about listing a medicine on the Pharmaceutical Benefits Scheme. As the PBAC has not determined the cost effectiveness of ruxolitinib in the treatment of myelofibrosis in the July 2013 and July 2104 submissions, a further submission to the PBAC will be required. The sponsor of ruxolitinib, Novartis Pharmaceuticals Australia Pty Ltd, was present and involved with the discussions at this Stakeholder meeting and expressed their intention to submit a new application to the PBAC for the PBS listing of ruxolitinib for myelofibrosis.

The PBAC Chair thanked participants for their time in attending the Stakeholder meeting and advice provided.