

An addendum to this Public Summary Document has been included at the end of the document.

6.08 RUXOLITINIB, Tablet 5 mg, Tablet 10 mg, Jakavi[®], Novartis Pharmaceuticals Australia Pty Limited.

1 Purpose of submission

1.1 The Category 2 submission requested the following PBS listings:

- A General Schedule listing of ruxolitinib for the treatment of patients with moderate to severe chronic graft-versus-host disease (cGVHD) who are steroid refractory, dependent or intolerant.
- A Section 100 (Highly Specialised Drugs Program) listing of ruxolitinib for the treatment of patients with Grade II to IV acute graft-versus-host disease (aGVHD) who are steroid refractory, dependent or intolerant.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best available therapy (BAT).

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
cGVHD	
Population	Adult and paediatric patients aged ≥12 years with moderate to severe cGVHD following allogeneic stem cell transplant who are refractory to, dependent on, or intolerant of corticosteroids.
Intervention	Ruxolitinib 10 mg orally twice a day ¹
Comparator	Best available therapy (BAT) ²
Outcomes	Overall response rate; failure-free survival; responders (as per the modified Lee Symptom Scale); best overall response; overall survival; duration of response; non-relapse mortality; incidence of malignancy relapse/recurrence; reduction in daily corticosteroid dose.
Clinical claim	Treatment with ruxolitinib is associated with superior efficacy (based on the overall response rate and duration of response) and non-inferior safety, compared with best available therapy.
aGVHD	
Population	Adult and paediatric patients aged ≥12 years with Grade II to IV aGVHD following allogeneic stem cell transplant who are refractory to, dependent on, or intolerant of corticosteroids.
Intervention	Ruxolitinib 10 mg orally twice a day ¹
Comparator	Best available therapy (BAT) ³
Outcomes	Overall response rate; duration of response; cumulative steroid dose; overall survival; event-free survival; failure-free survival; non-relapse mortality; incidence of malignancy relapse/progression; incidence of cGVHD.
Clinical claim	Treatment with ruxolitinib is associated with superior efficacy (based on overall response rate and duration of response) and non-inferior safety compared with best available therapy.

Source: Table 1.1-1, p7 of the submission.

Abbreviations: aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.

¹ Starting dose in REACH2 (aGVHD) and REACH3 (cGVHD). Dose adjustments to 5 mg twice daily and 5 mg once daily were permitted to manage haematological toxicity.

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² Treatments in the REACH3 trial included extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, mTOR inhibitors (everolimus and sirolimus), infliximab, rituximab, pentostatin, imatinib and ibrutinib.

³ Treatments in the REACH2 trial included low-dose methotrexate, mycophenolate mofetil, mTOR inhibitors (everolimus or sirolimus), anti-thymocyte globulin, extracorporeal photopheresis, mesenchymal stromal cells, etanercept and infliximab.

2 Background

Registration status

2.1 Ruxolitinib was registered on the ARTG on 28 January 2022 for the following GVHD indications:

- Treatment of patients aged 12 years and older with cGVHD who have inadequate response to corticosteroids.
- Treatment of patients aged 12 years and older with aGVHD who have inadequate response to corticosteroids.

2.2 Ruxolitinib is also registered for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis; and the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

Current PBS listing

2.3 Ruxolitinib is currently PBS listed for the treatment of high risk, intermediate-1 and intermediate-2 risk myelofibrosis.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

Chronic GVHD

3.1 The restrictions proposed in the submission are outlined below. Secretariat and PBAC proposed additions are in *italics* and deletions in ~~strikethrough~~.

Name, restriction, manner of administration, form	Maximum quantity (batches)	Maximum quantity (units)	No. of repeats	Published (effective) dispensed price for maximum quantity	Proprietary name and manufacturer
Initial/continuing treatment					
RUXOLITINIB Tablet 5 mg, 56	1	56	5	\$ ⁱ	JAKAVI®, Novartis
RUXOLITINIB Tablet 10 mg, 56	1	56	5	\$ ⁱ (\$)	JAKAVI®, Novartis

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Chronic graft versus host disease (cGVHD)
Severity: Moderate to severe

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PBS Indication: Moderate to severe chronic graft versus host disease (cGVHD)
Treatment phase: Initial
Restriction type: ☒ Authority Required - Streamlined
Clinical criteria:
The Patient must have has received prior systemic steroid treatment for this condition and has experienced refractory disease or is dependent or intolerant to steroid treatment
AND
Clinical criteria:
Patient must be one of the following (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment
AND
Clinical criteria:
The treatment must be the sole PBS subsidised treatment for this condition with the exception of: (i) corticosteroids, (ii) calcineurin inhibitors
Treatment criteria:
Must be treated by either (i) a haematologist,; OR (ii) Must be treated by an oncologist with allogeneic bone marrow transplantation experience,; OR (iii) Must be treated by a medical practitioner working under the direct supervision of one of the above afore mentioned specialist types
AND
Treatment criteria:
Patient must be undergoing treatment with this drug following allogenic haematopoietic stem cell transplantation
Population criteria:
Patient must be 12 years of age or older

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Prescriber instructions: The severity of cGVHD is defined by the <i>National Institutes of Health (NIH)</i> criteria available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329079/ (Jagasia et al., 2015): (a) Moderate cGVHD: At least one organ (not lung) with a score of 2, 3 or more organs involved with a score of 1 in each organ, or lung score of 1 (b) Severe cGVHD: at least 1 organ with a score of 3, or lung score of 2 or 3
Prescriber instructions: Steroid-refractory disease is defined by the <i>National Institutes of Health (NIH)</i> criteria available at: https://pubmed.ncbi.nlm.nih.gov/25985921/ as (Martin et al., 2015): (a) A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent) OR (b) Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent) Steroid-dependent disease is defined by the NIH criteria as (Martin et al., 2015) an increased prednisone dose to > 0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent) (criteria corresponding to steroid dependency) Steroid intolerance is defined as patient must have developed an intolerance to steroid treatment of a severity necessitating treatment withdrawal.
Prescriber instructions: Response is defined as attaining a complete or partial response as defined by the <i>National Institutes of Health (NIH)</i> criteria (Lee et al., 2015). Note that response is relative to the assessment of organ function affected by cGVHD prior to commencing initial treatment with ruxolitinib. • Complete response is defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without initiation or addition of new systemic therapy. • Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, initiation or addition of new systemic therapies.
Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
Administrative advice: <i>Special Pricing Arrangements apply</i>

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Chronic graft versus host disease (cGVHD)
Severity: Moderate to severe
PBS Indication: Moderate to severe chronic graft versus host disease (cGVHD)
Treatment phase: Continuing
Restriction type: ☒ Streamlined
Clinical criteria:

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Patient must have received initial PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have responding disease
AND
Clinical criteria:
<i>The treatment must be the sole PBS subsidised treatment for this condition with the exception of: (i) corticosteroids, (ii) calcineurin inhibitors</i>
Treatment criteria:
Must be treated by <i>either (i) a haematologist,; OR (ii) Must be treated by an oncologist with allogeneic bone marrow transplantation experience,; OR (iii) Must be treated by a medical practitioner working under the direct supervision of one of the above afore mentioned specialist types</i>
AND
Treatment criteria:
Patient must be undergoing treatment with this drug following allogeneic haematopoietic stem cell transplantation
Prescriber instructions:
To be eligible for continuing treatment, a patient must demonstrate a response to initial treatment. Response is defined as attaining a complete or partial response as defined by the National Institutes of Health (NIH) criteria (Lee et al., 2015) available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4744804/ . Note that response is relative to the assessment of organ function affected by cGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response is defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without initiation or addition of new systemic therapy. (b) Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, initiation or addition of new systemic therapies.
Administrative advice: <i>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting</i>
Administrative advice: <i>Special Pricing Arrangements apply</i>

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Chronic graft versus host disease (cGVHD)
Severity: Moderate to severe
PBS Indication: Moderate to severe chronic graft versus host disease (cGVHD)
Treatment phase: Grandfather
Restriction type: ☒ Streamlined

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Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this PBS-indication prior to [insert date of PBS listing]
AND
Clinical criteria:
<i>Patient must have received prior systemic steroid treatment prior to initiation of this drug for this condition</i>
AND
Clinical criteria:
<i>Patient must be one of the following (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment</i>
AND
Clinical criteria:
Patient must have responding disease
Treatment criteria:
Must be treated by either (i) a haematologist,; OR (ii) Must be treated by an oncologist with allogeneic bone marrow transplantation experience,; OR (iii) Must be treated by a medical practitioner working under the direct supervision of one of the above <i>one of the above</i> afore-mentioned specialist types
AND
Treatment criteria:
Patient must be undergoing treatment with this drug following allogeneic haematopoietic stem cell transplantation
Population criteria:
Patient must be 12 years of age or older
Prescriber instructions:
Response is defined as attaining a complete or partial response as defined by the <i>National Institutes of Health (NIH)</i> criteria (Lee et al., 2016) available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4744804/ . Note that response is relative to the assessment of organ function affected by cGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response is defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without initiation or addition of new systemic therapy. (b) Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, initiation or addition of new systemic therapies.
Administrative advice: <i>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting</i>
Administrative advice: <i>Special Pricing Arrangements apply</i>
Administrative Advice: <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>

¹ No effective price proposed for ruxolitinib 5 mg tablets.

- 3.2 A special pricing arrangement was requested for ruxolitinib 10 mg tablets. The submission requested an effective ex-manufacturer price of \$| for the 10 mg strength and \$| for the 5 mg strength (quantity of 56) in both the chronic and acute settings. For context, the current effective price for the existing ruxolitinib listing (in myelofibrosis) is lower for the 5 mg strength (\$| for a quantity of 56) and the same as requested for the 10 mg strength.
- 3.3 The proposed restriction is narrower than the ruxolitinib TGA indication, which does not restrict treatment on the basis of disease severity or include a definition for an

inadequate response to corticosteroids. The proposed PBS listing is also narrower than the MBS restriction for extracorporeal photopheresis (ECP) for the treatment of cGVHD (Item 13761), as it does not restrict on the basis of disease severity and does not include criteria to define steroid refractory disease, steroid dependent disease, or steroid intolerance.

- 3.4 The proposed disease severity (based on NIH criteria), patient age (>12 years) and definitions of steroid refractoriness and dependence are consistent with the REACH3 trial. Although the REACH3 trial did not include patients who were intolerant to corticosteroids, the ESC considered their inclusion in the proposed restriction was clinically appropriate. Only a small number of patients aged 12-17 years participated in the REACH3 trial (4 patients in the ruxolitinib arm and 8 patients in the BAT arm).
- 3.5 The proposed restriction is silent regarding concomitant therapies. The REACH3 trial allowed patients on ruxolitinib to continue corticosteroids and calcineurin inhibitors.
- 3.6 The proposed restriction did not specify a timeframe for the achievement of a response. The primary outcome in the REACH3 trial was the overall response rate at Week 24. The Pre-Sub-Committee Response (PSCR) stated that the proposed initial restriction aligns with the time point of assessment of the primary outcomes in the REACH3 trial at 24 weeks (i.e. the initial prescription provides 28 days of treatment with 5 repeats). The ESC considered that this was reasonable.
- 3.7 There is potential for use outside of the proposed restriction among patients with mild disease, patients who do not meet the proposed steroid refractory/dependence/intolerance criteria, patients who continue treatment despite not achieving a response, and patients who are public hospital inpatients.
- 3.8 The submission noted that the sponsor currently has a patient access program providing ruxolitinib to patients with moderate to severe steroid-refractory cGVHD and that, in addition, the REACH3 clinical trial is still ongoing in Australia. The submission stated there are currently < 500 active patients receiving treatment with ruxolitinib under the patient access program.

Acute GVHD

- 3.9 The restrictions proposed in the submission are outlined below. Secretariat and PBAC proposed additions are in italics and deletions in strikethrough.

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Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) dispensed price for maximum quantity	Proprietary name and manufacturer
Initial/continuing treatment					
RUXOLITINIB Tablet 5 mg, 56	1	56	0	Public hospital: \$1 Private hospital: \$1	JAKAVI®, Novartis
RUXOLITINIB Tablet 10 mg, 56	1	56	0	Public hospital: \$1 (\$) Private hospital: \$1 (\$)	JAKAVI®, Novartis
Continuing treatment					
RUXOLITINIB Tablet 5 mg, 56	1	56	5	Public hospital: \$1 Private hospital: \$1	JAKAVI®, Novartis
RUXOLITINIB Tablet 10 mg, 56	1	56	5	Public hospital: \$1 (\$) Private hospital: \$1 (\$)	JAKAVI®, Novartis

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Acute graft versus host disease (aGVHD)
Severity: Grade II to IV
PBS Indication: Grade II to IV acute graft versus host disease
Treatment phase: Initial/continuing
Restriction type: ☒ Streamlined
Clinical criteria:
The Patient must have has received prior systemic steroid treatment for this condition and has experienced refractory disease or is dependent or intolerant to steroid treatment
AND
Clinical criteria:
Patient must be one of the following (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment
Treatment criteria:
Must be treated by either (i) a haematologist,; OR (ii) Must be treated by an oncologist with allogeneic bone marrow transplantation experience,; OR (iii) Must be treated by a medical practitioner working under the direct supervision of one of the above above afore-mentioned specialist types
AND
Treatment criteria:
Patient must be undergoing treatment with this drug following allogeneic haematopoietic stem cell transplantation
Population criteria:
Patient must be 12 years of age or older

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Prescriber instructions: The severity of aGVHD is defined by the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Harris et al., 2016) available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4706482/ .
Prescriber instructions: Steroid-refractory disease is defined as: (a) Progression after at least 3 days of high-dose systemic corticosteroid (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]) with or without calcineurin inhibitors for the treatment of Grade II-IV aGVHD, OR (b) Failure to achieve a partial response after 5 days at the time of initiation of high-dose systemic corticosteroid (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]) with or without calcineurin inhibitors for the treatment of Grade II-IV aGVHD Steroid-dependent disease is defined as: (a) Failed corticosteroid taper defined as fulfilling involving either one of the following criteria: (i) Requirement for an increase in the corticosteroid dose to methylprednisolone $\geq$ 2 mg/kg/day (or equivalent prednisone dose $\geq$ 2.5 mg/kg/day) OR (ii) Failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days Steroid intolerance is defined as patient must have developed an intolerance to steroid treatment of a severity necessitating treatment withdrawal.
Prescriber instructions: A patient must demonstrate a response to initial treatment to be eligible for continuing treatment. Response is defined as attaining a complete or partial response as assessed by Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Harris et al., 2016). Note that response is relative to the assessment of organ function affected by aGVHD prior to commencing initial treatment with ruxolitinib. • Complete response was defined as a score of 0 for the aGVHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGVHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGVHD. • Partial response was defined as improvement of one stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGVHD.
Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
Administrative advice: Special Pricing Arrangements apply

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Acute graft versus host disease (aGVHD)
Severity: Grade II to IV
PBS Indication: Grade II to IV acute graft versus host disease
Treatment phase: Continuing
Restriction type: ☒ Streamlined
Clinical criteria: Patient must have received initial PBS subsidised treatment with this drug for this condition;
Treatment criteria: Must be treated by either (i) a haematologist,; OR (ii) Must be treated by an oncologist with allogeneic bone marrow transplantation experience,; OR (iii) Must be treated by a medical practitioner working under the direct supervision of one of the above afore-mentioned specialist types
AND
Treatment criteria:

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Patient must be undergoing treatment with this drug following allogeneic haematopoietic stem cell transplantation
Prescriber instructions: Response is defined as attaining a complete or partial response as assessed by <i>Mount Sinai Acute GVHD International Consortium (MAGIC) criteria</i> (Harris et al., 2016) available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4706482/ . Note that response is relative to the assessment of organ function affected by aGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response was defined as a score of 0 for the aGVHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGVHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGVHD. (b) Partial response was defined as improvement of one stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGVHD.
Prescriber instructions: Tapering the dose of corticosteroids should be considered in responding patients. Following successful taper of corticosteroids, tapering the dose of ruxolitinib can be initiated.
Administrative advice: <i>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting</i>
Administrative advice: <i>Special Pricing Arrangements apply</i>
Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Acute graft versus host disease (aGVHD)
Severity: Grade II to IV
PBS Indication: Grade II to IV acute graft versus host disease
Treatment phase: Grandfather
Restriction type: ☒ Streamlined
Clinical criteria: Patient must have received non-PBS-subsidised treatment with this drug for this PBS-indication prior to [insert date of PBS listing]
AND
Clinical criteria: <i>Patient must have received prior systemic steroid treatment prior to initiation of this drug for this condition</i>
AND
Clinical criteria: <i>Patient must be one of the following (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment</i>
Treatment criteria: Must be treated by either (i) a haematologist,; OR (ii) Must be treated by an oncologist with allogeneic bone marrow transplantation experience,; OR (iii) Must be treated by a medical practitioner working under the direct supervision of one of the above afore-mentioned specialist types
AND
Treatment criteria: Patient must be undergoing treatment with this drug following allogeneic haematopoietic stem cell transplantation

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Prescriber instructions:

Response is defined as attaining a complete or partial response as assessed by Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Harris et al., 2016) available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4706482/>. Note that response is relative to the assessment of organ function affected by aGVHD prior to commencing initial treatment with ruxolitinib.

(a) Complete response was defined as a score of 0 for the aGVHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGVHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGVHD.

(b) Partial response was defined as improvement of one stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGVHD.

Prescriber instructions:

Tapering the dose of corticosteroids should be considered in responding patients. Following successful taper of corticosteroids, tapering the dose of ruxolitinib can be initiated.

Administrative advice: *This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting*

Administrative advice: *Special Pricing Arrangements apply*

Administrative Advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*

¹ No effective price proposed for ruxolitinib 5 mg tablets.

- 3.10 A special pricing arrangement was requested for ruxolitinib 10 mg tablets.
- 3.11 The submission requested a Section 100 (Highly Specialised Drugs Program) authority required (streamlined) listing of ruxolitinib for the initial and continuing treatment of patients with aGVHD who are steroid refractory, dependent or intolerant. The submission also proposed an additional aGVHD continuing treatment restriction with 5 repeats. The continuing treatment component included in the proposed initial/continuing treatment restriction may not be required given that it overlaps with the continuing treatment restriction. The submission estimated that approximately 40% of patients would initiate ruxolitinib treatment as hospital inpatients due to the severity of the condition but noted that responding patients would require continuing treatment following discharge from hospital. The PSCR reiterated that the restriction would need to allow a patient who initiates ruxolitinib while admitted to a public hospital to receive PBS-subsidised treatment after discharge.
- 3.12 The proposed restriction is narrower than the ruxolitinib TGA indication, which does not restrict treatment on the basis of disease severity, require patients to achieve a response in order to continue treatment, or include a definition for what constitutes an inadequate response to corticosteroids.
- 3.13 The proposed severity criteria (based on MAGIC criteria) and patient age requirement (>12 years) are consistent with the REACH2 trial eligibility criteria. Only a small number of patients aged 12-17 years participated in the REACH2 trial (5 patients in the ruxolitinib arm and 4 patients in the BAT arm).
- 3.14 The included criteria relating to steroid refractoriness/dependence were generally consistent with the REACH2 trial, apart from a reduction in the timeframe for

achieving a response following initiation of high-dose systemic corticosteroid from 7 days to 5 days. The submission stated that feedback from clinicians recommended changing this requirement on the basis that patients with Stage IV aGVHD would be unable to meet the first criterion, and delayed initiation of second line aGVHD treatment may be life-threatening in some cases. The submission noted that aGVHD assessment criteria included in the NCCN guidelines specify a timeframe of 5 to 7 days for the assessment of failure to improve following steroid treatment initiation.

- 3.15 The proposed restriction is silent regarding concomitant therapies. The REACH2 trial allowed patients on ruxolitinib to continue corticosteroids and calcineurin inhibitors.
- 3.16 The proposed restriction does not specify a timeframe for the achievement of a response. The primary outcome in the REACH2 trial was the overall response rate at Day 28. The PSCR stated that the proposed initial restriction aligns with the time point of assessment of the primary outcomes in the REACH2 trial at 28 days (i.e. the initial prescription provides 28 days of treatment with 0 repeats). The ESC considered that this was reasonable.
- 3.17 There is potential for use outside of the proposed restriction among patients with Grade I disease, patients who do not meet the proposed steroid refractory/dependence/intolerance criteria, patients who continue treatment despite not achieving a response, and patients who are public hospital inpatients.
- 3.18 The submission noted that the sponsor currently has a patient access program providing ruxolitinib to patients with Grade II to IV steroid refractory aGVHD. The submission stated there are currently 40 patients receiving treatment with ruxolitinib under the patient access program.
- 3.19 The pre-PBAC response proposed adding the following wording to the treatment criteria of the continuing restriction: “Tapering criteria: Tapering the dose of corticosteroids should be considered in responding patients. Following successful taper of corticosteroids, tapering the dose of ruxolitinib can be initiated”.

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Allogeneic stem cell transplantation (alloSCT) is a potentially curative therapy option used in the management of haematologic malignancies, non-malignant haematologic conditions and inherited metabolic disorders. GVHD is a common and serious complication of alloSCT which occurs when the donor immune cells mount an immune response against the transplant recipient’s tissues. GVHD is associated with significant morbidity and a high mortality rate.
- 4.2 GVHD is classified as acute or chronic based on the timing of onset and the pattern of organ involvement. Acute GVHD typically occurs within the first 100 days following

alloSCT and primarily affects the skin, gastrointestinal tract and liver. Chronic GVHD typically occurs at least 100 days post allogeneic transplant, and commonly affects the skin, mouth, liver and lungs, although almost any organ may be involved. Overlap syndrome (simultaneous presence of aGVHD with features of cGVHD) may also occur.

- 4.3 Ruxolitinib is an inhibitor of intracellular tyrosine kinases JAK1 and JAK2, which mediate signalling of a number of cytokines and growth factors involved in haematopoiesis and immune function. The submission positioned ruxolitinib as an alternative treatment option for patients with cGVHD or aGVHD who are corticosteroid refractory, dependent or intolerant.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated best available therapy (BAT) as the main comparator for cGVHD and aGVHD. The main argument to support this nomination was that, while a variety of different treatments are used in the management of steroid-refractory/dependent cGVHD and aGVHD, treatment guidelines suggest that there is a lack of evidence to recommend any particular therapy over another.
- 5.2 The ESC considered that BAT was an appropriate comparator. The Australian eviQ guidelines state that common second line treatments for cGVHD include abatacept, alemtuzumab, calcineurin inhibitors, etanercept, ECP, hydroxychloroquine, ibrutinib, imatinib, interleukin-2, mycophenolate mofetil, mammalian target of rapamycin (mTOR) inhibitors, pentostatin, rituximab and ruxolitinib. The eviQ guidelines for aGVHD list the following systemic agents for use in conjunction with corticosteroids for the treatment of steroid refractory aGVHD: alemtuzumab, alpha-1 antitrypsin, anti-thymocyte globulin, basiliximab, calcineurin inhibitors, etanercept, infliximab, mTOR inhibitors, mycophenolate mofetil, pentostatin, ruxolitinib and tocilizumab.
- 5.3 Of the medicines listed in the eviQ guidelines for the treatment of cGVHD and aGVHD, everolimus, sirolimus, mycophenolate mofetil, ciclosporin, and methotrexate have unrestricted PBS listings. The submission noted that none of these medicines are specifically registered on the ARTG for the treatment of cGVHD or aGVHD.
- 5.4 Extracorporeal photopheresis (ECP) was nominated as a supplementary comparator for cGVHD on the basis that ECP received a positive recommendation at the July 2021 MSAC meeting for the treatment of steroid refractory, dependent or intolerant cGVHD. ECP is an appropriate comparator. ECP was added to the Medicare Benefits Schedule in March 2022.
- 5.5 A formal comparison of outcomes for ruxolitinib versus ECP was not presented in the submission. The submission argued that evidence from the REACH3 trial suggests that the efficacy of ECP is similar to the other BATs, and that, accordingly, the efficacy of

the BAT arm of REACH3 trial could be considered to be representative of ECP in cGVHD. However, the submission noted that the nominated comparator in the ECP MSAC submission was standard of care, and that MSAC considered that ECP likely had superior clinical effectiveness compared with standard of care, noting that the clinical studies presented involved small numbers of participants and short follow-up times (p4, extracorporeal photopheresis Public Summary Document (PSD), July 2021 MSAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural progression of GVHD and outlined the reduced quality of life particularly associated with cGVHD which is a multisystem disorder that can result in disability and mortality. The clinician indicated that although the rate of allogeneic HSCT in Australia was increasing, particularly in older patients who were historically less tolerant to GVHD, the incidence of aGVHD and cGVHD was declining. The clinician stated that the decline in GVHD was likely due to better understanding of the disease, better high resolution human leukocyte antigen (HLA) typing, increased T-cell depletion and better GVHD prophylaxis and treatment options, including ruxolitinib.
- 6.2 The clinician stated that early treatment of GVHD with ruxolitinib reduces the severity of disease and reduces the incidence of permanent organ dysfunction and disability, which in turn has resulted in improvements in quality of life and reduced the burden of medical care. The clinician also stated that ruxolitinib has meant that the cessation of corticosteroids is becoming a standard goal of treatment.
- 6.3 The clinician also addressed other matters in response to the Committee's questions, including indicating that the age of the patient did not result in any material differences in response to ruxolitinib and that they estimated that 10% to 20% of patients were steroid refractory. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating acute and chronic GVHD.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from organisations (3) via the Consumer Comments facility on the PBS website.
- 6.5 The PBAC noted the advice received from the Leukaemia Foundation, Rare Cancers Australia and the National Paediatric Medicines Forum. The PBAC noted that the advice outlined the high clinical need for effective acute and chronic GVHD treatments, the quality of life difficulties associated with GVHD and the significant side

effects associated with current glucocorticoid standard of care treatment. The PBAC noted the advice that ruxolitinib is less invasive than other currently available therapies. In addition, the PBAC noted that the National Paediatric Medicines Forum requested that the PBAC consider removing the age restriction for ruxolitinib (and other GVHD medications) if it is listed on the PBS to allow children to access the treatment.

Clinical trials

6.6 The submission was based on two head-to-head trials:

- A head-to-head trial comparing ruxolitinib with physician's choice of BAT in patients with steroid refractory/dependent cGVHD (REACH3).
- A head-to-head trial comparing ruxolitinib with physician's choice of BAT in patients with steroid refractory/dependent aGVHD (REACH2).

6.7 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Chronic GVHD		
REACH3 (NCT03112603)	A Phase III randomized open-label multi-center study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory chronic graft vs host disease after allogeneic stem cell transplantation Zeiser R, Polverelli N, Ram R, Hashmi SK et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. Jagasia M, Zeiser R, Arbushites M, Delaite P et al. Ruxolitinib for the treatment of patients with steroid-refractory GVHD: an introduction to the REACH trials.	Clinical study report, March 2020. <i>NEJM</i> 2015; 385(3): 228-238. <i>Immunotherapy</i> 2018; 10(5): 391-402.
Acute GVHD		
REACH2 (NCT02913261)	A Phase III randomized open-label multi-center study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs host disease after allogeneic stem cell transplantation. Zeiser R, von Bubnoff N, Butler J, Mohty M et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. Jagasia M, Zeiser R, Arbushites M, Delaite P et al. Ruxolitinib for the treatment of patients with steroid-refractory GVHD: an introduction to the REACH trials.	Clinical study report, March 2020. Clinical study report amendment, August 2020. <i>NEJM</i> 2015; 382(19): 1800-1810. <i>Immunotherapy</i> 2018; 10(5): 391-402.

Source: Table 2.2-2, p48 of the submission.

6.8 The key features of the included trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Used in modelled evaluation
Chronic GVHD						
REACH3	329	Phase 3, multicentre, randomised, open-label trial (median duration of follow-up 42.6 weeks for ruxolitinib; 25.2 weeks for BAT) ¹	Low	- Age ≥12 years - Previous alloSCT with evidence of myeloid and platelet engraftment - Moderate to severe cGVHD - Confirmed diagnosis of corticosteroid refractory/dependent cGVHD; - ECOG performance status 0-2 (or equivalent)	- ORR at Week 24 (primary) - Failure-free survival - Change in Lee symptom score - Duration of response - Overall survival - Adverse events - Health-related quality of life (FACT-BMT, EQ-5D-5L, PGIC, PGIS).	- ORR at Week 24 - Duration of response - Overall survival (by response status) - Time to treatment discontinuation - Adverse events - EQ-5D-5L
Acute GVHD						
REACH2	309	Phase 3, multicentre, randomised, open-label trial (median duration of follow-up 7.34 months for ruxolitinib; 3.81 months for BAT) ²	Low	- Age ≥12 years - Previous alloSCT with evidence of myeloid and platelet engraftment - Grade II to IV aGVHD - Confirmed diagnosis of corticosteroid refractory/dependent aGVHD.	- ORR at Day 28 (primary) - Durable ORR at Day 56 - Failure free survival - Duration of response - Overall survival - Adverse events - Duration of response - Health-related quality of life (FACT-BMT, EQ-5D-5L)	- ORR at Day 28 - Duration of response - Overall survival (by response status) - Time to treatment discontinuation - Adverse events - EQ-5D-5L

Source: Table 2.3-1, p51 and Table 2(a).2-1, p124 of the submission.

Abbreviations: aGVHD, acute graft-versus-host disease; alloSCT, allogeneic stem cell transplant; BAT, best available therapy; cGVHD, chronic graft-versus-host disease; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FACT-BMT, Functional Assessment of Cancer Therapy - Bone Marrow Transplantation; ORR, overall response rate; PGIC, Patients' Global Impression of Change; PGIS, Patient Global Impression of Severity.

¹ Median duration of follow-up at primary analysis.

² Median duration of follow-up at January 2020 data cut.

Chronic GVHD

6.9 The evaluators considered that the REACH3 trial had a high risk of bias. The trial was open-label, and investigators, patients, and study personnel were not blinded to treatment assignment, which may have influenced the treatment of patients in the trial. The primary outcome (overall response at Week 24) was assessed by investigators who were not blinded to treatment assignment. The PSCR noted that blinding was not possible due to the different modes of administration and the variety of treatments in the BAT arm. The PSCR stated that although investigators were not blinded, patients were only categorised as responders after fulfilling detailed criteria. The ESC noted that although the open label nature of the trial is inherently associated with bias, the trial was a large, randomised study with clear, pre-defined response criteria. The ESC agreed with the PSCR that it would not be possible to blind a trial in this disease setting and considered that overall, the risk of bias was likely to be low.

- 6.10 Patients were required to have a confirmed diagnosis of corticosteroid refractory/dependent cGVHD defined per 2014 NIH consensus criteria (irrespective of the concomitant use of a calcineurin inhibitor):
- A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent); or
 - Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent); or
 - Increased prednisone dose to > 0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent) (criteria corresponding to steroid dependency).
- 6.11 The REACH3 trial did not include patients who were steroid intolerant. The PSCR acknowledged that these patients were not included in the REACH3 trial but noted that in patients with severe intolerance it is impossible to sustain steroid therapy long enough to meet the criteria for steroid refractory or dependent. The ESC noted that MSAC described the steroid intolerant population as ‘relatively small’ (Extracorporeal photopheresis (Application 1651) PSD, July 2021 MSAC meeting) and noted that the steroid intolerant population was included in the restrictions for methoxsalen and extracorporeal photopheresis (ECP) on the PBS and MBS respectively.
- 6.12 At study entry, 41.2% and 44.5% of patients had moderate, and 58.8% and 54.9% of patients had severe cGVHD in the ruxolitinib and BAT arms, respectively.
- 6.13 The initial BAT treatment administered to each patient in the REACH3 trial was chosen by the investigator prior to patient randomisation from the following list of treatments: ECP, low-dose methotrexate, mycophenolate mofetil, mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, or ibrutinib. The most commonly used initial treatments in the BAT arm were ECP (34.8%), mycophenolate mofetil (22.2%) and ibrutinib (17.1%).
- 6.14 Patients in the BAT arm of the REACH3 trial who did not achieve a partial or complete response prior to Week 24 were eligible to add or initiate a new systemic BAT treatment. After Week 24, patients in the BAT arm who were not in partial or complete response were eligible to crossover to receive treatment with ruxolitinib.
- 6.15 In responding patients, tapering of immunosuppression therapy was performed in two steps. Taper of corticosteroids was attempted approximately two weeks after achieving a complete response. Taper of calcineurin inhibitor and/or ruxolitinib was not initiated until the patient was off corticosteroids and completed assessments for Week 24.

Acute GVHD

- 6.16 The evaluators considered that the REACH2 trial had a high risk of bias. The trial was an open-label trial, and investigators, patients, and study personnel were not blinded to treatment assignment, which may have influenced the treatment of patients in the trial. The primary outcome (overall response at Day 28) was assessed by investigators who were not blinded to treatment assignment. The PSCR noted that blinding was not possible due to the different modes of administration and the variety of treatments in the BAT arm. The PSCR stated that although investigators were not blinded, patients were only categorised as responders after fulfilling detailed criteria. The ESC noted that although the open label nature of the trial is inherently associated with bias, the trial was a large, randomised study with clear, pre-defined response criteria. The ESC agreed that it would not be possible to blind a trial in this disease setting and considered that overall, the risk of bias was likely to be low.
- 6.17 Patients in the REACH2 trial were considered to have steroid-refractory/dependent aGVHD if they had received high-dose systemic corticosteroids (methylprednisolone 2 mg/kg/day or prednisone equivalent; either alone or combined with a calcineurin inhibitor) and met one of the following criteria:
- Progressed based on organ assessment after at least 3 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid +/- calcineurin inhibitor for the treatment of Grade II-IV aGVHD; or
 - Failed to achieve at a minimum a partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid +/- calcineurin inhibitor for the treatment of Grade II-IV aGVHD; or
 - Failed corticosteroid taper defined as fulfilling either one of the following criteria:
 - Requirement for an increase in the corticosteroid dose to methylprednisolone ≥ 2 mg/kg/day (or equivalent prednisone dose ≥ 2.5 mg/kg/day); or
 - Failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days.
- 6.18 The REACH2 trial did not include patients who were steroid intolerant. The PSCR acknowledged that these patients were not included in the REACH2 trial but noted that in patients with severe intolerance it is impossible to sustain steroid therapy long enough to meet the criteria for steroid refractory or dependent. The ESC noted that MSAC described the steroid intolerant population as 'relatively small' (Extracorporeal photopheresis (Application 1651) PSD, July 2021 MSAC meeting) and noted that the steroid intolerant population was included in the restrictions for methoxsalen and extracorporeal photopheresis (ECP) on the PBS and MBS respectively.
- 6.19 At study entry, approximately 34% of patients had Grade II, 44% of patients had Grade III, and 20% of patients had Grade IV aGVHD.

- 6.20 The initial BAT treatment administered to each patient in the study was chosen by the investigator prior to patient randomisation from the following list of treatments: anti-thymocyte globulin, ECP, mesenchymal stromal cells, low-dose methotrexate, mycophenolate mofetil, mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. The most commonly used initial treatments in the BAT arm were ECP (27.3%), mycophenolate mofetil (16.7%) and etanercept (14.7%).
- 6.21 Within the first 28 days, patients meeting the criteria for disease progression, mixed response, or no response could move onto treatment with a second BAT. The patient could be switched to the second BAT, or the second BAT could be used in combination with the initial BAT. The requirement to initiate a second BAT was considered a failure of the first BAT.
- 6.22 Patients randomised to BAT were eligible to cross over to ruxolitinib between Day 28 and Week 24 if they failed to meet the primary endpoint response definition (CR or PR) at Day 28, lost the response thereafter and met criteria for progression, mixed response, or no response, necessitating new additional systemic immunosuppressive treatment for aGVHD. Patients must not have had signs/symptoms of cGVHD (overlap syndrome, progressive, or de novo cGVHD).
- 6.23 Tapering of immunosuppression therapy in responding patients was performed in two steps. Corticosteroid tapering was initiated no earlier than Day 7 and performed as per institutional guidelines. Taper of calcineurin inhibitor and/or ruxolitinib was initiated once the patient's corticosteroids were ceased. Ruxolitinib taper was initiated after Day 56, and performed according on the condition of the patient, current dosing regimen and the clinical judgement of the investigator.

Comparative effectiveness

Chronic GVHD

- 6.24 Results for the REACH3 primary outcome of overall response rate at Week 24 are presented in the table below.

Table 4: Overall response rate at Week 24 in REACH3

	Ruxolitinib (N = 165)	BAT (N = 164)	Risk difference (95% CI)
Overall response rate, n (%)	82 (49.7)	42 (25.6)	0.24 (0.14, 0.34)
Overall response components:			
- Complete response, n (%)	11 (6.7)	5 (3.0)	0.04 (NR)
- Partial response, n (%)	71 (43.0)	37 (22.6)	0.20 (NR)

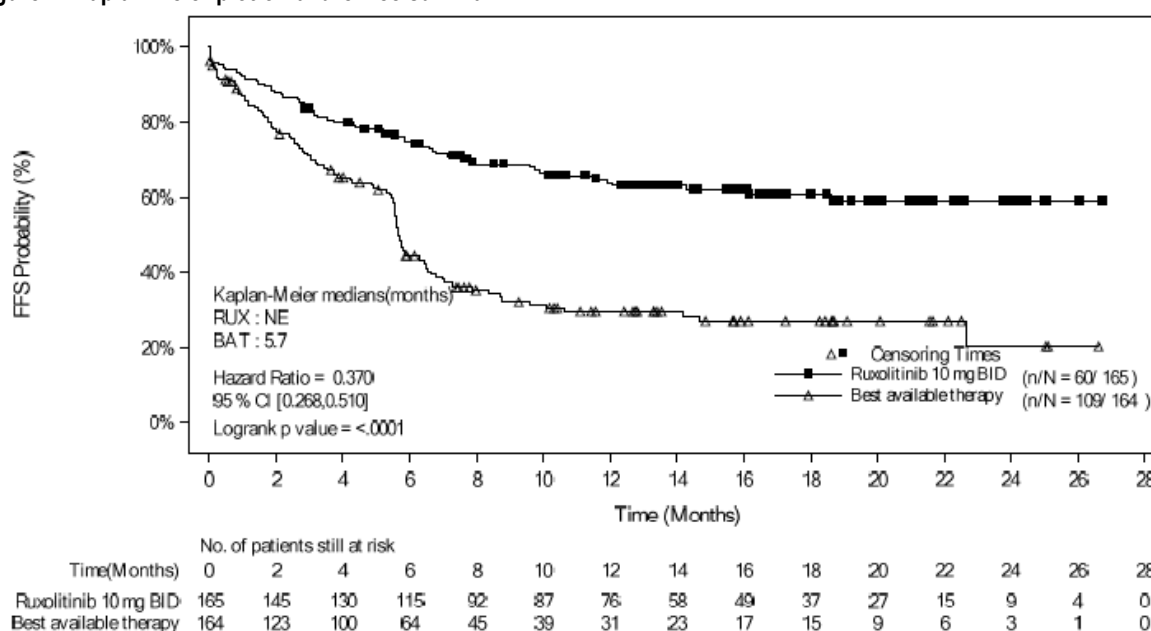
Source: Table 2.5.1, p80 of the submission.

Abbreviations: BAT, best available therapy; CI, confidence interval; NR, note reported.

Note: Complete response was defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without initiation or addition of new systemic therapy. Partial response was defined as an improvement in at least one organ (e.g., improvement of 1 or more points on a 4 to 7-point scale, or an improvement of 2 or more points on a 10 to 12-point scale) without progression in other organs or sites, initiation or addition of new systemic therapy.

- 6.25 Treatment with ruxolitinib was associated with a statistically significantly higher overall response rate compared to treatment with BAT.
- 6.26 The Kaplan-Meier plot for the key secondary outcome of failure-free survival in the REACH3 trial is presented in the figure below.

Figure 1: Kaplan-Meier plot of failure-free survival



Source: Figure 2.5-1, p81 of the submission.

Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; FFS, failure-free survival; RUX, ruxolitinib.

Note: Failure-free survival was a composite time to event endpoint incorporating the following failure-free survival events: relapse or recurrence of underlying disease or death due to underlying disease; non-relapse mortality; or addition or initiation of another systemic therapy for cGVHD.

- 6.27 Kaplan-Meier estimates for the key secondary outcome of failure-free survival in the REACH3 trial are presented in the table below.

Table 5: Kaplan-Meier estimate of failure-free survival

	Ruxolitinib (N = 165)	BAT (N = 164)
Number of events, n (%)	60 (36.4)	109 (66.5)
Number censored, n (%)	105 (63.6)	55 (33.5)
Hazard ratio (95% CI)	0.37 (0.27, 0.51)	
Median FFS, (95% CI)	NE (18.6, NE)	5.7 (5.6, 6.5)
Kaplan Meier of FFS, % (95% CI)		
- 6 months	74.9 (67.5, 80.9)	44.5 (36.5, 52.1)
- 12 months	64.0 (55.8, 71.1)	29.6 (22.3, 37.2)
- 18 months	60.7 (52.1, 68.3)	27.0 (19.7, 34.9)
- 24 months	58.9 (49.8, 67.0)	20.3 (9.3, 34.2)

Source: Table 2.5-2, p81 of the submission.

Abbreviations: BAT, best available therapy; CI, confidence interval; FFS, failure-free survival; NE, not estimable.

Note: Failure-free survival was a composite time to event endpoint incorporating the following failure-free survival events: relapse or recurrence of underlying disease or death due to underlying disease; non-relapse mortality; or addition or initiation of another systemic therapy for cGVHD.

6.28 Treatment with ruxolitinib was associated with a statistically significant improvement in failure-free survival compared to BAT.

6.29 Results for the key secondary outcome of response at Week 24 based on the modified Lee symptom scale total symptom score are presented in the table below.

Table 6: Responders at Week 24 based on the modified Lee symptom scale total symptom score

	Ruxolitinib (N = 165)	BAT (N = 164)	Risk difference (95% CI)
Patients with a valid TSS at baseline, n (%)	149 (90.3)	141 (86.0)	-
Patients with a valid TSS at Cycle 7 Day 1, n (%)			
- All patients	92 (55.8)	87 (53.0)	-
- No prior change of systemic cGVHD treatment	89 (53.9)	64 (39.0)	-
Responders (TSS reduction ≥ 7 points), n (%)	40 (24.2)	18 (11.0)	0.13 (0.05, 0.21)

Source: Table 2.5-3, p82 of the submission.

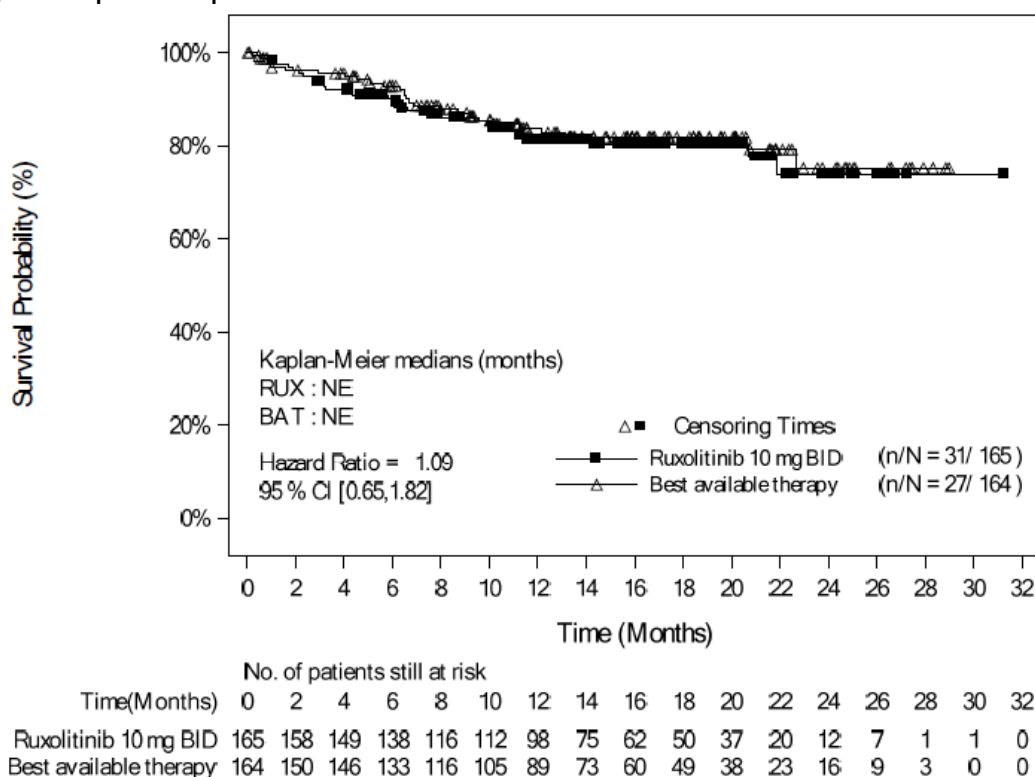
Abbreviations: BAT, best available therapy; cGVHD, chronic graft-versus-host-disease; CI, confidence interval; TSS, total symptom score.

Note: The Modified Lee cGVHD Symptom Scale consists of 30 items in 7 subscales (skin, eye, mouth, lung, nutrition, energy, and psychological). A reduction of 7 or more points in the total symptom score was considered to be a response. Subjects with change of or addition of new systemic cGVHD treatment are counted as non-responders irrespective of the TSS value.

6.30 Treatment with ruxolitinib was associated with a higher proportion of responders (total symptom score reduction ≥ 7 points) compared to BAT.

6.31 The Kaplan-Meier plot of overall survival for the REACH3 trial is presented in the figure below.

Figure 2: Kaplan-Meier plot of overall survival



Source: Figure 2.5-2, p85 of the submission.

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Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; NE, not estimable; OS, overall survival; RUX, ruxolitinib.

6.32 Kaplan-Meier estimates of overall survival for the REACH3 trial are presented in the table below.

Table 7: Kaplan-Meier estimate of overall survival

	Ruxolitinib (N = 165)	BAT (N = 164)
Overall survival		
Number of events, n (%)	31 (18.8)	27 (16.5)
Number censored, n (%)	134 (81.2)	137 (83.5)
Hazard ratio (95% CI)	1.09 (0.65, 1.82)	
Median OS, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Kaplan Meier of OS, % (95% CI)		
- 6 months	90.7 (84.4, 93.9)	92.9 (87.5, 96.0)
- 12 months	81.4 (74.1, 86.8)	83.8 (76.5, 89.0)
- 18 months	80.3 (72.7, 86.0)	81.8 (74.2, 87.4)
- 24 months	74.0 (61.8, 82.8)	75.2 (62.4, 84.2)

Source: Table 2.5-6, p84 of the submission.

Abbreviations: BAT, best available therapy; CI, confidence interval; NE, not estimable; OS, overall survival.

- 6.33 There was no statistically significant difference in overall survival between the ruxolitinib and BAT arms. The PSCR stated that the REACH3 trial was not powered to detect a difference in OS. The overall results were relatively immature, with the median overall survival not reached in either arm. The PSCR stated that the next data cut is not expected until 2023. The ESC noted that overall survival results were likely to have been impacted by subsequent treatments, including patients in the BAT arm crossing over to receive treatment with ruxolitinib.
- 6.34 The estimated Kaplan-Meier duration of response was longer in the ruxolitinib arm compared to the BAT arm (median duration of response: ruxolitinib = not reached versus BAT = 6.2 months; Kaplan-Meier estimate of response duration at 18 months: ruxolitinib = 63.5% versus BAT = 36.7%).
- 6.35 A higher proportion of patients in the ruxolitinib arm had completely tapered off systemic corticosteroids compared to the BAT arm after 24 weeks (ruxolitinib = 24% versus BAT = 17%).
- 6.36 At Week 24, the mean change from baseline of the FACT-BMT trial outcome index was numerically higher in the ruxolitinib arm (4.1) compared to the BAT arm (-0.2). The mean (SD) change from baseline of EQ-5D-5L score was similar between two arms, 0.07 (0.233) in the ruxolitinib arm (n = 90) versus 0.00 (0.226) in the BAT arm (n = 84).

Acute GVHD

- 6.37 Results for the REACH2 primary outcome of overall response rate at Day 28 and key secondary outcome of durable overall response at Day 56 are presented in the table below.

Table 8: Results of the primary and key secondary outcomes in the REACH2 trial

	Ruxolitinib (N = 154)	BAT (N = 155)	Risk difference (95% CI)
Overall response rate at Day 28 (primary)			
Overall response rate, n (%)	96 (62.3)	61 (39.4)	0.23 (0.12, 0.34)
Overall response components:			
- Complete response, n (%)	53 (34.4)	30 (19.4)	0.15 (NR)
- Partial response, n (%)	43 (27.9)	31 (20.0)	0.08 (NR)
Durable overall response at Day 56 (key secondary)¹			
Overall response rate, n (%)	61 (39.6)	34 (21.9)	0.18 (0.08, 0.28)
Overall response components:			
- Complete response, n (%)	41 (26.6)	25 (16.1)	0.11 (NR)
- Partial response, n (%)	20 (13.0)	9 (5.8)	0.07 (NR)

Source: Table 2(a).5-1, p160; Table 2(a).5-2, p161 of the submission.

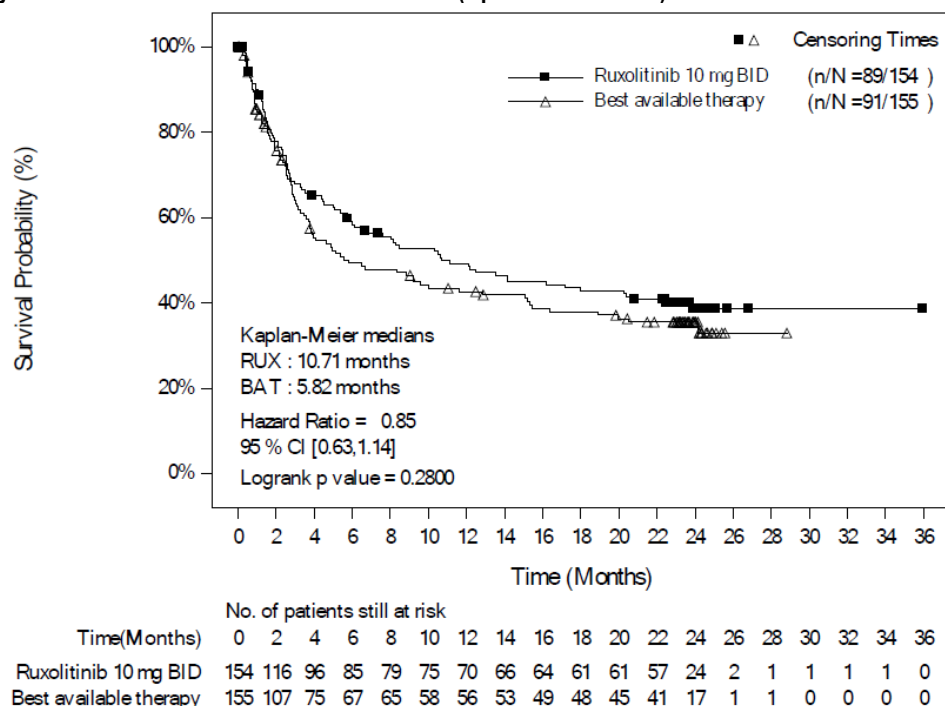
Abbreviations: BAT, best available therapy; CI, confidence interval; NR, not reported.

Note: Complete response was defined as a score of 0 for the aGVHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGVHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGVHD. Partial response was defined as improvement of one stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response or non-response of aGVHD.

¹ The proportion of all patients in each arm who achieved a complete or partial response at Day 28 and maintained a complete or partial response at Day 56.

- 6.38 Treatment with ruxolitinib was associated with a statistically significantly higher overall response rate at Day 28 compared to treatment with BAT and a statistically significant improvement in durable overall response at Day 56.
- 6.39 The Kaplan-Meier plot of overall survival for the REACH2 trial is presented in the figure below. The PSCR provided an updated plot for the final data cut for OS, 23 April 2021.

Figure 3: Overall survival for the REACH2 trial (April 2021 data cut)



Source: Figure 1, p5 of the pre-sub-committee response.

Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; RUX, ruxolitinib.

6.40 Kaplan-Meier estimates of overall survival for the REACH3 trial are presented in the table below.

Table 9: Overall survival for the REACH2 trial at the January 2020 data cut

	Ruxolitinib (N = 154)	BAT (N = 155)
Duration of follow-up, mean (SD)	8.89 (7.607)	7.83 (7.731)
Number of deaths, n (%)	82 (53.2)	88 (56.8)
Number censored, n (%)	72 (46.8)	67 (43.2)
Median OS, months (95% CI)	10.71 (NR)	5.82 (NR)
Hazard ratio (95% CI)	0.83 (0.62, 1.13)	
Kaplan-Meier estimates of overall survival, % (95% CI)		
0 to < 1 month	90.04 (84.02, 93.87)	85.48 (78.79, 90.19)
1 to < 2 months	77.95 (70.42, 83.79)	75.69 (67.92, 81.83)
2 to < 6 months	58.27 (49.90, 65.73)	49.42 (40.89, 57.37)
6 to < 12 months	48.92 (40.43, 56.87)	42.03 (33.62, 50.19)
12 to < 18 months	40.84 (31.69, 49.77)	35.04 (26.54, 43.65)
18 to < 24 months	36.95 (27.35, 46.56)	32.98 (24.18, 42.03)

Source: Table 2(a).5-4, p163 of the submission.

Abbreviations: BAT, SD, standard deviation.

6.41 Treatment with ruxolitinib was associated with longer median overall survival compared to the BAT arm (10.7 months versus 5.8 months); however, the difference was not statistically significant (January 2020 data cut hazard ratio: 0.83; 95% CI: 0.62, 1.13). The PSCR stated that the REACH2 trial was not powered to detect a difference

in OS. The ESC considered that the overall survival results were likely to have been affected by crossover of patients in the BAT arm to receive ruxolitinib.

- 6.42 Treatment with ruxolitinib was associated with a longer median duration of response compared to the BAT (163 days versus 101 days at the January 2020 data cut).
- 6.43 A numerically higher proportion of patients in the ruxolitinib arm had completely tapered off corticosteroids by Day 56 (22.1% versus 14.8%), although the difference was not statistically significant (odds ratio = 1.63; 95% CI: 0.91, 2.92).
- 6.44 At baseline, the mean FACT-BMT and mean EQ-5D-5L scores were numerically higher in the ruxolitinib arm. Over the initial 24 weeks, both treatment arms experienced improvements from baseline. The results should be interpreted with caution due to the differences between treatment arms at baseline, and the low number of respondents included at later time periods.

Comparative harms

Chronic GVHD

- 6.45 Adverse event data for the REACH3 trial was presented for the initial treatment period (median follow-up 25.6 weeks in the ruxolitinib arm and 24.0 weeks in the BAT arm) and the main treatment period (median follow-up 41.3 weeks in the ruxolitinib arm and 22.3 weeks in the BAT arm). Adverse event results for the main treatment period should be interpreted with caution due to differences in exposure durations.
- 6.46 Adverse event results for the REACH3 trial are summarised in the table below.

Table 10: Summary of adverse events of in the REACH3 trial

	Initial treatment period		Main treatment period	
	RUX (N=165)	BAT (N=158)	RUX (N=165)	BAT (N=158)
Median duration of exposure, weeks (range)	25.6 (0.7 - 25.6)	24.0 (0.6 - 25.6)	41.3 (0.7 - 127.3)	22.3 (0.0 - 108.4)
Any Grade AEs				
Any AE, n (%)	161 (97.6)	145 (91.8)	162 (98.2)	146 (92.4)
Serious AE, n (%)	55 (33.3)	58 (36.7)	72 (43.6)	63 (39.9)
Fatal serious AE, n (%)	12 (7.3)	8 (5.1)	15 (9.1)	10 (6.3)
Discontinuation due to AE, n (%)	27 (16.4)	11 (7.0)	34 (20.6)	14 (8.9)
Treatment-related AE, n (%)				
- Treatment-emergent AE	104 (63.0)	45 (28.5)	112 (67.9)	48 (30.4)
- Serious AE	27 (16.4)	16 (10.1)	35 (21.2)	16 (10.1)
- Fatal serious AE	7 (4.2)	4 (2.5)	8 (4.8)	4 (2.5)
- Discontinuation due to AE	16 (9.7)	6 (3.8)	21 (12.7)	7 (4.4)
Grade ≥3 AEs				
Any AE, n (%)	94 (57.0)	91 (57.6)	109 (66.1)	93 (58.9)
Serious AE, n (%)	49 (29.7)	53 (33.5)	66 (40.0)	57 (36.1)
Fatal serious AE, n (%)	12 (7.3)	8 (5.1)	15 (9.1)	10 (6.3)
Discontinuation due to AE, n (%)	20 (12.1)	8 (5.1)	25 (15.2)	10 (6.3)
Treatment-related AE, n (%)				
- Treatment-emergent AE	56 (33.9)	23 (14.6)	70 (42.4)	26 (16.5)
- Serious AE	25 (15.2)	12 (7.6)	34 (20.6)	13 (8.2)
- Fatal serious AE	7 (4.2)	4 (2.5)	8 (4.8)	4 (2.5)
- Discontinuation due to AE	12 (7.3)	5 (3.2)	16 (9.7)	5 (3.2)
Grade ≥3 AE incidence >5%, n (%)				
- Anaemia	21 (12.7)	12 (7.6)	25 (15.2)	12 (7.6)
- Thrombocytopenia	17 (10.3)	9 (5.7)	19 (11.5)	9 (5.7)
- Neutropenia	14 (8.5)	6 (3.8)	20 (12.1)	6 (3.8)
- Pneumonia	14 (8.5)	15 (9.5)	22 (13.3)	16 (10.1)
- Gamma-glutamyl transferase increased	11 (6.7)	3 (1.9)	12 (7.3)	4 (2.5)
- Alanine aminotransferase increased	7 (4.2)	0	10 (6.1)	0
- Hypertension	8 (4.8)	11 (7.0)	9 (5.5)	11 (7.0)
- Platelet count decreased	8 (4.8)	7 (4.4)	10 (6.1)	9 (5.7)
- Hypokalaemia	3 (1.8)	7 (4.4)	3 (1.8)	9 (5.7)

Source: Table 2.5-11, pp93-94; Table 2.5-12, p96; Table 2.5-13, pp98-99; Table 2.5-14, p100 of the submission.

Abbreviations: AE, adverse event; BAT, best available therapy; RUX, ruxolitinib.

- 6.47 Treatment-related adverse events were higher in the ruxolitinib arm compared to the BAT arm for treatment-emergent adverse events, serious adverse events, Grade ≥3 adverse events, discontinuations due to adverse events, and fatal serious adverse events for the initial and main treatment periods.
- 6.48 The most commonly reported (>15%) treatment-emergent adverse events for the initial treatment period in the ruxolitinib arm were anaemia (29.1%), pyrexia (15.8%), hypertension (15.8%) and alanine aminotransferase (ALT) increase (15.2%). The most commonly reported (>15%) treatment-emergent adverse events for the main treatment period were anaemia, pyrexia, ALT increase, hypertension, blood creatinine increase, diarrhoea and pneumonia.

- 6.49 The most commonly reported Grade ≥ 3 adverse events ($\geq 10\%$) in the ruxolitinib arm for the main treatment period were anaemia (15.2%), thrombocytopenia (11.5%), neutropenia (12.1%) and pneumonia (13.3%).
- 6.50 The PSCR noted that the BAT arm consisted of 9 different therapies in the REACH3 trial which may have resulted in the AEs experienced in the BAT arm being less likely to be attributed to treatment. In addition, the PSCR noted that approximately 20% of patients were treated with 2 or more BATs. The PSCR stated that the safety profile of ruxolitinib was different compared to the BATs used in REACH3 and may be preferable depending on a patient's co-morbidities.

Acute GVHD

- 6.51 Adverse event data in REACH2 were presented for the primary analysis (median follow-up 5.0 months in the ruxolitinib arm and 3.6 months in the BAT arm) and the January 2020 data cut (median follow-up 7.3 months in the ruxolitinib arm and 3.8 months in the BAT arm). Adverse event results should be interpreted with caution due to differences in exposure durations between treatment arms.
- 6.52 Adverse event results for the REACH2 trial are summarised in the table below.

Table 11: Summary of adverse events in the REACH2 trial

	Primary analysis		January 2020 data cut	
	RUX (N=152)	BAT (N=150)	RUX (N=152)	BAT (N=150)
Mean duration of exposure, days (range)	82.5 (8.0 - 396.0)	45.5 (2.0 - 218.0)	85.5 (8.0 - 498.0)	45.5 (2.0 - 218.0)
Any Grade AEs				
Any AE, n (%)	146 (96.1)	142 (94.7)	151 (99.3)	148 (98.7)
Serious AE, n (%)	57 (37.5)	51 (34.0)	101 (66.4)	80 (53.3)
Fatal serious AE, n (%)	12 (7.9)	18 (12.0)	33 (21.7)	32 (21.3)
Discontinuation due to AE, n (%)	17 (11.2)	6 (4.0)	41 (27.0)	14 (9.3)
Treatment-related AE, n (%)				
- Treatment-emergent AE	79 (52.0)	43 (28.7)	101 (66.4)	55 (36.7)
- Serious AE	17 (11.2)	12 (8.0)	41 (27.0)	18 (12.0)
- Fatal serious AE	2 (1.3)	3 (2.0)	10 (6.6)	4 (2.7)
- Discontinuation due to AE	10 (6.6)	2 (1.3)	25 (16.4)	5 (3.3)
Grade ≥3 AEs				
Any AE, n (%)	119 (78.3)	119 (79.3)	139 (91.4)	131 (87.3)
Serious AE, n (%)	55 (36.2)	47 (31.3)	97 (63.8)	75 (50.0)
Fatal serious AE, n (%)	12 (7.9)	18 (12.0)	33 (21.7)	32 (21.3)
Discontinuation due to AE, n (%)	17 (11.2)	6 (4.0)	35 (23.0)	13 (8.7)
Treatment-related AE, n (%)				
- Treatment-emergent AE	62 (40.8)	30 (20.0)	88 (57.9)	40 (26.7)
- Serious AE	17 (11.2)	11 (7.3)	39 (25.7)	17 (11.3)
- Fatal serious AE	2 (1.3)	3 (2.0)	10 (6.6)	4 (2.7)
- Discontinuation due to AE	10 (6.6)	2 (1.3)	22 (14.5)	5 (3.3)
Grade ≥3 AE incidence >10%, n (%)				
- Anaemia	34 (22.4)	28 (18.7)	54 (35.5)	36 (24.0)
- Thrombocytopenia	41 (27.0)	24 (16.0)	51 (33.6)	25 (16.7)
- Cytomegalovirus infection	11 (7.2)	12 (8.0)	14 (9.2)	18 (12.0)
- Neutropenia	20 (13.2)	14 (9.3)	33 (21.7)	18 (12.0)
- Hypokalaemia	9 (5.9)	9 (6.0)	15 (9.9)	18 (12.0)
- Platelet count decreased	22 (14.5)	20 (13.3)	27 (17.8)	23 (15.3)
- White blood cell count decreased	11 (7.2)	20 (13.3)	20 (13.2)	13 (8.7)
- Neutrophil count decreased	10 (6.6)	12 (8.0)	17 (11.2)	14 (9.3)
- Pneumonia	5 (3.3)	7 (4.7)	11 (7.2)	13 (8.7)
- Sepsis	10 (6.6)	5 (3.3)	13 (8.6)	18 (12.0)

Source: Table 2(a).5-14, pp187-188; Table 2(a).5-15, p190; Table 2(a).5-16, pp192-193; Table 2(a).5-17, pp195-196 of the submission.
Abbreviations: AE, adverse event; BAT, best available therapy; RUX, ruxolitinib.

- 6.53 Treatment-related adverse events were higher in the ruxolitinib arm compared to the BAT arm for treatment-emergent adverse events, serious adverse events, Grade ≥3 adverse events, and discontinuations due to adverse events for the primary analysis and at the January 2020 data cut. Treatment-related fatal serious adverse events were higher in the ruxolitinib at the January 2020 data cut.
- 6.54 The most commonly reported (>25%) adverse events for the primary treatment period in the ruxolitinib arm were thrombocytopenia (32.9%), anaemia (30.3%), and cytomegalovirus infection (25.7%). The most commonly reported adverse events in the January 2020 data cut period were anaemia (40.1%), thrombocytopenia (36.8%) and cytomegalovirus infection (30.9%).

- 6.55 The most commonly reported (>20%) Grade ≥ 3 adverse events at the January 2020 data cut were anaemia (35.5%), thrombocytopenia (33.6%), and neutropenia (21.7%).
- 6.56 The PSCR noted that the BAT arm in the consisted of 8 different therapies in the REACH2 trial which may have resulted in the AEs experienced in the BAT arm being less likely to be attributed to treatment. In addition, the PSCR noted that approximately 20% of patients were treated with 2 or more BATs. The PSCR stated that the safety profile of ruxolitinib was different compared to the BATs used in REACH2 and may be preferable depending on a patient's co-morbidities. The pre-PBAC response stated that any treatment-related adverse event comparisons were biased against ruxolitinib as the studies compared ruxolitinib with a defined safety profile with a basket of different therapies, each with different safety profiles.

Benefits/harms

- 6.57 A summary of the comparative benefits and harms for ruxolitinib and BAT for cGVHD is presented in the table below.

Table 12: Summary of comparative benefits and harms for ruxolitinib and BAT for cGVHD

	Ruxolitinib n/N	BAT n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Ruxolitinib	BAT	
Benefits						
ORR at Week 24	82/165	42/164	1.94 (1.43, 2.63)	49.7	25.6	0.24 (0.14, 0.34)
Proportion tapered off corticosteroids ¹	29/120	20/119	NR	24.2	16.8	0.074 (NR)
Harms						
Adverse event	Ruxolitinib n/N	BAT n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Ruxolitinib	BAT	
Grade ≥3 anaemia	21/165	12/158	1.68 (0.85, 3.29)	12.7	7.6	0.05 (-0.01, 0.12)
Grade ≥3 thrombocytopenia	17/165	9/158	1.81 (0.83, 3.94)	10.3	5.7	0.05 (-0.01, 0.10)
Grade ≥3 neutropenia	14/165	6/158	2.23 (0.88, 5.67)	8.5	3.8	0.05 (-0.01, 0.10)

Source: Table 2.5.1, p80; Table 2.5-2, p81; Table 2.5-6, p84; Table 2.5-13, pp98-99 of the submission.

Abbreviations: BAT, best available therapy; CI, confidence interval; FFS, failure-free survival; HR, hazard ratio; NE, not estimable; NR, not reported; ORR, overall response rate; OS, overall survival; HR, hazard ratio; RD, risk difference; RR, relative risk.

¹ Proportion of patients completely tapered off corticosteroids at Week 24.

² Median duration of exposure 25.6 weeks for ruxolitinib and 24.0 weeks for BAT.

- 6.58 On the basis of the direct evidence presented in the submission, for every 100 cGVHD patients treated with ruxolitinib in comparison with BAT:
- Approximately 24 additional patients will achieve an overall response at 24 weeks, with 4 additional patients achieving a complete response and 20 additional patients achieving a partial response.
 - Approximately 7 additional patients will completely taper off systemic corticosteroids at 24 weeks.
 - An additional 5 patients will experience severe anaemia requiring medical intervention at 24 weeks.

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- An additional 5 patients will experience severe thrombocytopenia requiring medical intervention at 24 weeks.
- An additional 5 patients will experience severe neutropenia requiring medical intervention at 24 weeks.

6.59 A summary of the comparative benefits and harms for ruxolitinib and BAT for aGVHD is presented in the table below.

Table 13: Summary of comparative benefits and harms for ruxolitinib and BAT for aGVHD

	Ruxolitinib n/N	BAT n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Ruxolitinib	BAT	
Benefits						
ORR at Day 28	96/154	61/155	1.58 (1.26, 2.00)	62.3	39.4	0.23 (0.12, 0.34)
Proportion tapered off corticosteroids ¹	34/154	23/155	OR: 1.63 (0.91, 2.92)	22.1	14.8	7.3 (NR)
Duration of response (median duration of follow-up 5.0 months for ruxolitinib; 3.6 months for BAT) ²						
Event	Ruxolitinib		BAT	Absolute difference		HR (95% CI)
Median duration of response (95% CI)	168.0 (NR)		101.0 (NR)	67.0		NR
Harms						
Adverse event ³	Ruxolitinib n/N	BAT n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Ruxolitinib	BAT	
Grade ≥3 anaemia	34/152	28/150	1.20 (0.77, 1.87)	22.4	18.7	0.04 (-0.05, 0.13)
Grade ≥3 thrombocytopenia	41/152	24/150	1.69 (1.07, 2.65)	27.0	16.0	0.11 (0.02, 0.20)
Grade ≥3 neutropenia	20/152	14/150	1.41 (0.74, 2.69)	13.2	9.3	0.04 (-0.03, 0.11)

Source: Table 2(a).5-1, p160; Table 2(a).5-4, p163; Table 2(a).5-4, p163; Table 2(a).5-17, pp195-196 of the submission.

Abbreviations: BAT, best available therapy; CI, confidence interval; FFS, failure-free survival; HR, hazard ratio; NE, not estimable; NR, not reported; OR, odds ratio; ORR, overall response rate; OS, overall survival; HR, hazard ratio; RD, risk difference; RR, relative risk.

¹ Proportion of patients tapered off corticosteroids at Day 56

² Duration of response among patients who achieved a response at Day 28.

³ Mean duration of exposure 82.5 days for ruxolitinib and 45.5 days for BAT.

6.60 On the basis of the direct evidence presented in the submission, for every 100 aGVHD patients treated with ruxolitinib in comparison with BAT:

- Approximately 23 additional patients will achieve overall response at 28 days, with 15 additional patients achieving complete response and 8 additional patients achieving partial response.
- Patients who achieve a response will experience an additional 67 days of response.
- Approximately 7 additional patients will completely taper off systemic corticosteroids at Day 56.
- An additional 4 patients will experience severe anaemia requiring medical intervention (based on 5 months of follow-up for ruxolitinib and 3.8 months for BAT).
- An additional 11 patients will experience severe thrombocytopenia requiring medical intervention (based on 5 months of follow-up for ruxolitinib and 3.8 months for BAT).

- An additional 4 patients will experience severe neutropenia requiring medical intervention (based on 5 months of follow-up for ruxolitinib and 3.8 months for BAT).

Clinical claim

Chronic GVHD

- 6.61 The submission described ruxolitinib as superior in terms of effectiveness (based on the overall response rate at Week 24 and duration of response) and non-inferior in terms of safety compared to best available therapy for the treatment of patients aged ≥ 12 years with moderate to severe cGVHD who are refractory to, dependent on or intolerant to corticosteroids.
- 6.62 The ESC considered that the clinical claim was reasonable for effectiveness. Treatment with ruxolitinib was associated with a statistically significant improvement in overall response rate at Week 24, failure-free survival and the proportion of patients with a response at Week 24 based on the modified Lee symptom scale total symptom score. From Week 8 onwards, a numerically higher proportion of patients in the ruxolitinib arm had completely tapered corticosteroids. However, the ESC noted the following issues:
- There was no difference between the ruxolitinib arm and the BAT arm in overall survival. Overall survival results were relatively immature (median overall survival was not reached in either arm) and were potentially affected by the use of subsequent treatments, including crossover of patients from the BAT arm to receive ruxolitinib after Week 24. The PSCR noted that the REACH3 trial was not powered to detect a difference in OS.
 - The cGVHD treatments used in the REACH3 trial may not be representative of treatments that are used in Australian clinical practice due to differences in availability and utilisation of cGVHD therapies.
- 6.63 Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.64 The evaluators noted that the claim of non-inferior safety was not supported given treatment-related adverse events were higher in the ruxolitinib arm compared to the BAT arm for treatment-emergent adverse events, serious adverse events, grade ≥ 3 adverse events, discontinuations due to adverse events, and fatal serious adverse events in the REACH3 trial. The PSCR stated that the safety profile of ruxolitinib was different compared to the BATs used in REACH3 and may be preferable depending on a patient's co-morbidities. The ESC considered that although the broad range of BATs may have exaggerated the incremental effect of adverse events in the ruxolitinib arms, there was uncertainty in the safety comparisons.

- 6.65 The PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 6.66 The submission did not present a formal clinical claim for ruxolitinib versus ECP.

Acute GVHD

- 6.67 The submission described ruxolitinib as superior in terms of effectiveness (based on the overall response rate at Day 28 and duration of response) and non-inferior in terms of safety compared to best available therapy for the treatment of patients aged ≥ 12 years with moderate to severe aGVHD who are refractory to, dependent on or intolerant to corticosteroids.
- 6.68 The ESC considered that the clinical claim was reasonable for effectiveness. Treatment with ruxolitinib was associated with a statistically significant improvement in overall response rate at Day 28, durable overall response at Day 56, failure-free survival and the proportion of patients with a response at Week 24 based on the modified Lee symptom scale total symptom score. However, the ESC noted the following issues:
- There was no statistically significant difference between the ruxolitinib and BAT arms in overall survival. However, overall survival results may have been affected by the use of subsequent treatments, including crossover of patients from the BAT arm to receive ruxolitinib. The PSCR noted that the REACH2 trial was not powered to detect a difference in OS.
 - The aGVHD treatments used in the REACH2 trial may not be representative of treatments that are used in Australian clinical practice due to differences in availability and utilisation of aGVHD therapies.
- 6.69 Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.70 The evaluators noted that the claim of non-inferior safety was not reasonable given treatment-related adverse events were higher in the ruxolitinib arm compared to the BAT arm for treatment-emergent adverse events, serious adverse events, grade ≥ 3 adverse events, and discontinuations due to adverse events in the REACH2 trial. The PSCR stated that the safety profile of ruxolitinib was different compared to the BATs used in REACH2 and may be preferable depending on a patient's co-morbidities. The ESC considered that although the broad range of BATs may have exaggerated the incremental effect of adverse events in the ruxolitinib arms, there was uncertainty in the safety comparisons.
- 6.71 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.72 The submission presented the following modelled economic evaluations:

- A modelled economic evaluation comparing initial treatment with ruxolitinib versus BAT, in patients with moderate to severe cGVHD who are steroid refractory/dependent. The economic model was based on the results of the REACH3 trial with additional modelled data.
- A modelled economic evaluation comparing initial treatment with ruxolitinib versus BAT, in patients with Grade II to IV aGVHD who are steroid refractory/dependent. The economic model was based on the results of the REACH2 trial with additional modelled data.

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Table 14: Summary of model structure, key inputs and rationale

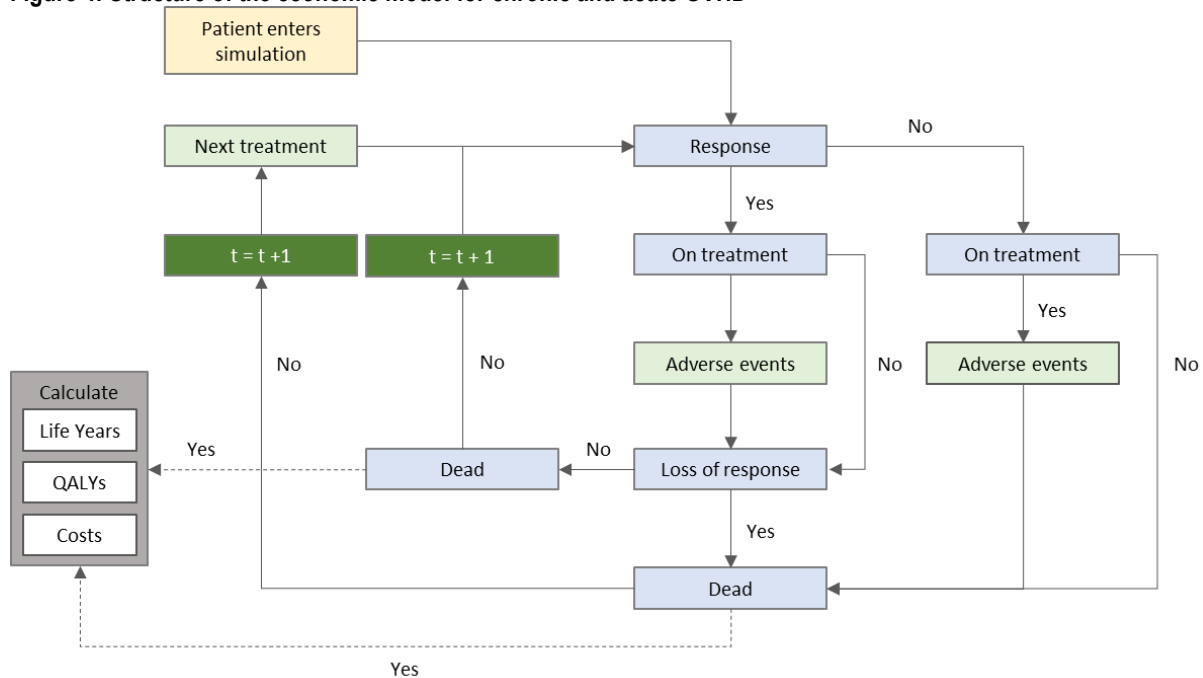
Component	Chronic GVHD	Acute GVHD
Treatments	Ruxolitinib arm: initial treatment with ruxolitinib followed by up to an additional 9 lines of cGVHD therapy. BAT arm: up to 9 lines of cGVHD therapy.	Ruxolitinib arm: initial treatment with ruxolitinib followed by up to an additional 9 lines of cGVHD therapy. BAT arm: up to 9 lines of cGVHD therapy.
Age	Based on a normal distribution with a mean age (SD) of 46.5 years (15.92)	Based on a normal distribution with a mean age (SD) of 49.5 years (15.69)
Time horizon	30 years in the base case versus median follow-up of 57.3 weeks in the REACH3 trial	15 years in the base case versus median follow-up of 5.7 months in the REACH2 trial
Outcomes	Quality-adjusted life years; life years gained.	Quality-adjusted life years; life years gained.
Methods used to generate results	Microsimulation model	Microsimulation model
Health states	Responder; non-responder; dead.	Responder; non-responder; dead.
Cycle length	4 weeks	4 weeks
Transition probabilities	Overall response at 24 weeks based on the overall response rate at 24 weeks reported in the REACH3 trial. Duration of response based on a post-hoc analysis of REACH3 trial data, with Kaplan-Meier estimates for the ruxolitinib and BAT arms extrapolated using exponential functions. Survival to Week 24 based on overall survival for the ruxolitinib and BAT arms in the REACH3 trial. Survival beyond Week 24 based on a post-hoc analysis of REACH3 trial data, with Kaplan-Meier estimates of overall survival for responders and non-responders extrapolated using Weibull functions. Treatment duration based on a post-hoc analysis of the REACH3 trial, with Kaplan-Meier estimates of time to treatment discontinuation for the ruxolitinib and BAT arms extrapolated using exponential functions.	Overall response rate at Day 28 based on the REACH2 trial. Duration of response based on post-hoc analysis of REACH2 trial. Kaplan-Meier estimates for ruxolitinib and BAT extrapolated using exponential and lognormal functions, respectively. Survival to Day 28 based on overall survival for the ruxolitinib and BAT arms in the REACH2 trial. Survival beyond Day 28 based on Kaplan-Meier estimates of overall survival for responders and non-responders in the REACH2 trial, extrapolated using a lognormal function. Treatment duration based on post-hoc analysis of REACH2 trial. Kaplan-Meier estimates of time to treatment discontinuation for ruxolitinib and BAT extrapolated using an exponential distribution.
Utilities	Utility values according to response status (responder/non-responder) derived from EQ-5D-5L data collected in the REACH3 trial. Higher utilities for responders and non-responders are applied to the ruxolitinib arm versus the BAT arm. No disutilities associated with adverse events were explicitly applied.	Utility values according to response status (responder/non-responder) derived from EQ-5D-5L data collected in the REACH2 trial. The same responder and non-responder utilities are applied to the ruxolitinib and BAT arms. No disutilities associated with adverse events were explicitly applied.

Source: Source: Table 3.1-1, p230 of the submission; Table 3(a).1-1, pp298-299 of the submission.

Abbreviations: aGVHD, acute graft-versus-host disease; AR-DRGs, Australian Refined Diagnosis Related Group; BAT, best available therapy; cGVHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; EQ-5D-5L, EuroQol 5-Dimension 5-Level; GP, general practitioner; MBS, Medicare Benefits Schedule.

6.73 The figure below depicts the structure of the economic model for chronic and acute GVHD.

Figure 4: Structure of the economic model for chronic and acute GVHD



Source: Figure 3.2.1, p248 of the submission.
Abbreviations: QALY, quality-adjusted life year.

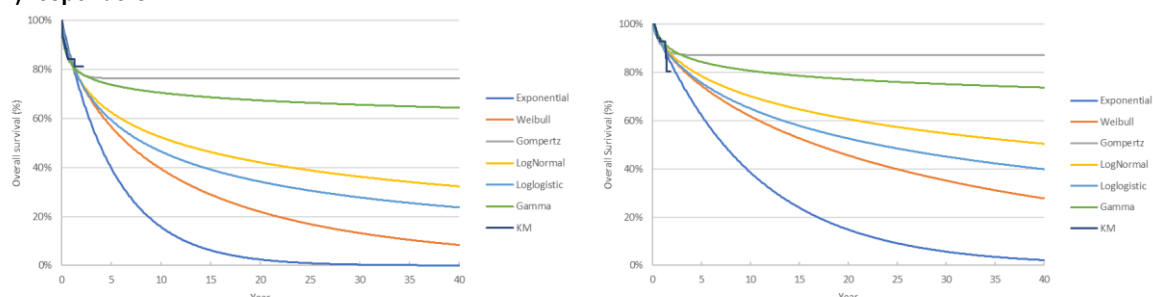
Chronic GVHD

- 6.74 Chronic GVHD treatments in the model were based on the initial treatments used in the BAT arm of the REACH3 trial, and included methotrexate, mycophenolate mofetil, everolimus, sirolimus, infliximab, rituximab, imatinib, ibrutinib and ECP. Patients in the ruxolitinib arm of the model receive initial treatment with ruxolitinib followed by up to an additional 9 lines of cGVHD therapy. Patients in the BAT arm receive up to 9 lines of cGVHD therapy. The initial therapy in the BAT arm was based on the distribution of initial treatments used by patients in the REACH3 trial. Subsequent treatments were randomly selected from the remaining therapies. Although the submission did not adequately justify the inclusion of so many lines of therapy, the ESC considered the multiple lines of therapy was reflective of clinical practice.
- 6.75 There are likely to be differences in the availability and utilisation of cGVHD treatments between the REACH3 trial and Australian clinical practice that impact clinical outcomes and costs. The most commonly used initial therapies in the BAT arm of the REACH3 trial were ECP (34.8%), mycophenolate mofetil (22.2%) and ibrutinib (17.1%). A number of the cGVHD therapies included in the trial, including ibrutinib, are not subsidised for treatment of cGVHD in Australia, and therefore their use is likely to be limited.

- 6.76 The economic model included the benefit of all treatments that comprised BAT in the REACH3 trial, but only included the cost of medicines that are available on the PBS or MBS (ECP, mycophenolate mofetil, methotrexate, sirolimus and everolimus). The impact of excluding these costs on the outcome of the economic model appeared to be small and favoured the comparator.
- 6.77 The model assumed that, in the BAT arm, 35% of patients would receive ECP (plus methoxsalen) as their initial treatment, with the model estimating that the overall average overall cost for ECP in the BAT arm would be \$51,510 per patient. The ESC considered that ECP utilisation and costs may have been overestimated as uptake in the Australian setting is currently limited due to its complexity and lack of availability. The pre-PBAC response noted that while access to ECP is currently limited, the PSD suggested that there would be an increase in uptake from 20% to 60% over the next 6 years (pp24-25, Extracorporeal photopheresis (Application 1651) PSD, July 2021 MSAC meeting) and that the assumption that 35% of patients would receive ECP treatment was likely to be underestimated.
- 6.78 GVHD mortality risk, duration of response among responding patients, and treatment duration were estimated from parametric extrapolation of Kaplan-Meier curves from the REACH3 trial. The evaluation and ESC considered that the extrapolation of GVHD-related mortality, duration of response and treatment duration results from the REACH3 trial were highly uncertain due to the limited duration of clinical data compared to the modelled time horizons (30 years in the base case versus median follow-up of 57.3 weeks in the REACH3 trial). The resulting extrapolations may not be reliable predictors of GVHD-related mortality, duration of response and duration of treatment in clinical practice.
- 6.79 Survival beyond Week 24 was extrapolated according to response status (responder/non-responder). GVHD-related mortality in the model was based on the results of a post-hoc analysis of survival according to response status at Week 24 in the REACH3 trial (i.e., responder or non-responder). The submission noted that the Kaplan-Meier estimates for responders and non-responders were similar beyond 75 weeks but argued that there was clear separation of the responder and non-responder survival curves prior to this, suggesting improved survival among patients who achieve a response. However, the evaluation and the ESC considered that while the tails of the curves were likely to be impacted by patient censoring (and crossover, which commenced from Week 24), it was unclear whether the censoring and crossover were the only reasons for the convergence of the survival curves given that patients who did not achieve a response at Week 24 (or who had discontinued treatment prior to Week 24) may have achieved a response with a subsequent therapy.
- 6.80 While the submission acknowledged that an independent model would be the most appropriate for extrapolation of the GVHD-related survival data (due to violation of the proportional hazards assumption), most of the tested parametric distributions

favoured non-responders. The submission argued that this was not clinically plausible, and instead conducted extrapolation using a dependent parametric model based on a Weibull function (shown in the figure below).

Figure 5: Dependent parametric models fitted to the Kaplan-Meier plot of overall survival for (A) non-responders; and (B) responders



Source: Figure 3.4-7, p259 of the submission.

Abbreviations: KM, Kaplan-Meier.

- 6.81 The submission claimed that a survival advantage for patients who achieve and maintain a response is consistent with the published literature and Australian clinician opinion. Further, the PSCR noted that there was biological plausibility that patients who achieved and maintained an overall response experienced improved survival compared to those who did not. However, the ESC considered the extrapolation was likely optimistic as the magnitude of any improvement in overall survival in responders, and thus improved overall survival with ruxolitinib (given there were higher numbers of responders in the ruxolitinib arm) was uncertain. For example, there was no statistically significant difference in overall survival between responders and non-responders in the post-hoc analysis, and also no statistically significant difference in overall survival for ruxolitinib versus BAT in the REACH3 trial, noting that the overall survival data was immature. (However, the ESC acknowledged that the survival data may have been impacted by non-responders in the BAT arm crossing over to ruxolitinib). The pre-PBAC response stated that the economic model incorporated survival impacts from subsequent lines of therapy and that the modelled discounted incremental survival for ruxolitinib was only 4.5 months over the 30 year time horizon.
- 6.82 The ESC noted that the various parametric extrapolations produced a wide range of survival outcomes, further indicating the uncertainty with the extrapolation.
- 6.83 Each time a patient initiated a new line of therapy, the overall response rate at Week 24 for the BAT arm was applied, regardless of which BAT therapy was being used. This may not have been reasonable given that response rates were likely to decline following multiple failed therapies. The PSCR stated that although the effectiveness of each individual BAT may reduce in each subsequent line of therapy, the magnitude of any reduction was unknown. The PSCR noted that although the effectiveness of each subsequent line of therapy may have been overestimated, as the assumption affected

both arms the impact was expected to be small. However, the ESC considered that the assumption that subsequent lines of therapy had the same effectiveness (overall response rate, duration of response and survival outcomes) as the initial treatment lacked face validity and did not appear to be clinically plausible.

- 6.84 Health state utilities used in the model were derived from a post-hoc analysis of EQ-5D-5L quality of life data collected in the REACH3 trial. The model assumed a utility of 0.746 for responders receiving ruxolitinib, 0.687 for non-responders receiving ruxolitinib, 0.695 for responders receiving BAT treatment, and 0.636 for non-responders receiving BAT treatment. The evaluation and the ESC considered that the inclusion of a utility benefit for being on treatment with ruxolitinib versus BAT was not adequately justified in the submission. The PSCR stated that the utility of patients treated with ruxolitinib was more favourable than those treated with BAT as more patients achieved a complete response, which was defined as complete resolution of all signs and symptoms of cGVHD. In addition, the PSCR stated that the steroid-sparing effect provided by ruxolitinib was likely to contribute to the higher utility values for patients responding to ruxolitinib. However, the ESC considered there was a high risk of bias with the EQ-5D results from REACH3 given it was an open-label trial and knowledge of treatment assignment may have influenced the EQ-5D results collected during the trial. The ESC considered that the extent and timing of missing EQ-5D data were unclear but noted there was a low number of respondents included at later time periods, particularly in the BAT arm. Overall, the ESC considered that the inclusion of a utility benefit for patients receiving/responding to ruxolitinib was not adequately justified.
- 6.85 Key drivers of the economic model for cGVHD are summarised in the table below.

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Table 15: Key drivers of the model for cGVHD

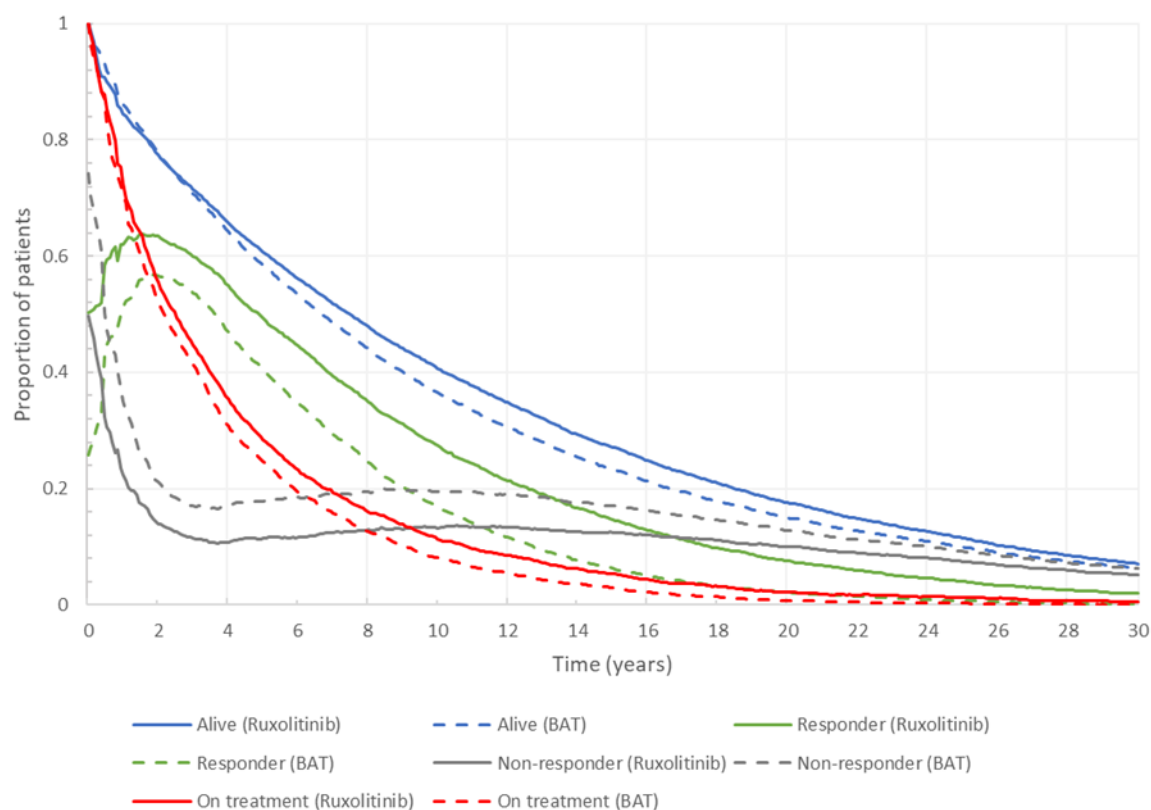
Description	Method/Value	Impact
GVHD-related mortality	GVHD-related mortality in the model was based on the results of a post-hoc analysis of survival according to response status at Week 24 in the REACH3 trial (i.e., responder or non-responder). The higher number of responders in the ruxolitinib arm resulted in a survival benefit being applied to the ruxolitinib arm, which the ESC considered may not be appropriate (refer to Paragraph 6.81).	High, favours ruxolitinib
Utilities	Health state utilities were derived from a post-hoc analysis of EQ-5D-5L data collected in the REACH3 trial. The model assumed utilities of 0.746 for responders and 0.687 for non-responders receiving ruxolitinib; and 0.695 for responders, 0.636 for non-responders receiving BAT. The inclusion of a utility benefit for being on treatment with ruxolitinib versus BAT was not adequately justified.	High, favours ruxolitinib
Time horizon	30 years in the base case versus median follow-up of 57.3 weeks in the REACH3 trial. The submission noted that a 10-year time horizon was used in the ECP economic model considered by MSAC at the July 2021 meeting (the ESC noted that a 5 year time horizon was accepted by MSAC) but argued that a 10-year time horizon would be too short to capture the clinical and economic outcomes for ruxolitinib and BAT in this patient population. The extrapolation of GVHD-related mortality, duration of response and treatment duration results was highly uncertain given the limited duration of clinical data compared to the extrapolated time period (91.6% of incremental QALYs and 98.9% of incremental costs occur in the extrapolated period). The selection of the parametric models that were used to extrapolate the observed REACH3 trial data was highly subjective. The resulting extrapolations may not reliably characterise GVHD-related mortality, duration of response and duration of treatment in clinical practice.	High, favours ruxolitinib
Subsequent treatments	Patients in the ruxolitinib arm received initial treatment with ruxolitinib followed by up to 9 additional lines of cGVHD therapy. Patients in the BAT arm received up to 9 lines of cGVHD therapy. The submission assumed that each time a new line of therapy was started, survival, response and response duration in responders was the same as for the initial therapy in the BAT arm. This assumption lacked face validity and did not appear to be clinically plausible.	Unclear impact

Source: Constructed during the evaluation.

Abbreviations: BAT, best available therapy; cGVHD, chronic graft-versus-host disease; EQ-5D-5L, EuroQol 5-Dimension 5-Level; GVHD, graft-versus-host disease.

6.86 Model traces for the ruxolitinib and BAT arms of the model are presented in the figure below.

Figure 6: Model traces for the ruxolitinib and BAT arms



Source: Constructed during the evaluation using the 'Jakavi (ruxolitinib) – cGVHD – CEA' Excel workbook.
Abbreviations: BAT, best available therapy.

6.87 Higher proportions of patients in the ruxolitinib arm were alive compared to the BAT arm at 10 years (41% versus 37%), 20 years (18% versus 15%) and 30 years (7% versus 6%). Higher proportions of patients in the ruxolitinib arm were in the responder health state compared to the BAT arm at 10 years (28% versus 17%) and 20 years (8% versus 2%). Higher proportions of patients in the ruxolitinib arm were on (any) treatment compared to the BAT arm at 10 years (11% versus 8%) and 20 years (2% versus 1%).

6.88 The table below summarises the results of the modelled economic evaluation for chronic GVHD.

Table 16: Results of the economic evaluation for chronic GVHD

	Ruxolitinib	BAT	Increment
Costs	\$1	\$100,561	\$1
Life-years gained	7.0669	6.7059	0.3610
QALYs	4.9270	4.4795	0.4475
Incremental cost per QALY gained			\$1[†]

Source: Table 3.8-1, p288 of the submission.

Abbreviations: QALY, quality adjusted life year.

The redacted values correspond to the following ranges:

[†] \$55,000 to < \$65,000

- 6.89 In patients with moderate to severe cGVHD who are steroid refractory/dependent, initial treatment with ruxolitinib was associated with an incremental cost per QALY gained of \$55,000 to < \$65,000 compared to initial treatment with BAT.
- 6.90 On average, for every patient with steroid refractory/dependent moderate to severe cGVHD receiving initial treatment with ruxolitinib versus BAT and followed up to 30 years, the (undiscounted) economic model estimates that there would be:
- Ruxolitinib drug costs of \$|, plus additional costs associated with treating adverse events of \$|.
 - Additional survival of 0.70 years.
 - Additional time in response of 2.14 years, which would be associated with savings in disease management costs of \$| and with improved quality of life.
- 6.91 The results of sensitivity analyses presented in the submission and conducted during the evaluation for the cGVHD model are summarised in the table below.

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Table 17: Results of sensitivity analyses for the cGVHD model

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$	0.4475	\$
Initial randomisation seed (base case 53,149)			
Initial seed 27	\$	0.5165	\$
Initial seed 256	\$	0.4207	\$
Discount rate (base case: 5% for benefits and costs)			
0% for costs and benefits	\$	0.7546	\$
3.5% for costs and benefits	\$	0.5159	\$
Time horizon (base case: 30 years)			
5 years	\$	0.1158	\$
10 years	\$	0.2460	\$
15 years	\$	0.3471	\$
20 years	\$	0.4060	\$
Overall response rate (base case: ruxolitinib 49.70%; BAT 25.61%)			
Applying lower 95% CL to ruxolitinib ORR to derive BAT ORR ORR: Ruxolitinib 49.7%; BAT 35.7%	\$	0.3632	\$
Applying upper 95% CL to ruxolitinib ORR to derive BAT ORR ORR: Ruxolitinib 49.7%; BAT 15.7%	\$	0.5232	\$
Applying lower 95% CL to BAT ORR to derive ruxolitinib ORR ORR: Ruxolitinib 39.6%; BAT 25.6%	\$	0.3210	\$
Applying upper 95% CL to BAT ORR to derive ruxolitinib ORR ORR: Ruxolitinib 59.6%; BAT 25.6%	\$	0.5812	\$
10% relative decrease in ORR with each subsequent BAT therapy	\$	0.5165	\$
GVHD-related mortality extrapolation (base case: dependent model – responder and non-responder Weibull)			
Dependent – responder and non-responder exponential	\$	0.2898	\$
Dependent – responder and non-responder loglogistic	\$	0.4431	\$
Independent – responder lognormal; non-responder exponential	\$	0.3114	\$
Exclude general population mortality	\$	0.4916	\$
Time to treatment discontinuation extrapolation (base case: independent model – ruxolitinib and BAT exponential)			
Independent – ruxolitinib and BAT Weibull	\$	0.4475	\$
Independent – ruxolitinib Weibull; BAT exponential	\$	0.4475	\$
Duration of response extrapolation (base case: dependent model – ruxolitinib and BAT exponential)			
Dependent – ruxolitinib and BAT loglogistic	\$	0.3974	\$
Dependent – ruxolitinib and BAT lognormal	\$	0.4159	\$
Independent – ruxolitinib and BAT exponential	\$	0.4475	\$
Independent – ruxolitinib and BAT loglogistic	\$	0.2456	\$
Utilities (baseline: ruxolitinib responder 0.746, non-responder 0.687; BAT responder 0.695, non-responder 0.636)			
Alternative model: Ruxolitinib responder 0.716, non-responder 0.687; BAT responder 0.669, non-responder 0.640	\$	0.3983	\$
Using ruxolitinib utilities in both arms	\$	0.3260	\$
Using BAT utilities in both arms	\$	0.3076	\$
Number of lines of BAT therapy (base case: 9)			
1 line of BAT therapy	\$	0.5192	\$
3 lines of BAT therapy	\$	0.4930	\$
6 lines of BAT therapy	\$	0.4862	\$
Costs (base case: \$0 for therapies not listed on the PBS; adverse event, disease monitoring and hospitalisation costs included)			
Using average cost of 4 therapies on the PBS for all lines of BAT therapy (\$277.74 per cycle)	\$	0.4475	\$

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Analyses	Incremental cost	Incremental QALY	ICER
Disease monitoring costs and hospitalisation costs excluded	\$ [REDACTED]	0.4475	\$ [REDACTED] ⁶
Multivariate sensitivity analyses			
5 year time horizon and ruxolitinib utilities in both arms	\$ [REDACTED]	0.0285	\$ [REDACTED] ¹⁰
10 year time horizon and ruxolitinib utilities in both arms	\$ [REDACTED]	0.1339	\$ [REDACTED] ⁴
15 year time horizon and ruxolitinib utilities in both arms	\$ [REDACTED]	0.2281	\$ [REDACTED] ⁸

Source: Table 3.9-1, p291 of the submission; additional analyses conducted using the 'Jakavi (ruxolitinib) – cGVHD – CEA' Excel spreadsheet.

Abbreviations: BAT, best available therapy; GVHD, graft-versus-host disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$65,000

² \$45,000 to < \$55,000

³ \$35,000 to < \$45,000

⁴ \$155,000 to < \$255,000

⁵ \$95,000 to < \$115,000

⁶ \$75,000 to < \$85,000

⁷ \$65,000 to < \$75,000

⁸ \$115,000 to < \$135,000

⁹ \$85,000 to < \$95,000

¹⁰ \$655,000 to < \$755,000

- 6.92 The model was most sensitive to changes in the discount rate, the time horizon, response rates, the choice of GVHD-related mortality extrapolation method and changes in utility values (including the removal of the benefit associated with being on ruxolitinib treatment). The modelled results appeared to be relatively consistent when alternative random number generator seeds were used.
- 6.93 The ESC considered the submission's base case ICER of \$65,000 to < \$75,000 per QALY was optimistic given the uncertain and likely optimistic model extrapolations (particularly for GVHD-related mortality) in the context of the long modelled time horizon (30 years) compared with the limited duration of trial data (57.3 weeks follow-up in the REACH3 trial).
- 6.94 The ESC considered that a more appropriate base case would include: a shorter time horizon; more conservative extrapolations; removal of the utility benefit associated with being on ruxolitinib; and reduced use of ECP. The ESC noted that the time horizon accepted by MSAC for ECP in July 2021 was 5 years, which the MSAC considered adequately addressed the uncertainty relating to the duration of response in that application. Further, the MSAC noted this was consistent with published models which used 5 and 7 year time horizons.
- 6.95 Further, the ESC considered that adjusting the REACH3 results for crossover (treatment switching) may be informative, but also acknowledged that methods for adjusting rely on assumptions that are difficult to validate and may be problematic given the extent of crossover (37% of patients in the BAT arm crossed over to receive ruxolitinib) and the multiple lines of subsequent therapy.

Acute GVHD

- 6.96 Acute GVHD treatments in the model were based on initial treatments used in the BAT arm of the REACH2 trial, and included anti-thymocyte globulin, ECP, mesenchymal stromal cells, low-dose methotrexate, mycophenolate mofetil, everolimus, etanercept, and infliximab. Patients in the ruxolitinib arm of the model receive initial treatment with ruxolitinib followed by up to an additional 9 lines of aGVHD therapy. Patients in the BAT arm receive up to 9 lines of aGVHD therapy. The initial therapy in the BAT arm was based on the distribution of initial treatments used by patients in the REACH2 trial. Subsequent treatments were randomly selected from the remaining therapies. Although, the submission did not adequately justify the inclusion of so many lines of therapy, the ESC considered it was reflective of clinical practice.
- 6.97 There are likely to be differences in the availability and utilisation of aGVHD treatments between the REACH2 trial and Australian clinical practice that impact clinical outcomes and costs. The most commonly used initial treatments in the BAT arm of the REACH2 trial were ECP (27.3%), mycophenolate mofetil (16.7%) and etanercept (14.7%). A number of the aGVHD treatments included in the trial, including ECP and etanercept, are not subsidised in Australia for the treatment of aGVHD, which is likely to limit their use.
- 6.98 The economic model included the benefit of all treatments that comprise BAT, but only included the cost of medicines that are available on the PBS. The impact of excluding these costs on the outcome of the economic model appeared to be small and favoured the comparator.
- 6.99 GVHD mortality risk, and the duration of response among responding patients were estimated from parametric extrapolation of Kaplan-Meier curves from the REACH2 trial. The extrapolation of GVHD-related mortality and duration of response from the REACH2 trial was considered uncertain due to the limited duration of clinical data compared to the modelled time horizons (15 years in the base case versus median follow-up of 5.7 months in the REACH2 trial). The evaluation considered that it was unclear whether the resulting extrapolations are reliable predictors of GVHD-related mortality or duration of response in clinical practice.
- 6.100 GVHD-related mortality in the model was based on the results of a *post-hoc* analysis of survival according to response status at Day 28 in the REACH2 trial (i.e., responder or non-responder). The submission argued that there was clear separation of the curves favouring responders beginning at approximately 4 to 8 weeks, suggesting improved survival among patients who achieve a response. The submission claimed that a survival advantage for patients who achieve and maintain a response is consistent with the published literature and Australian clinician opinion. The ESC noted that there was a lack of longer-term survival data for patients with Grade II to IV steroid refractory/dependent aGVHD available for comparison.

- 6.101 The resulting extrapolations of GVHD-related mortality for responders and non-responders assumed more favourable survival for patients who achieved a response at 28 days. This resulted in a survival benefit being applied to the ruxolitinib arm due to the higher number of responders in the ruxolitinib arm. While treatment with ruxolitinib in the REACH2 was associated with longer median overall survival compared to the BAT (10.7 months versus 5.8 months at the January 2020 data cut), the difference was not statistically significant. However, the reported overall survival outcomes may have been impacted by patients in the BAT arm crossing over to receive treatment with ruxolitinib. The pre-PBAC response stated that the undiscounted incremental overall survival for ruxolitinib was 5.4 months over the 15 year time horizon, which was comparable to the observed improvement in median overall survival in REACH2 (4.9 months).
- 6.102 Each time a patient initiated a new line of therapy, the overall response rate at Day 28 for the BAT arm was applied, regardless of which BAT therapy was being used. The PSCR stated that although the effectiveness of each individual BAT may reduce in each subsequent line of therapy, the magnitude of any reduction was unknown. The PSCR noted that although the effectiveness of each subsequent line of therapy may have been overestimated, as the assumption affected both arms the impact was expected to be small. However, the ESC considered that the assumption that subsequent lines of therapy had the same effectiveness (overall response rate, duration of response and survival outcomes) as the initial treatment lacked face validity and did not appear to be clinically plausible.
- 6.103 Health state utilities used in the model were derived from a post-hoc analysis of EQ-5D-5L quality of life data collected in the REACH2 trial. The model assumed a utility of 0.553 for responders and 0.441 for non-responders. No utility benefit was included for being on treatment with ruxolitinib in the aGVHD model.
- 6.104 Key drivers of the economic model for aGVHD are summarised in the table below.

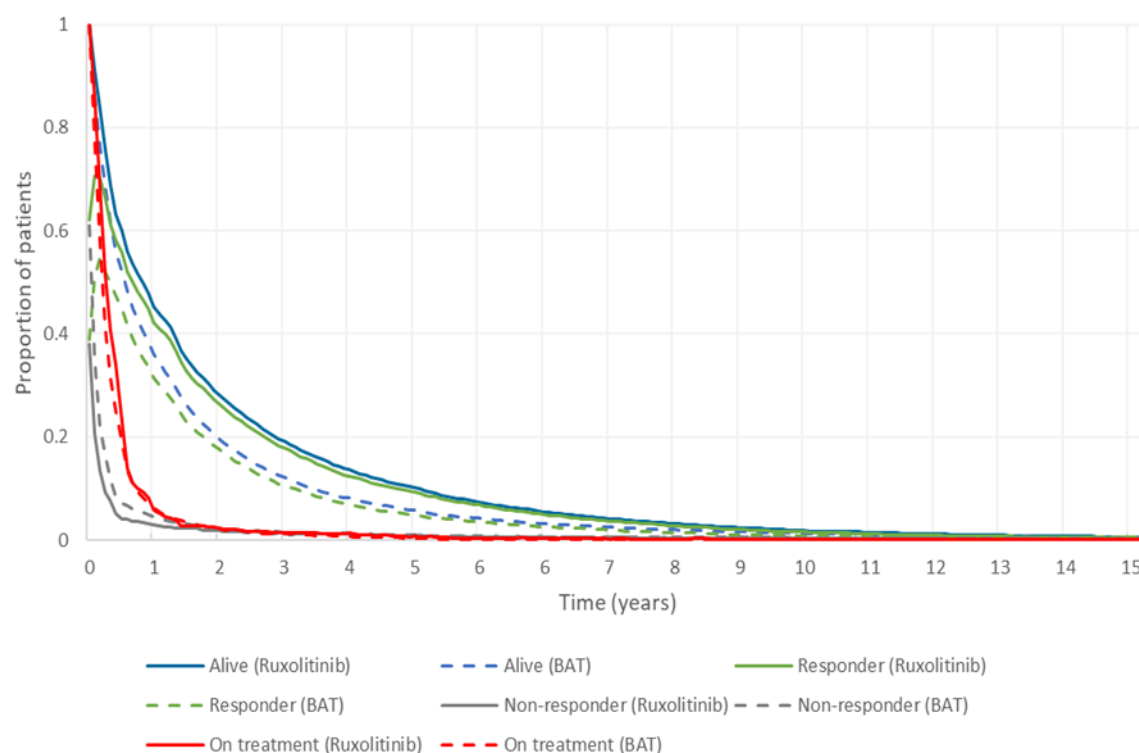
Table 18: Key drivers of the model for aGVHD

Description	Method/Value	Impact
GVHD-related mortality	GVHD-related mortality in the model was based on the results of a post-hoc analysis of survival according to response status at Day 28 in the REACH2 trial (i.e., responder or non-responder). The higher number of responders in the ruxolitinib arm resulted in a survival benefit being applied to the ruxolitinib arm, which the ESC considered may not be appropriate (refer to Paragraph 6.101).	High, favours ruxolitinib
Time horizon	15 years in the base case versus median follow-up of 5.7 months in the REACH2 trial. The extrapolation of GVHD-related mortality and duration of response results was highly uncertain given the limited duration of clinical data compared to the extrapolated time period (89.2% of incremental QALYs and 40.5% of incremental costs occur in the extrapolated period). The selection of the parametric models that were used to extrapolate the observed REACH2 trial data was highly subjective. The resulting extrapolations may not reliably characterise GVHD-related mortality and duration of response in clinical practice.	High, favours ruxolitinib
Subsequent treatments	Patients in the ruxolitinib arm received initial treatment with ruxolitinib followed by up to 9 additional lines of aGVHD therapy. Patients in the BAT arm received up to 9 lines of aGVHD therapy. The submission assumed that each time a new line of therapy was started, survival, response and response duration in responders was the same as for the initial therapy in the BAT arm. This assumption lacked face validity and did not appear to be clinically plausible.	Unclear impact

Source: Constructed during the evaluation.

6.105 Model traces for the ruxolitinib and BAT arms of the model are presented in the figure below.

Figure 7: Model traces for the ruxolitinib and BAT arms



Source: Constructed during the evaluation using the 'Jakavi (ruxolitinib) – aGVHD – CEA' Excel workbook.

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Abbreviations: BAT, best available therapy.

6.106 Higher proportions of patients in the ruxolitinib arm were alive compared to the BAT arm at 1 year (44% versus 34%), 2 years (27% versus 18%) and 5 years (9% versus 5%). Higher proportions of patients in the ruxolitinib were in the responder health state compared to the BAT arm at 1 year (41% versus 30%) and 2 years (25% versus 16%) and 5 years (8% versus 4%). A similar proportion of patients in the ruxolitinib and BAT arms were on (any) treatment at 1 year (5%).

6.107 The table below summarises the results of the modelled economic evaluation for acute GVHD.

Table 19: Results of the economic evaluation for acute GVHD

	Ruxolitinib	BAT	Increment
Cost per responder (ORR with time horizon of 4 weeks)			
Cost	\$█	\$42	\$█
Response	62.03%	38.90%	23.13%
Incremental cost per responder			\$█/ORR
Results of economic evaluation for aGVHD			
Costs	\$█	\$23,958	\$█
Life-years gained	1.5552	1.1630	0.3922
QALYs	0.8430	0.6187	0.2243
Incremental cost per QALY gained			\$█¹

Source: Table 3(a).8-1, p354 of the submission.

Abbreviations: QALY, quality adjusted life year.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$65,000

6.108 In patients with Grade II to IV aGVHD who are steroid refractory/dependent, initial treatment with ruxolitinib was associated with an incremental cost per QALY gained of \$55,000 to < \$65,000 compared to initial treatment with BAT.

6.109 On average, for every patient with steroid refractory/dependent Grade II to IV aGVHD receiving initial treatment with ruxolitinib versus BAT and followed up to 15 years, the (undiscounted) economic model estimates that there would be:

- Ruxolitinib drug costs of \$█, plus additional costs associated with treating adverse events of \$█.
- Additional survival of 0.45 years.
- Additional time in response of 0.52 years, which would be associated with additional disease management costs of \$█ and with improved quality of life.

6.110 The results of sensitivity analyses presented in the submission and conducted during the evaluation for the aGVHD model are summarised in the table below.

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Table 20: Results of sensitivity analyses for the aGVHD model

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$	0.2243	\$
Initial randomisation seed (base case 53,149)			
Initial seed 4	\$	0.2220	\$
Initial seed 27	\$	0.2337	\$
Discount rate (base case: 5% for costs and outcomes)			
0% for costs and benefits	\$	0.2559	\$
3.5% for costs and benefits	\$	0.2328	\$
Time horizon (base case: 15 years)			
5 years	\$	0.1830	\$
10 years	\$	0.2338	\$
20 years	\$	0.2245	\$
Overall response rate (base case: ruxolitinib 62.3%; BAT 39.4%)			
Applying lower 95% CL to ruxolitinib ORR to derive BAT ORR ORR: Ruxolitinib 62.3%; BAT 50.3%	\$	0.2065	\$
Applying upper 95% CL to ruxolitinib ORR to derive BAT ORR ORR: Ruxolitinib 62.3%; BAT 28.3%	\$	0.2550	\$
Applying lower 95% CL to BAT ORR to derive ruxolitinib ORR ORR: Ruxolitinib 51.4%; BAT 39.4%	\$	0.1815	\$
Applying upper 95% CL to BAT ORR to derive ruxolitinib ORR ORR: Ruxolitinib 73.4%; BAT 39.4%	\$	0.2696	\$
10% relative decrease in ORR with each subsequent BAT therapy	\$	0.4110	\$
GVHD-related mortality extrapolation (base case: independent model – responder and non-responder lognormal)			
Independent – responder gamma; non-responder lognormal	\$	0.2668	\$
Independent – responder exponential; non-responder lognormal	\$	0.1415	\$
Independent – responder Weibull; non-responder lognormal	\$	0.1784	\$
Independent – responder lognormal; non-responder gamma	\$	0.2219	\$
Independent – responder lognormal; non-responder exponential	\$	0.2302	\$
Independent – responder lognormal; non-responder Weibull	\$	0.2267	\$
General population mortality excluded	\$	0.2272	\$
Time to treatment discontinuation extrapolation (base case: REACH2 trial observed data)			
Independent – ruxolitinib Weibull from 19 weeks;	\$	0.2243	\$
Independent – ruxolitinib exponential from 19 weeks	\$	0.2243	\$
Independent – BAT Weibull from 5 weeks	\$	0.2243	\$
Independent – BAT exponential from 5 weeks	\$	0.2238	\$
Duration of response extrapolation (base case: independent model – ruxolitinib exponential; BAT lognormal)			
Independent – ruxolitinib Weibull; BAT lognormal	\$	0.2468	\$
Independent – ruxolitinib exponential; BAT exponential	\$	0.2793	\$
Independent – ruxolitinib exponential; BAT Weibull	\$	0.2658	\$
Utilities (baseline: ruxolitinib and BAT responder 0.553; ruxolitinib and BAT non-responder 0.441)			
Alternative model: ruxolitinib and BAT responder 0.523; non-responder 0.457	\$	0.2095	\$
Number of lines of BAT therapy (base case: 9)			
1 line of BAT therapy	\$	0.1983	\$
3 lines of BAT therapy	\$	0.2056	\$
6 lines of BAT therapy	\$	0.2193	\$
Costs (base case: \$0 for therapies not listed on the PBS; adverse event, disease monitoring and hospitalisation costs included)			
Using average cost of 4 therapies on the PBS for all lines of BAT therapy (\$422.16 per cycle)	\$	0.2243	\$

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Analyses	Incremental cost	Incremental QALY	ICER
Adverse event costs excluded	\$ [redacted]	0.2243	\$ [redacted] ²
Disease monitoring costs and hospitalisation costs excluded	\$ [redacted]	0.2243	\$ [redacted] ⁵
Multivariate analyses			
5 year time horizon and ruxolitinib 5 mg price as per myelofibrosis*	\$ [redacted]	0.1830	\$ [redacted] ¹
10 year time horizon and ruxolitinib 5 mg price as per myelofibrosis*	\$ [redacted]	0.2197	\$ [redacted] ²

Source: Table 3(a).9-1, p357 of the submission; additional analyses conducted using the 'Jakavi (ruxolitinib) – aGVHD – CEA' Excel spreadsheet.

Abbreviations: BAT, best available therapy; GVHD, graft-versus-host disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

* AEMP = [redacted]; 82% public hospital - 18% private hospital split

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$65,000

² \$45,000 to < \$55,000

³ \$65,000 to < \$75,000

⁴ \$15,000 to < \$25,000

⁵ \$35,000 to < \$45,000

- 6.111 The model was most sensitive to the number of lines of BAT therapy and the inclusion of disease monitoring/hospitalisation costs. The modelled results appeared to be relatively consistent when alternative random number generator seeds were used. The ESC noted that when disease monitoring/hospitalisation costs were removed, the ICER decreased. The ESC considered that this was due to the longer survival of patients in the ruxolitinib arm and the resultant accruing of higher disease management costs.
- 6.112 The ESC noted that there was less uncertainty in the structure of the aGVHD model as the REACH2 trial provided more mature overall survival data and there was separation of the overall survival Kaplan-Meier curves despite the lack of adjustment for crossover. However, notwithstanding this, the ESC considered the submission's base case ICER of \$55,000 to < \$65,000 per QALY was optimistic given the uncertain and likely optimistic model extrapolations in the context of a long time horizon (15 years) based on a short duration of follow-up in the REACH2 trial (5.7 months). The ESC considered that a shorter model time horizon and more conservative extrapolations would be more appropriate.
- 6.113 The ESC considered that for aGVHD, an alternative modelling approach may have been extrapolating overall survival estimates by treatment arm, rather than by responder/non-responder status.

Drug cost/patient

Chronic GVHD

- 6.114 Based on the economic model, the cost of ruxolitinib was \$ [redacted] per patient based on an average treatment duration of 87.0 weeks. Patients receiving ruxolitinib received subsequent BAT therapies, at a cost of \$ [redacted] per patient over an average treatment duration of 140.5 weeks based on treatment in the REACH3 trial that included

ECP+methoxsalen (\$), everolimus (\$), sirolimus (\$), mycophenolate mofetil (\$), and methotrexate (\$). Ibrutinib, imatinib, rituximab and infliximab, but these treatments were not costed in the submission.

- 6.115 The cost of BAT therapies for the comparator was \$56,873 per patient over an average treatment duration of 192.0 weeks based on treatment in the REACH3 trial that included ECP+methoxsalen (\$51,510), everolimus (\$3,611), sirolimus (\$1,028), mycophenolate mofetil (\$575), and methotrexate (\$149). Ibrutinib, imatinib, rituximab and infliximab, but these treatments were not costed in the submission.
- 6.116 The drug costs in the financial implications were based on durations of treatment (persistence) derived from the economic model. Both the economic model and financial implications derived the cost of ruxolitinib based on the average daily dose from the REACH3 trial (16.7 mg).

Acute GVHD

- 6.117 Based on the economic model, the cost of ruxolitinib was \$ per patient based on an average treatment duration of 12.3 weeks. Patients receiving ruxolitinib received subsequent BAT therapies, at a cost of \$ per patient over an average treatment duration of 10.5 weeks based on treatment in the REACH2 trial that included everolimus (\$), mycophenolate mofetil (\$), sirolimus (\$), and methotrexate (\$). Mesenchymal stromal cells, ECP+methoxsalen, etanercept, anti-thymocyte globulin, and infliximab, but these treatments were not costed in the submission.
- 6.118 The cost of BAT therapies for the comparator was \$388 per patient over an average treatment duration of 19.7 weeks based on treatment in the REACH2 trial that included everolimus (\$259), mycophenolate mofetil (\$75), sirolimus (\$47), and methotrexate (\$7). Mesenchymal stromal cells, ECP+methoxsalen, etanercept, anti-thymocyte globulin, and infliximab, but these treatments were not costed in the submission.
- 6.119 The drug costs in the financial implications were based on durations of treatment (persistence) derived from the economic model. Both the economic model and financial implications derived the cost of ruxolitinib based on the average daily dose from the REACH3 trial (15.7 mg).

Estimated PBS usage & financial implications

- 6.120 This submission was not considered by DUSC. The submission used an epidemiological approach. Due to differences between the cGVHD and aGVHD populations in prevalence, duration of treatment and response rates, the eligible populations were estimated separately.
- 6.121 Key inputs used to derive the financial estimates are presented in the table below.

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Table 21: Key inputs for financial estimates

Parameter	Value applied		Comment and source
Eligible population			
Australian prevalent alloSCT population aged ≥12 years	6,800; based on the sum of incident populations from 2010 (N=396) to 2022 (N=626)		ABMTRR Report 2021. Based on Australian data from 2010 to 2020, extrapolated with a linear trendline.
Proportion of prevalent population alive at Year 1	45%		Gifford et al. 2016. Gifford (2016) used data 10-20 years old spanning 13 years, including living patients (survival not defined), excluding patients aged 12 to ≤18 years, and may not be applicable to contemporary clinical practice and the eligible population. The evaluation considered that the estimated proportion of alloSCT survivors was most likely underestimated. Based on the most recent publication from the ABMTRR (Klinmann, 2022), this was increased to 55% in the pre-PBAC response.
Proportion of prevalent alloSCT survivors with cGVHD	69%		Gifford et al. 2016: The estimated proportion of survivors with cGVHD was based on the number of patients responding and/or consenting (443/669, 66%), with data (301/434, 69.4%). Given only 66% of survivors contributed data, the evaluation considered this estimate may not reflect the overall proportion of Australian alloSCT survivors with cGVHD.
Australian incident alloSCT population aged ≥12 years	2022: 626 ¹ 2023: 643 2024: 660 2025: 677 2026: 694 2027: 711		ABMTRR Report 2021. Based on Australian data from 2010 to 2020, extrapolated with a linear trendline. Linear extrapolation of the incidence of alloSCT was not adequately justified. However, the submission presented sensitivity analysis using logarithmic extrapolation.
Proportion of incident alloSCT patients with GVHD	cGVHD 38.8%	aGVHD 36.2%	ABMTRR Report 2021: The evaluation considered this may be reasonable. However, the analysis and methodology used to generate the ABMTRR report were not provided and could not be evaluated.
Distribution of aGVHD and cGVHD severity	cGVHD Mod: 29.9% Severe: 15.0%	aGVHD Grade II: 36.9% Grade III: 19.9% Grade IV: 5.9%	
Proportion of aGVHD and cGVHD patients who are steroid refractory	cGVHD Mild: 9.1% Mod: 22.2% Severe: 60.0%	aGVHD Grade II: 12.2% Grade III: 47.4% Grade IV: 78.9%	(Axt et al. 2019): Given Axt (2019) was small single centre German study of adults ≥18 years undergoing alloSCT, reporting data from 2004-2013, the evaluation considered these proportions may not be applicable to the Australian setting. The pre-PBAC response increased the proportion of cGVHD patients with moderate disease from 22.2% to 60% which it stated was to align with that reported in the MSAC PICO for ECP (p7, Extracorporeal photopheresis (application 1651) PICO).

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Parameter	Value applied		Comment and source
Utilisation of ruxolitinib			
Duration of treatment and persistence (ruxolitinib)	cGVHD Year 1: Initial 20.15 Continuing: 11.13 (weeks of treatment) Year 2: 29.2% Year 3: 72.6% Year 4: 73.0% Year 5: 74.0% Year 6: 71.1%	aGVHD Year 1: Initial: 4.00 Continuing: 8.13 (weeks of treatment) Grandfathered: 13.79 (weeks of treatment) Year 2: 0.31% Years 3-6: 0	Year 1 duration of treatment derived from number of weeks on ruxolitinib in Year 1 of the model (cGVHD - initial 24 weeks, continuing 28 weeks; aGVHD - initial 4 weeks, continuing 48 weeks). Years 2-6 proportions derived from the mean proportion of patients remaining on ruxolitinib in each year, derived from the economic model. Extrapolation of time to treatment discontinuation data in the economic model was considered uncertain during evaluation due to the limited duration of observed data (median follow-up of 57 weeks).
Proportion of aGVHD hospitalised at ruxolitinib initiation	39.5%		REACH2 mean proportion of ruxolitinib and BAT patients initiating treatment in hospital.
Ruxolitinib scripts per patient per year	cGVHD Initiating: 5.05 scripts Year 1 continuing: 2.79 scripts Years 2-6 continuing: 13.04 scripts aGVHD Initiating in community: 1.0 script Initiating in hospital: Nil Year 1 continuing: 2.04 scripts Year 2 continuing: 13.04 scripts/year aGVHD Grandfathered Year 1 continuing: 3.46 scripts		Scripts in year 1 informed by duration of treatment from the economic model (informed by the proportion of patients on treatment; see above). Scripts in subsequent years based on perfect adherence. Assumed 100% adherence was not reasonable, and overestimated script numbers.
Change in utilisation of BAT therapies			
Net change in the proportions of patients receiving BAT therapies	Generated by the economic model		The utilisation of cGVHD and aGVHD BAT therapies was estimated from the modelled outputs of the economic model. The evaluation considered the estimated utilisation was uncertain due to the likely differences in availability and utilisation of treatments between the clinical trial setting and Australian clinical practice. Differences in the proportions of patients using BAT therapies were applied to ruxolitinib patient numbers; with scripts derived assuming perfect adherence.
Net change in the number of ECP administrations and associated prescriptions for methoxsalen	cGVHD Year 1: -2,979 Year 2: -267 Year 3: -287 Year 4: -335 Year 5: -307 Year 6: -304		Derived from the number of administrations per patient starting treatment with ruxolitinib/BAT in the economic model: Assumed one methoxsalen administration (1 vial) was for each ECP administration. The evaluation considered the estimated number of ECP administrations was most likely overestimated, particularly in Year 1 of the estimates, given ECP has only recently been listed on the MBS, is not widely available, and may not be suitable for all patients.

Source: Sections 4.1-1, pp360-362 of the submission; Excel workbooks Ruxolitinib SR-aGVHD – UCM.xlsx and Ruxolitinib SR-cGVHD – UCM.xlsx, attached to the submission.

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Abbreviations: aGVHD, acute graft versus host disease; alloSCT, allogenic stem cell transplantation; AMBTRR, Australian Bone Marrow Transplant Recipient Registry; cGVHD, chronic graft versus host disease; GVHD, graft versus host disease; mod, moderate; PBS, Pharmaceutical Benefits Scheme

¹The estimated alloSCT incident population in 2022 was included in the prevalent population for cGVHD and the incident population for aGVHD.

6.122 The table below summarises the estimated utilisation and cost of ruxolitinib to the PBS/RPBS for the treatment of cGVHD. Incident patients for Year 1, and < 500 patients currently receiving ruxolitinib via the sponsor's managed access program were assumed to be included in the estimated prevalent population.

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Table 22: Estimated use and financial implications for cGVHD

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Steroid refractory moderate to severe cGVHD (incident and prevalent)						
alloSCT patients aged ≥12 years ¹	4	4	4	4	4	4
Patients with cGVHD ²	4	5	5	5	5	5
All steroid refractory moderate-severe cGVHD	5	5	5	5	5	5
Uptake of ruxolitinib	85%	90%	90%	90%	90%	90%
Initiating patients	5	5	5	5	5	5
Total continuing patients	-	5	5	5	5	5
Total treated patients	5	5	5	5	5	5
Ruxolitinib 5 mg scripts (33%) ³	4	5	5	5	5	5
Ruxolitinib 10 mg scripts (67%) ³	4	4	4	4	4	4
Total scripts	4	4	4	4	4	4
Cost of ruxolitinib to the PBS/RPBS (effective price)						
Cost of ruxolitinib 5 mg	\$6	\$6	\$6	\$6	\$6	\$6
Cost of ruxolitinib 10 mg	\$6	\$6	\$6	\$6	\$6	\$6
Cost of ruxolitinib	\$6	\$6	\$6	\$6	\$6	\$6
Patient copayment	\$6	\$6	\$6	\$6	\$6	\$6
Total cost of ruxolitinib to the PBS/RPBS (less copayment)	\$6	\$6	\$6	\$6	\$6	\$6
Changes in BAT therapy scripts for steroid refractory moderate to severe cGVHD substituted by ruxolitinib						
Mycophenolate 500 mg tab	5	5	5	5	5	5
Methotrexate 10 mg tab	5	5	5	5	5	5
Sirolimus 1 mg tab	5	5	5	5	5	5
Everolimus 1 mg tab	5	5	5	5	5	5
Methoxsalen inj 200 mcg	4	5	5	5	5	5
Cost offsets from substitution of BAT therapies for steroid refractory moderate to severe cGVHD						
Mycophenolate cost to PBS (less copayment)	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Methotrexate cost to PBS (less copayment)	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Sirolimus cost to PBS (less copayment)	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Everolimus cost to PBS (less copayment)	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Methoxsalen cost to PBS (less copayment)	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Total cost offset less copayment	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Net cost to the PBS/RPBS	\$6	\$6	\$6	\$6	\$6	\$6
Net changes to MBS from substituted ECP sessions for steroid refractory moderate to severe cGVHD						
ECP sessions offset	4	5	5	5	5	5
Cost to MBS (80% benefit, \$1,526,68)	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Net changes to financial implications for the health budget for cGVHD (effective price)						
Total net change (less copayment)	\$6	\$6	\$6	\$6	\$6	\$6
Revised estimated provided in the pre-PBAC response						
Total treated patients	4	5	5	5	5	5
Total cost of ruxolitinib to the PBS/RPBS (less copayment)	\$7	\$6	\$6	\$6	\$6	\$6
Net cost to the PBS/RPBS	\$7	\$6	\$6	\$6	\$6	\$6
Cost to MBS (80% benefit, \$1,526,68)	-\$6	-\$6	-\$6	-\$6	-\$6	-\$6
Net implication to health budget (effective price)	\$6	\$6	\$6	\$6	\$6	\$6

Source: Tables 4.2-1, p.375, 4.2-2, p376, 4.2-3, p377, 4.2-5, p379, 4.2-6, p380, 4.2-8, p382 of the submission; Excel workbooks Ruxolitinib SR-aGVHD – UCM.xlsx and Ruxolitinib SR-cGVHD – UCM.xlsx, attached to the submission.

Abbreviations: aGVHD, acute graft versus host disease; alloSCT, allogeneic stem cell transplantation; cGVHD, chronic graft versus host disease.

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¹ Year 1 estimate comprised of prevalent alloSCT patients aged ≥12 years (6,800 incident patients from 2010 to 2022) expected to be alive in 2022 (45% of alloSCT). Year 2-6 estimates comprised of expected incident alloSCT patients aged ≥12 years (based on extrapolated ABSTRR 2021 analysis).

² Year 1 estimate comprised of prevalent patients in 2022 with cGVHD (69.35%). Years 2-6 comprised of incident patients with cGVHD (38.8%).

³ Based on 5.05 initiating scripts and 2.09 continuing scripts for patients in their first year of treatment; 13.04 scripts/year for patients continuing in subsequent years.

The redacted values correspond to the following ranges:

⁴ 500 to < 5,000

⁵ < 500

⁶ \$0 to < \$10 million

⁷ \$10 to < \$20 million

6.123 The submission estimated a net cost of ruxolitinib to the PBS/RPBS for the treatment of cGVHD of \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6 and \$10 million to < \$20 million over the first 6 years of listing.

6.124 The table below summarises the estimated utilisation and cost of ruxolitinib to the PBS/RPBS for the treatment of aGVHD. The submission assumed no prevalent pool of aGVHD patients given the poor prognosis and short duration of acute disease. The submission noted that < 500 patients with steroid refractory aGVHD receiving ruxolitinib via the sponsor's managed access program are expected to be grandfathered to the ruxolitinib PBS listing and have been added to the incident aGVHD population.

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Table 23: Estimated use and financial implications for aGVHD

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Steroid refractory Grade II to IV aGVHD						
Estimated alloSCT patients aged ≥12 years	2	2	2	2	2	2
All initiating steroid refractory Grade II/IV aGVHD	3	3	3	3	3	3
Uptake of ruxolitinib	90%	90%	90%	90%	90%	90%
Total incident patients	3	3	3	3	3	3
Grandfathered (100% uptake)	3	-	-	-	-	-
Total treated patients	3	3	3	3	3	3
Total ruxolitinib 5 mg scripts (43%) ¹	3	3	3	3	3	3
Total ruxolitinib 10 mg scripts (57%) ¹	3	3	3	3	3	3
Total scripts	3	3	3	3	3	3
Cost of ruxolitinib to the PBS/RPBS (effective price)						
Cost of ruxolitinib 5 mg	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Cost of ruxolitinib 10 mg	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Cost of ruxolitinib	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Patient copayment	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Total cost to the PBS/RPBS (less copayment)	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Changes in BAT therapy scripts for steroid refractory Grade II to IV aGVHD substituted by ruxolitinib						
Mycophenolate 500 mg tab	3	3	3	3	3	3
Methotrexate 10 mg tab	3	3	3	3	3	3
Sirolimus 1 mg tab	3	3	3	3	3	3
Everolimus 1 mg tab	3	3	3	3	3	3
Cost offsets from substitution of BAT therapies for steroid refractory Grade II to IV aGVHD						
Mycophenolate cost to PBS (less copayment)	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Methotrexate cost to PBS (less copayment)	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Sirolimus cost to PBS (less copayment)	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Everolimus cost to PBS (less copayment)	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Total cost offset (less copayment)	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Net changes to financial implications to the PBS/RPBS for aGVHD (effective price)						
Total net change (less copayment)	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4

Source: Tables 4.2-1, p.375, 4.2-2, p376 and 4.2-3, p377 of the submission; Excel workbooks Ruxolitinib SR-aGVHD – UCM.xlsx attached to the submission.

Abbreviations: aGVHD, acute graft versus host disease; alloSCT, allogeneic stem cell transplantation; BAT, best available therapy; Grandf., grandfathered; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

¹Based on 1 initiating script and 2.04 continuing scripts for patients in their first year of treatment; 13.04 scripts in year 2 for 0.31% of patients continuing in their second year of treatment. No patients continue to a third or subsequent year of treatment.

The redacted values correspond to the following ranges:

² 500 to < 5,000

³ < 500

⁴ \$0 to < \$10 million

6.125 The estimated overall financial impact to the PBS/RPBS of listing ruxolitinib for the treatment of aGVHD based on the effective price was \$0 to < \$10 million in Year 1, decreasing to \$0 to < \$10 million in Year 2 before increasing to \$0 to < \$10 million in Year 6. The total over the first 6 years of listing was \$0 to < \$10 million.

6.126 The table below summarises the estimated financial implications for the PBS/RPBS of listing ruxolitinib for the treatment of steroid refractory Grade II-IV aGVHD and moderate-severe cGVHD.

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Table 24: Estimated financial implications for the PBS/RPBS of listing ruxolitinib for cGVHD and aGVHD (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost of ruxolitinib to health budgets for steroid refractory moderate to severe cGVHD						
Net cost to PBS/RPBS (less copayment)	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
Net cost of ruxolitinib to the PBS/RPBS for steroid refractory Grade II to IV aGVHD						
Net cost to PBS/RPBS (less copayment)	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
Net total cost of ruxolitinib to the PBS/RPBS for steroid refractory GVHD						
Net total cost of ruxolitinib to PBS/RPBS (less copayment)	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
MBS cost offsets of ECP administration	-\$ ¹	-\$ ¹	-\$ ¹	-\$ ¹	-\$ ¹	-\$ ¹
Net total cost of ruxolitinib to PBS/RPBS and MBS	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
Incorporating the revised estimates provided in the pre-PBAC response for cGVHD						
Net total cost of ruxolitinib to PBS/RPBS (less copayment)	\$ ²	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
Net total cost of ruxolitinib to PBS/RPBS and MBS	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹

Source: Tables 4.4-1, p387.

Abbreviations: aGVHD, acute graft versus host disease; alloSCT, allogenic stem cell transplantation; BAT, best available therapy; cGVHD, chronic graft versus host disease; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$10 million to < \$20 million

6.127 The submission estimated that the overall financial impact to the PBS/RPBS of listing ruxolitinib for acute and chronic GVHD was \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6, and totalling \$20 million to < \$30 million over the first 6 years of listing. The submission estimated the total cost to the PBS/ RPBS and MBS (including estimated MBS offsets for ECP) would be \$10 million to < \$20 million over the first 6 years of listing, and this was increased in the pre-PBAC response to \$20 million to < \$30 million over 6 years.

6.128 The evaluation and ESC considered that the financial estimates were uncertain for the following reasons:

- The estimates were based on patients with steroid refractory disease only and did not appear to account for patients with steroid dependent disease or patients with steroid intolerance. The PSCR stated that the analysis included cGVHD patients with steroid dependent disease, but not aGVHD steroid dependent disease; therefore, the PSCR acknowledged that it was possible that the total eligible population may have been slightly underestimated due to the omission of these patients. The ESC and PBAC considered that the steroid intolerant population was expected to be small.
- The estimated proportion of alloSCT survivors derived from Gifford et al. (2016) most likely underestimated the eligible population in the contemporary Australian setting, given the study was based on patients transplanted between 2000 and

2013 and excluded patients aged 12 to ≤ 18 years. The pre-PBAC response increased the proportion of prevalent patients alive at Year 1 from 45% to 55% based on the most recent publication from the Australasian Bone Marrow Transplant Recipient Registry.

- The proportions of patients with steroid refractory GVHD derived from Axt et al. (2019) may not be applicable to the Australian setting, given Axt (2019) was a small German study based on data from 2004 to 2013 that excluded patients aged 12 to 18 years. The pre-PBAC response increased the proportion of patients with moderate cGVHD who were steroid refractory from 22.2% to 60% which it stated was to align with the values reported in the ratified MSAC PICO for ECP (p7, Extracorporeal photopheresis (Application 1651) Ratified PICO). The PBAC noted that the change appeared to be based on a statement in the PICO that 'it is estimated that 40% of patients achieve a complete or partial response to first-line treatment' and that no source was provided.
- The estimated duration of ruxolitinib treatment for initial and continuing treatment for cGVHD was based on outcomes from the economic model derived from extrapolated time to treatment discontinuation data. The evaluation considered that the extrapolated time to treatment discontinuation data were uncertain due to the limited duration of observed data (median follow-up of 57 weeks). However, the ESC noted that the base case financial estimates applied the exponential extrapolation and that this resulted in the shortest treatment duration. The PBAC noted that the estimated treatment duration was consistent with the economic model.
- The utilisation of cGVHD BAT treatments was estimated from the modelled outputs of the economic model. The estimated utilisation was considered uncertain due to the likely differences in availability and utilisation of treatments between the clinical trial setting and Australian clinical practice.

Financial Management – Risk Sharing Arrangements

6.129 No risk-sharing arrangement was proposed.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

Ruxolitinib for acute graft versus host disease

- 7.1 The PBAC recommended the listing of ruxolitinib for the treatment of acute graft versus host disease (aGVHD), on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drug Program). The PBAC was satisfied that ruxolitinib provides, for some patients, a significant improvement in efficacy, including an improvement in overall response rate (ORR), compared with best available therapy (BAT). The PBAC considered that ruxolitinib would be cost

- effective with some minor changes to the model presented, and that the financial impact of listing would be modest.
- 7.2 The PBAC considered that there was a high unmet need for effective therapies to treat this condition.
- 7.3 The PBAC considered that the nominated comparator, BAT, was appropriate.
- 7.4 The PBAC considered that the claim that ruxolitinib demonstrated superior efficacy compared to BAT in the key clinical trial, REACH2, was reasonable. The PBAC noted that treatment with ruxolitinib was associated with a statistically significant improvement in ORR at Day 28 (risk difference (RD) = 0.23; 95% CI: 0.12, 0.34) and durable overall response at Day 56 (RD = 0.18; 95% CI: 0.08, 0.28). The PBAC also noted that ruxolitinib was associated with a longer median overall survival compared to BAT (10.7 months versus 5.8 months) with clear separation of the Kaplan Meier curves (Figure 3), but that this difference was not statistically significant (HR = 0.83; 95% CI: 0.62, 1.13). The PBAC noted that patients who did not respond to BAT by Day 28 were eligible to crossover and receive ruxolitinib treatment and considered that this likely confounded the overall survival data.
- 7.5 In terms of safety, the PBAC noted that ruxolitinib was associated with higher rates of treatment-emergent adverse events, serious adverse events and discontinuations due to adverse events than BAT in the REACH2 trial. The PBAC considered that the broad range of BATs may have exaggerated the incremental effect of adverse events in the ruxolitinib arm and considered that ruxolitinib was generally well tolerated and that, overall, the claim that ruxolitinib was non-inferior in terms of safety compared to BAT was reasonable.
- 7.6 The submission presented a cost-utility analysis of ruxolitinib versus BAT. The PBAC noted that the economic evaluation was a microsimulation model and was based on the results of the REACH2 trial. The PBAC considered that the assumption in the model that patients could receive multiple additional lines of therapy (i.e. patients in the ruxolitinib arm received initial treatment with ruxolitinib followed by up to 9 lines of BAT therapy and patients in the BAT arm received up to 9 lines of therapy) was reasonable and reflective of clinical practice. While the PBAC considered that the assumption in the model that each line of BAT had the same efficacy as the initial BAT was not clinically plausible, the Committee acknowledged that no evidence was provided to inform alternative efficacy estimates and noted that sensitivity analyses indicated the assumption was likely to be appropriately conservative.
- 7.7 The PBAC noted the submission's base case incremental cost effectiveness ratio (ICER) was \$55,000 to < \$65,000 per quality adjusted life year (QALY). The PBAC considered that the ICER was optimistic given the uncertain extrapolation in the context of the long time horizon (15 years) which was based on a short duration of follow up in the REACH2 trial (5.7 months) and resulted in an incremental overall survival benefit

despite the non-statistically significant result in the trial. The PBAC considered that a 5 year time horizon was more reasonable and would minimise the uncertainties in the extrapolations due to the short duration of follow up in the trial. The PBAC noted this resulted in an ICER of \$65,000 to < \$75,000 per QALY.

- 7.8 The PBAC noted the multivariate sensitivity analysis that applied a 5 year time horizon and the current myelofibrosis 5 mg tablet price resulted in an ICER of \$55,000 to < \$65,000 per QALY, which was similar to the ICER presented in the submission base case. The PBAC considered that this was a more appropriate base case.
- 7.9 The PBAC noted the estimated financial impact of listing ruxolitinib for aGVHD was modest and considered that the estimates presented were reasonable.
- 7.10 The PBAC noted that the literature¹ proposed that aGVHD patients could be considered refractory to ruxolitinib if there was no improvement (partial response or better) compared with baseline after ≥ 14 days of treatment with ruxolitinib. Therefore, the PBAC considered that this definition should be included in the continuing supply restriction to allow supply in responsive disease only.
- 7.11 The PBAC also considered that treatment for aGVHD should commence within 100 days of allogenic stem cell transplant.
- 7.12 The PBAC noted the inclusion to the continuing supply restriction proposed in the pre-PBAC response relating to the tapering criteria and considered that this addition was reasonable (see paragraph 3.19).
- 7.13 The PBAC recommended that the restriction be silent with respect to the age of the patient.
- 7.14 The PBAC considered that the proposed grandfather restriction was appropriate.
- 7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for ruxolitinib for the treatment of aGVHD:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over BAT on the basis of the ORR gain observed in REACH2;
 - b) The treatment is expected to address a high and urgent unmet clinical need in the proposed population;

¹ Mohty M, Holler E, Jagasia M, et al. Refractory acute graft-versus-host disease: a new working definition beyond corticosteroid refractoriness. *Blood*. 2020. DOI: 10.1182/blood.2020007336

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

Outcome for acute graft versus host disease:

Recommended

Ruxolitinib for chronic graft versus host disease

- 7.16 The PBAC did not recommend the listing of ruxolitinib for the treatment of chronic graft versus host disease (cGVHD). The PBAC was satisfied that ruxolitinib provides, for some patients, a significant improvement in efficacy, including an improvement in ORR, compared with BAT. However, the PBAC considered that changes to the economic model inputs, including a reduction in the price of ruxolitinib, would be required to achieve acceptable incremental cost-effectiveness. Further, the PBAC considered that the financial estimates provided in the pre-PBAC response were overestimated.
- 7.17 The PBAC considered that there was a high unmet need for effective therapies to treat this condition.
- 7.18 The PBAC considered that the nominated comparator, BAT, was appropriate.
- 7.19 The PBAC considered that the claim that ruxolitinib demonstrated superior efficacy compared to BAT in the key clinical trial, REACH3, was reasonable. The PBAC noted that treatment with ruxolitinib was associated with a statistically significant improvement in ORR at Week 24 (RD = 0.24; 95% CI: 0.14, 0.34) and a statistically significant improvement in failure-free survival (HR = 0.37; 95% CI: 0.27, 0.51).
- 7.20 The PBAC noted that the overall survival data were relatively immature, with median overall survival not reached in either arm. The PBAC noted there was no statistically significant difference in overall survival between the ruxolitinib and BAT arms (HR = 1.09; 95% CI: 0.65, 1.82) and no separation of the Kaplan Meier curves (Figure 2) but acknowledged that these results were likely confounded by the use of subsequent treatments, including crossover of patients from the BAT arm to receive ruxolitinib after Week 24. Further, the PBAC noted that the trial was not powered to detect a difference in overall survival.
- 7.21 In terms of safety, the PBAC noted that ruxolitinib was associated with higher rates of treatment-emergent adverse events, serious adverse events and discontinuations due to adverse events than BAT in the REACH3 trial. The PBAC considered that the broad range of BATs may have exaggerated the incremental effect of adverse events in the ruxolitinib arm and considered that ruxolitinib was generally well tolerated and that, overall, the claim that ruxolitinib was non-inferior in terms of safety compared to BAT was reasonable.
- 7.22 The submission presented a cost-utility analysis of ruxolitinib versus BAT. The PBAC

noted that the economic evaluation was a microsimulation model and was based on the results of the REACH3 trial. The PBAC considered the assumption in the model that patients could receive multiple additional lines of therapy was reasonable and reflective of clinical practice. However, like the aGVHD model, the PBAC considered that the assumption that each line of BAT had the same efficacy as the initial BAT was not clinically plausible. The PBAC acknowledged that no evidence was provided to inform alternative efficacy estimates and noted that sensitivity analyses indicated the assumption was likely to be appropriately conservative.

- 7.23 The PBAC noted the submission's base case ICER was \$65,000 to < \$75,000 per QALY. The PBAC considered that the extrapolation of cGVHD-related mortality and duration of response in the model were likely optimistic and highly uncertain particularly in the context of the long modelled time horizon (30 years) compared with the limited duration of trial data (median duration of follow-up = 57.3 weeks). In particular, the PBAC considered that the extrapolation of overall survival was likely optimistic given there was no separation of the Kaplan Meier curves for overall survival in REACH3, and the hazard ratio for overall survival was 1.09 (95% CI: 0.65, 1.82). Further, the use of alternate parametric functions resulted in a wide range of incremental survival outcomes. The PBAC considered that a shorter time horizon, of 10 years, would be required to reduce the uncertainties associated with these extrapolations. The PBAC acknowledged that 10 years was longer than the time horizon of five years which was accepted by MSAC for ECP, but considered there were key differences between the two models including differences in the assumptions applied around mortality.
- 7.24 The PBAC noted that the health state utilities were derived from a post-hoc analysis of EQ-5D data collected in the REACH3 trial. The model assumed there would be a utility benefit for patients on treatment with ruxolitinib. The PBAC noted that the pre-Sub-Committee Response (PSCR) stated that the increased utility in patients treated with ruxolitinib (versus those treated with BAT) was likely due to the steroid-sparing effect of ruxolitinib and the higher proportion of patients achieving a complete response. The PBAC considered that a difference in quality of life and consequently in utilities between the arms was possible given the potential for reductions in steroid use with ruxolitinib therapy, noting that in REACH3 a higher proportion of patients in the ruxolitinib arm had completely tapered off systemic corticosteroids compared to the BAT arm after 24 weeks (ruxolitinib = 24% versus BAT = 17%).
- 7.25 The PBAC noted that there were likely to be applicability differences between the REACH3 trial and Australian clinical practice relating to the availability and utilisation of BAT treatments and that these may have impacted the clinical outcomes and costs. In particular, the PBAC noted that the model assumed that 35% of patients in the BAT arm would receive extracorporeal photopheresis (ECP) as their initial treatment, consistent with the clinical trial data. The PBAC considered that this may be overestimated as uptake in the Australian setting is currently limited due to its lack of

availability and the complexity associated with treatment. However, the PBAC also acknowledged that the trial-based data from REACH3 was the best estimate available in terms of determining the likely outcomes associated with BAT in this patient population.

7.26 The PBAC considered that a more appropriate base case for cGVHD would:

- apply a time horizon of ten years; and
- result in an ICER similar to the ICER accepted for aGVHD.

The PBAC considered that, with the above parameters, a reduction in the price of ruxolitinib would be required to achieve acceptable incremental cost-effectiveness.

7.27 The PBAC noted that the pre-PBAC response made two changes to the financial estimates. Firstly, the pre-PBAC response increased the proportion of prevalent patients alive at Year 1 from 45% to 55%, which appeared to be based on a recent publication from the Australasian Bone Marrow Transplant Recipient Registry (Kliman 2022). The PBAC considered that this change was reasonable. Secondly, the pre-PBAC response increased the proportion of patients with moderate cGVHD who are assumed to be steroid refractory/dependent/intolerant from 22.2% to 60%, which it stated was to align with that reported in the MSAC PICO for ESC. The PBAC considered this change was not reasonable as it was unsourced estimate (paragraph 6.128). The PBAC considered that it would be more appropriate to apply the proportions from Axt et al, 2019 as per the submission, noting these were more consistent with the estimates provided by the clinician at the sponsor hearing. The PBAC considered that the other financial impact inputs were reasonable.

7.28 The PBAC considered that a risk sharing arrangement (RSA) would be required to manage the risk associated with the uncertainties in the number of eligible patients and the duration of ruxolitinib treatment. The PBAC considered that a rebate of 1% for any expenditure above the cap would be required, particularly given the uncertainty around the duration of treatment.

7.29 The PBAC recommended that the restriction be silent with respect to the age of the patient.

7.30 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for ruxolitinib for cGVHD. The PBAC also considered that ruxolitinib addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- A revised economic model that incorporates that changes outlined in paragraph

7.26; and

- An RSA with expenditure caps based on the advice provided in paragraphs 7.26, 7.27 and 7.28, with a reduced price as derived from revised model outlined above.

7.31 The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or for the next PBAC cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

Outcome for chronic graft versus host disease:

Not recommended

7.32 The PBAC noted that this submission is not eligible for an Independent Review as the aGVHD indication received a positive recommendation.

8 Recommended listing

8.1 Add new item for aGVHD:

Name, restriction, manner of administration, form	PBS item code	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
aGVHD – initial					
RUXOLITINIB					
Tablet 5 mg, 56	NEW	1	56	0	JAKAVI®, Novartis
Tablet 10 mg, 56	NEW				
aGVHD – continuing treatment and grandfather treatment					
RUXOLITINIB					
Tablet 5 mg, 56	NEW	1	56	5	JAKAVI®, Novartis
Tablet 10 mg, 56	NEW				

	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
	Condition: Acute graft versus host disease (aGVHD)
	Severity: Grade II to IV
	PBS Indication: Grade II to IV acute graft versus host disease
	Treatment phase: Initial
	Restriction type: ☒ Streamlined
	Clinical criteria:
	Patient must have received prior systemic steroid treatment for this condition
	AND
	Clinical criteria:
	Patient must be one of the following: (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment
	AND
	Clinical criteria:

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	The treatment must be commenced no more than 100 days after receiving an allogeneic haematopoietic stem cell transplantation
	Treatment criteria:
	Must be treated by a medical practitioner who is either: (i) a haematologist, (ii) an oncologist with allogeneic bone marrow transplantation experience, (iii) a medical practitioner working under the direct supervision of one of the afore-mentioned specialist types
	Prescriber instructions: The severity of aGVHD is defined by the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Harris et al., 2016)
	Prescriber instructions: Steroid-refractory disease is defined as: (a) Progression after at least 3 days of high-dose systemic corticosteroid (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]) with or without calcineurin inhibitors for the treatment of Grade II-IV aGVHD, OR (b) Failure to achieve a partial response after 5 days at the time of initiation of high-dose systemic corticosteroid (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]) with or without calcineurin inhibitors for the treatment of Grade II-IV aGVHD Steroid-dependent disease is defined as failed corticosteroid taper involving either one of the following criteria: (i) an increase in the corticosteroid dose to methylprednisolone ≥ 2 mg/kg/day (or equivalent prednisone dose ≥ 2.5 mg/kg/day) OR (ii) Failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days Steroid intolerance is defined as a patient developing an intolerance of a severity necessitating treatment withdrawal. Details of prior steroid use should be documented in the patient's medical records
	Prescriber instructions: A patient must demonstrate a response 14 days after initiating treatment with ruxolitinib to be eligible for continuing treatment. Response is defined as attaining a complete or partial response as assessed by <i>Mount Sinai Acute GVHD International Consortium (MAGIC) criteria</i> (Harris et al., 2016). Note that response is relative to the assessment of organ function affected by aGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response is defined as a score of 0 for the aGVHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGVHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGVHD. (b) Partial response is defined as improvement of one stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGVHD. The assessment of response must be documented in the patient's medical records
	Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
	Administrative advice: Special Pricing Arrangements apply

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	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
	Condition: Acute graft versus host disease (aGVHD)
	Severity: Grade II to IV
	PBS Indication: Grade II to IV acute graft versus host disease
	Treatment phase: Continuing
	Restriction type: ☒ Streamlined
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition;
	AND
	Clinical criteria:
	Patient must have responding disease compared with baseline after 14 days of treatment demonstrated by either a: (i) partial response (ii) complete response
	Treatment criteria:
	Must be treated by a medical practitioner who is either: (i) a haematologist, (ii) an oncologist with allogeneic bone marrow transplantation experience, (iii) a medical practitioner working under the direct supervision of one of the afore-mentioned specialist types
	Prescriber instructions: Response is defined as attaining a complete or partial response as assessed by Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Harris et al., 2016). Note that response is relative to the assessment of organ function affected by aGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response is defined as a score of 0 for the aGVHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGVHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGVHD. (b) Partial response is defined as improvement of one stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGVHD. The assessment of response must be documented in the patient's medical records
	Prescriber instructions: Tapering the dose of corticosteroids should be considered in patients with responding disease. Following successful tapering of corticosteroids, tapering the dose of ruxolitinib can be initiated.
	Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
	Administrative advice: Special Pricing Arrangements apply

	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
	Condition: Acute graft versus host disease (aGVHD)
	Severity: Grade II to IV
	PBS Indication: Grade II to IV acute graft versus host disease
	Treatment phase: Grandfather
	Restriction type: ☒ Streamlined
	Clinical criteria:

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	Patient must have received non-PBS-subsidised treatment with this drug for this PBS-indication prior to [insert date of PBS listing]
	AND
	Clinical criteria:
	Patient must have received prior systemic steroid treatment prior to initiation of this drug for this condition
	AND
	Clinical criteria:
	Patient must be one of the following: (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment
	AND
	Clinical criteria:
	The treatment must be commenced no more than 100 days after receiving an allogenic haematopoietic stem cell transplantation
	AND
	Clinical criteria:
	Patient must have responding disease compared with baseline after 14 days of treatment demonstrated by either a: (i) partial response (ii) complete response
	Treatment criteria:
	Must be treated by a medical practitioner who is either: (i) a haematologist, (ii) an oncologist with allogeneic bone marrow transplantation experience, (iii) a medical practitioner working under the direct supervision of one of the afore-mentioned specialist types
	Prescriber instructions: Steroid-refractory disease is defined as: (a) Progression after at least 3 days of high-dose systemic corticosteroid (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]) with or without calcineurin inhibitors for the treatment of Grade II-IV aGVHD, OR (b) Failure to achieve a partial response after 5 days at the time of initiation of high-dose systemic corticosteroid (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]) with or without calcineurin inhibitors for the treatment of Grade II-IV aGVHD Steroid-dependent disease is defined as failed corticosteroid taper involving either one of the following criteria: (a) an increase in the corticosteroid dose to methylprednisolone ≥ 2 mg/kg/day (or equivalent prednisone dose ≥ 2.5 mg/kg/day) OR (b) failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days Steroid intolerance is defined as a patient developing an intolerance of a severity necessitating treatment withdrawal. Details of prior steroid use should be documented in the patient's medical records

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	Prescriber instructions: Response is defined as attaining a complete or partial response as assessed by Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Harris et al., 2016). Note that response is relative to the assessment of organ function affected by aGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response is defined as a score of 0 for the aGVHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGVHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGVHD. (b) Partial response is defined as improvement of one stage in one or more organs involved with aGVHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGVHD. The assessment of response must be documented in the patient's medical records
	Prescriber instructions: Tapering the dose of corticosteroids should be considered in patients with responding disease. Following successful tapering of corticosteroids, tapering the dose of ruxolitinib can be initiated.
	Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
	Administrative advice: Special Pricing Arrangements apply
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Novartis are committed to working with the PBAC to achieve PBS listing for Jakavi® (ruxolitinib) in patients with graft vs host disease.

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Addendum to the July 2022 PBAC PSD:

**7.04 RUXOLITINIB,
Tablet 5 mg, Tablet 10 mg,
Jakavi[®],
Novartis Pharmaceuticals Australia Pty Limited.**

11 Background

- 11.1 The resubmission requested a General Schedule Authority Required (STREAMLINED) listing for the treatment of patients with moderate to severe chronic graft versus host disease (cGVHD) who are refractory to, dependent on or intolerant of corticosteroids.
- 11.2 At the July 2022 PBAC meeting, ruxolitinib was recommended for the treatment of acute graft versus host disease (aGVHD), but not for the treatment of cGVHD. The resubmission for cGVHD was made under the early resolution pathway and sought to address the PBAC's concerns from its July 2022 meeting.

12 Consideration of the evidence

- 12.1 In July 2022 the PBAC considered the outstanding issues could be resolved in a simple resubmission and that the following changes may address the outstanding issues without requiring re-evaluation:
- A revised economic model that incorporates the changes outlined in paragraph 7.26; and
 - An RSA with expenditure caps based on the advice provided in paragraphs 7.26, 7.27 and 7.28, with a reduced price as derived from revised model outlined above.
- 12.2 Table 25 summarises how the resubmission addressed each of these issues.

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Table 25: Summary of changes made in the resubmission

PBAC PSD recommended change	Early resolution resubmission changes
Economic model	
Time horizon: 10 years (versus 30 years in July 2022 base case) (para 7.26).	Time horizon was reduced to 15 years.
Provide a reduction in the price to result in an ICER similar to the ICER accepted for aGVHD (\$ ¹ /QALY) (para 7.26).	Price of 5 mg tablets was reduced to be the same as the existing price in myelofibrosis. No change was made to the price of 10 mg tablets. The resubmission stated that the resultant ICER was \$ ² /QALY
Financial estimates	
The proportion of patients with moderate cGVHD who are assumed to be steroid refractory/dependent/intolerant should be 22.2% (per the submission's estimate, noting this was increased to 60% in the pre-PBAC response) (para 7.27).	The resubmission assumed that 22.2% of incident patients with moderate cGVHD were steroid refractory/dependent/intolerant. The resubmission assumed that 40% of prevalent patients with moderate and severe cGVHD were steroid refractory/dependent/intolerant. The resubmission argued "the proportion of cGVHD patients who are steroid refractory has reduced due to the recent advances in HSCT techniques and prophylaxis methodology. However, these techniques have only come into place over the last couple of years. For the prevalent pool of patients, roughly half of the patients treated with corticosteroids are refractory, dependent or intolerant as cited multiple literature sources".
The PBAC recommended that the restriction be silent with respect to the age of the patient (para 7.29).	The resubmission included patients under the age of 12 who had undergone HSCT.
The PBAC considered that the other financial impact inputs were reasonable (para 7.27).	The resubmission also made the following changes: - The proportion of survivors following an allogeneic SCT was increased from 55% (based on patients > 16 years of age) to 58% to represent patients of all ages. - The prevalent pool of patients was spread over 4 years (rather than all commencing in Year 1): 57% of the prevalent pool of patients were assumed to start treatment in Year 1, followed by 23%, 15% and 5% in Years 2, 3 and 4 respectively. - Uptake rate was increased from 90% to 100%.
Total financial impact Total scripts: ³ over 6 years proposed in submission The PBAC revised scenario would have resulted in around ³ scripts over 6 years. July 2022 submission estimated a cost to R/PBS of ruxolitinib: \$ ⁴ over 6 years	Total scripts: ⁵ over 6 years (an increase of around 48% vs PBAC scenario) Cost to R/PBS of ruxolitinib: \$ ⁴ over 6 years (increase of 43% versus the July 2022 submission) Net impact to R/PBS and MBS: \$ ⁶ over 6 years
RSA	
RSA with ⁷ % rebate for any expenditure above the cap would be required to manage the risk associated with the uncertainties in the number of eligible patients and the duration of ruxolitinib treatment (para 7.28).	The resubmission proposed a ⁸ % rebate for use above the estimated expenditure cap.

aGVHD = acute graft versus host disease; cGVHD = chronic graft versus host disease; HSCT = haemopoietic stem cell transplant; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; RSA = risk sharing arrangement; SCT = stem cell transplant

The redacted values correspond to the following ranges:

¹\$55,000 to < \$75,000

²\$45,000 to < \$55,000

³\$5,000 to < 10,000

⁴\$20 million to < \$30 million

⁵10,000 to < 20,000

⁴\$10 million to < \$20 million

Economic analysis

- 12.3 In July 2022, the PBAC advised that the time horizon applied to the economic model should be reduced from 30 years to 10 years and that the price of ruxolitinib should be reduced to result in an incremental cost effectiveness ratio (ICER) that was similar to that which was accepted in the aGVHD setting (i.e. approximately \$55,000 to < \$75,000 per quality adjusted life year (QALY); paragraph 7.26).
- 12.4 The resubmission applied a time horizon of 15 years, rather than 10 years as advised by PBAC, stating this was “a reasonable compromise between addressing the PBAC’s concerns about the long time horizon while allowing for sufficient time to capture the benefits in a chronic disease such as cGVHD.”
- 12.5 The resubmission stated that, with a 15 year time horizon and a reduction to the price of the 5 mg tablets (to the current myelofibrosis 5 mg tablet price), the ICER would be \$45,000 to < \$55,000 per QALY. The changes to the economic model were not evaluated as the resubmission was made under the early resubmission pathway.

Estimated PBS usage & financial implications

- 12.6 The resubmission made a number of changes to the utilisation and financial impact estimates provided in the July 2022 submission.
- 12.7 The changes recommended by the PBAC in July 2022 were that the resubmission:
- included patients under the age of 12 (paragraph 7.29), and
 - reduced the proportion of incident patients assumed to be steroid refractory/dependent/intolerant from 60% (as applied in the pre-PBAC response) to 22.2% (as originally proposed in the July 2022 submission; paragraph 7.27).
- 12.8 Changes made in the resubmission which were not recommended by the PBAC in July 2022 were:
- the proportion of prevalent patients with moderate and severe cGVHD who were assumed to be steroid refractory/dependent/intolerant was changed to 40%. The resubmission stated that the proportion of prevalent patients who were steroid refractory/dependent/intolerant has reduced due to advancements in HSCT techniques and in prophylaxis methodology;
 - the proportion of HSCT survivors was increased from 55% (in the July 2022 submission) to 58% to match the survival rate of all patients (i.e. to include patients less than 16 years);

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- the commencement of treatment for the prevalent pool of patients was spread over the first 4 years of listing rather than all prevalent patients commencing in Year 1; and
- the uptake rate was increased from 90% to 100%. The resubmission argued that ruxolitinib is the only oral treatment indicated for the treatment of steroid refractory/dependent/intolerant cGVHD.

12.9 The estimated use and financial implications from the resubmission are presented below.

Table 26: Estimated use and financial implications for cGVHD

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Early resolution resubmission						
Total scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total cost of ruxolitinib to the PBS/RPBS (less copayment)	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net cost to the PBS/RPBS (including offsets)	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Cost to MBS	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²
Total net cost to R/PBS + MBS	-\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
July 2022 submission						
Total scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total cost of ruxolitinib to the PBS/RPBS (less copayment)	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net cost to the PBS/RPBS (including offsets)	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Cost to MBS	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²
Total net cost to R/PBS + MBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
July 2022 pre-PBAC response						
Total scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total cost of ruxolitinib to the PBS/RPBS (less copayment)	\$█ ³	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net cost to the PBS/RPBS (including offsets)	\$█ ³	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Cost to MBS	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²	-\$█ ²
Total net cost to R/PBS + MBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²

Source: Table 22 of July 2022 PSD; worksheet 'SR-cGVHD – UCM – Post PBAC – Aug 2022.xlsx'

Abbreviations: cGVHD, chronic graft versus host disease.

The redacted values correspond to the following ranges:

¹500 to < 5,000

²\$0 to < \$10 million

³\$10 million to < \$20 million

Financial Management – Risk Sharing Arrangements

12.10 The resubmission acknowledged that there were uncertainties about the duration of ruxolitinib treatment in clinical practice, stating that patients would only remain on treatment whilst they were benefiting, and thus any extension of use compared to the submission would not constitute inappropriate use. The resubmission stated that a %

rebate for use over the financial impact estimates implied that these patients were obtaining no further benefit of treatment. The resubmission therefore proposed a rebate of |%.

13 PBAC Outcome

- 13.1 The PBAC did not recommend ruxolitinib for the treatment of patients with chronic graft versus host disease (cGVHD). The PBAC considered that the changes made in the resubmission did not sufficiently address the Committee's previous advice regarding the requirements of a simple resubmission. Overall, the PBAC considered that ruxolitinib was not acceptably cost-effective at the price proposed noting that the economic model was not revised as requested, the financial implications were increased compared with the previous submission and the proposed risk sharing arrangement (RSA) would not adequately manage the risk associated with the uncertain treatment duration.
- 13.2 The PBAC reiterated its July 2022 advice that ruxolitinib provides, for some patients, a significant improvement in efficacy, including an improvement in overall response rate (ORR), compared with best available therapy (BAT). The PBAC considered that the claims of superior effectiveness and non-inferior safety compared with BAT were reasonable.
- 13.3 In terms of the economic evaluation, the PBAC noted that the resubmission stated that it had applied a time horizon of 15 years and reduced the price of the 5 mg ruxolitinib tablets, resulting in an incremental cost effectiveness ratio (ICER) of \$45,000 to < \$55,000 per quality adjusted life year (QALY). The PBAC reiterated its July 2022 advice that a time horizon of 10 years would be more appropriate to reduce the uncertainties associated with the extrapolation of cGVHD-related mortality and duration of response. The PBAC also reiterated that a more appropriate base case should result in an ICER similar to the ICER accepted for acute GVHD, and that a reduction in the price of ruxolitinib would be required to achieve acceptable incremental cost-effectiveness.
- 13.4 The PBAC noted that in addition to the changes requested in July 2022 (see paragraph 11.7), the resubmission made a number of additional changes to the utilisation and financial impact estimates (see paragraph 11.8) which increased the estimated number of prescriptions by around 48% compared with the scenario advised by the PBAC in July 2022.
- 13.5 The PBAC noted that the resubmission proposed a RSA which consisted of a ■■■■■% rebate for use above the estimated financial implications. The PBAC recalled its previous advice that a rebate of |% for any expenditure above the cap would be appropriate, particularly given the uncertainty around the duration of treatment and the lack of data on when patients should cease ruxolitinib treatment.

- 13.6 The PBAC reiterated that a resubmission for ruxolitinib in cGVHD should address the issues outlined in paragraph 7.30 of the July 2022 PBAC PSD.
- 13.7 The PBAC noted that an early resolution pathway had been made available in July 2022 but considered that the remaining issues had not been resolved by the approach proposed in the sponsor's resubmission. The PBAC noted that any resubmission would be through the standard re-entry pathway. A resubmission may be lodged for consideration at any future PBAC meeting in accordance with lodgement timelines applicable to a standard re-entry pathway submission for that PBAC meeting.
- 13.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

14 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

15 Sponsor's Comment

Novartis are committed to working with the PBAC to achieve the PBS listing of Jakavi® (ruxolitinib) for patients with graft vs host disease.

Addendum to the September 2022 PBAC Minutes:

3.01 RUXOLITINIB, Tablet 5 mg, Tablet 10 mg, Jakavi[®], Novartis Pharmaceuticals Australia Pty Limited.

16 Background

- 16.1 At its March 2022 and September 2022 meetings, the PBAC did not recommend the PBS listing of ruxolitinib for the treatment of patients with moderate to severe cGVHD who are refractory to, dependent on or intolerant of corticosteroids. As noted in paragraph **Error! Reference source not found.**, the decision to not recommend in September 2022 was due to: the PBAC's consideration that ruxolitinib was not acceptably cost-effective at the price proposed noting that the economic model was not revised as requested, the financial implications were increased compared with the previous submission and the proposed RSA would not adequately manage the risk associated with the uncertain treatment duration.
- 16.2 Following the September 2022 intra-cycle meeting, the sponsor for ruxolitinib provided a revised pricing proposal that: updated the economic model and financial estimates; offered an $\frac{1}{2}$ % reduction to the price; and provided an updated RSA proposal. The revised approved ex-manufacturer prices (AEMP) were:
- \$ $\frac{1}{2}$ per 10 mg x 56 tablets compared with \$ $\frac{1}{2}$ in March and September 2022; and
 - \$ $\frac{1}{2}$ per 5 mg x 56 tablets compared with \$ $\frac{1}{2}$ in September 2022, and \$ $\frac{1}{2}$ in March 2022.
- 16.3 The pricing proposal updated the economic model with the following changes: a 10 year time horizon (as advised by PBAC in March and September 2022); and incorporation of the revised AEMPs. The pricing proposal stated this resulted in an ICER of \$45,000 to < \$55,000 per QALY, as shown in Table 27, which is similar to that accepted for aGVHD (i.e. approximately \$45,000 to < \$55,000/QALY). These changes were consistent with the PBAC's previous advice (refer to paragraphs 7.26 and **Error! Reference source not found.**). As a pricing proposal, the changes to the economic model were not evaluated.

Table 27: Updated cost effectiveness results

	Ruxolitinib	BAT	Increment
Revised proposal: Time horizon = 10 years; AEMP = \$ $\frac{1}{2}$ for 10 mg; \$ $\frac{1}{2}$ for 5 mg			
Costs	\$ $\frac{1}{2}$	\$87,394	\$ $\frac{1}{2}$
QALY	3.71	3.47	0.23
Incremental cost/extra QALY gained			\$ $\frac{1}{2}$

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March 2022 submission: Time horizon = 30 years; AEMP = \$ [REDACTED] for 10 mg; \$ [REDACTED] for 5 mg			
Costs	\$ [REDACTED]	\$100,561	\$ [REDACTED]
QALY	4.93	4.48	0.45
Incremental cost/extra QALY gained			\$ [REDACTED] ²

Source: Figure 1, Attachment 1 of the revised pricing proposal; Table 16 of March 2022 PBAC PSD [REDACTED] AEMP = approved ex-manufacturer price; BAT = best available therapy; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

16.4 The pricing proposal made the following changes to the financial estimates model submitted in July 2022:

- The proportion of prevalent patients alive at Year 1 was increased from 45% to 55%, which the PBAC had previously advised to be reasonable (refer to paragraph 7.27);
- Patients under the age of 12 years were included, which the PBAC had previously advised to be reasonable (refer to paragraph 12.7);
- The distribution of prevalent patients estimated to commence ruxolitinib across the first three years was changed from 85% in Year 1 (with no use in the prevalent pool of patients in later years) to 57% in Year 1, 27% in Year 2, and 1% in Year 3. The pricing proposal stated that this change would not increase the number of patients or prescriptions; and
- The revised price was incorporated.

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Table 28: Updated financial impact estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total continuing patient years of treatment	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Total scripts	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Total cost of ruxolitinib to the PBS/RPBS (less copayment)(\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Net cost to the PBS/RPBS (including R/PBS offsets)(\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Cost to MBS (\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Total net cost to R/PBS + MBS (\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
September 2022 resubmission						
Cost of ruxolitinib to the PBS/RPBS (less copayment) (\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
March 2022						
Cost of ruxolitinib to the PBS/RPBS (less copayment)(\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³

Source: Table 1, Attachment 1 of the revised pricing proposal; Table 26 of the September 2022 PBAC PSD.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

Note: In calculating the DPMQ, the financial estimates assumed a maximum quantity of two packs for the 5 mg strength, however this did not appear appropriate as the requested restriction was for a maximum quantity of one pack.

- 16.5 The pricing proposal stated that these changes resulted in an estimated net cost to the PBS/RPBS of \$10 million to < \$20 million over the first six years of listing, excluding PBS/RPBS and MBS offsets (compared to \$20 million to < \$30 million in the March 2022 resubmission, excluding PBS/RPBS and MBS offsets). As a pricing proposal, the changes to the financial estimates were not evaluated.
- 16.6 The pricing proposal offered a risk sharing arrangement (RSA) with a rebate of ■■■% for any expenditure over the financial impact estimates.

17 PBAC Outcome

- 17.1 The PBAC recommended the listing of ruxolitinib for the treatment of patients with moderate to severe cGVHD who are refractory to, dependent on, or intolerant of corticosteroids. The PBAC was satisfied that ruxolitinib provides, for some patients, a significant improvement in efficacy, including an improvement in ORR, compared with BAT. The PBAC considered that the pricing proposal's changes to the economic model parameters adequately addressed its previous concerns and that ruxolitinib would be acceptably cost-effective at the price proposed. Further, the PBAC considered that the pricing proposal's changes to the financial estimates were reasonable.

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- 17.2 The PBAC considered that there was a high unmet need for effective therapies to treat this condition. The PBAC re-iterated its previous consideration that the claims of superior effectiveness and non-inferior safety compared with BAT were reasonable.
- 17.3 The PBAC noted the pricing proposal, in which the economic model was revised to apply a ten year time horizon and a reduction to the price of ruxolitinib, resulted in an ICER of \$45,000 to < \$55,000 per QALY. The PBAC noted these changes were consistent with its previous advice (refer to paragraphs 7.26 and **Error! Reference source not found.**). The PBAC considered that the cost-effectiveness of ruxolitinib would be acceptable at the revised price proposed.
- 17.4 The PBAC considered that the proposed changes to the financial estimates were consistent with its suggestions in the July and September 2022 PBAC PSD. The PBAC considered that the revised estimated financial impact of listing ruxolitinib for cGVHD, as outlined in the pricing proposal, was reasonable.
- 17.5 The PBAC noted a [REDACTED] % rebate was proposed for use above the estimated financial implications. The PBAC considered this was appropriate and would adequately address the uncertainty around the duration of treatment and the lack of data on when patients should cease ruxolitinib treatment.
- 17.6 The PBAC considered that the restrictions proposed in July 2022, with the amendments previously suggested by the Secretariat and the PBAC in paragraph **Error! Reference source not found.**, were reasonable. The PBAC also considered that a response to ruxolitinib should be confirmed after 24 weeks and that a prescribing instruction should be added to the continuing restriction regarding the tapering of corticosteroids and ruxolitinib.
- 17.7 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for ruxolitinib for the treatment of cGVHD:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over BAT on the basis of the ORR gain observed in REACH3;
 - b) The treatment is expected to address a high and urgent unmet clinical need in the proposed population;
 - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 17.8 The PBAC noted that this submission was not eligible for an Independent Review as it is a positive recommendation.

Outcome:

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Recommended

18 Recommended listing

Add new item for cGVHD:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
Initial/continuing treatment				
RUXOLITINIB Tablet 5 mg, 56	1	56	5	JAKAVI®, Novartis
RUXOLITINIB Tablet 10 mg, 56	1	56	5	JAKAVI®, Novartis

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Chronic graft versus host disease (cGVHD)
Severity: Moderate to severe
PBS Indication: Moderate to severe chronic graft versus host disease (cGVHD)
Treatment phase: Initial
Restriction type: ☒ Authority Required - Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative advice: No increase in the maximum number of repeats may be authorised.
Clinical criteria:
Patient must have received prior systemic steroid treatment for this condition
AND
Clinical criteria:
Patient must be one of the following (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment
AND
Clinical criteria:
The treatment must be the sole PBS subsidised treatment for this condition with the exception of: (i) corticosteroids, (ii) calcineurin inhibitors

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Treatment criteria:
Must be treated by a medical practitioner who is either: (i) a haematologist, (ii) an oncologist with allogeneic bone marrow transplantation experience, (iii) a medical practitioner working under the direct supervision of one of the afore mentioned specialist types
AND
Treatment criteria:
Patient must be undergoing treatment with this drug following allogenic haematopoietic stem cell transplantation
Prescriber instructions:
The severity of cGVHD is defined by the <i>National Institutes of Health</i> (NIH) criteria (Jagasia et al, 2015): (a) Moderate cGVHD: At least one organ (not lung) with a score of 2, 3 or more organs involved with a score of 1 in each organ, or lung score of 1 (b) Severe cGVHD: at least 1 organ with a score of 3, or lung score of 2 or 3
Prescriber instructions:
Steroid-refractory disease is defined as: (a) A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent) OR (b) Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent).
Steroid-dependent disease is defined as an increased prednisone dose to > 0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent).
Steroid intolerance is defined as a patient developing an intolerance of a severity necessitating treatment withdrawal.
Details of prior steroid use should be documented in the patient's medical records.
Prescriber instructions:
A patient must demonstrate a response 24 weeks after initiating treatment with ruxolitinib to be eligible for continuing treatment.
Response is defined as attaining a complete or partial response as defined by the <i>National Institutes of Health</i> (NIH) criteria (Lee et al., 2015). Note that response is relative to the assessment of organ function affected by cGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response is defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without initiation or addition of new systemic therapy. (b) Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4-to-7-point scale, or an improvement of 2 or more points on a 10-to-12-point scale) without progression in other organs or sites, initiation or addition of new systemic therapies.
The assessment of response must be documented in the patient's medical records.
Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
Administrative advice: Special Pricing Arrangements apply
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Chronic graft versus host disease (cGVHD)
Severity: Moderate to severe
PBS Indication: Moderate to severe chronic graft versus host disease (cGVHD)
Treatment phase: Continuing

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Restriction type: ☒ Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative advice: No increase in the maximum number of repeats may be authorised.
Clinical criteria:
Patient must have received initial PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have responding disease at 24 weeks compared with baseline, demonstrated by either a: (i) partial response, (ii) complete response
AND
Clinical criteria:
The treatment must be the sole PBS subsidised treatment for this condition with the exception of: (i) corticosteroids, (ii) calcineurin inhibitors
Treatment criteria:
Must be treated by a medical practitioner who is either: (i) a haematologist, (ii) an oncologist with allogeneic bone marrow transplantation experience, (iii) a medical practitioner working under the direct supervision of one of the afore mentioned specialist types
Prescriber instructions:
Response is defined as attaining a complete or partial response as defined by the <i>National Institutes of Health</i> (NIH) criteria (Lee et al., 2015). Note that response is relative to the assessment of organ function affected by cGVHD prior to commencing initial treatment with ruxolitinib.
(a) Complete response is defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without initiation or addition of new systemic therapy.
(b) Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4-to-7-point scale, or an improvement of 2 or more points on a 10-to-12-point scale) without progression in other organs or sites, initiation or addition of new systemic therapies.
The assessment of response must be documented in the patient's medical records.
Prescriber instructions:
Tapering the dose of corticosteroids should be considered in patients with responding disease. Following successful tapering of corticosteroids, tapering the dose of ruxolitinib can be initiated.
Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
Administrative advice: Special Pricing Arrangements apply

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition: Chronic graft versus host disease (cGVHD)
Severity: Moderate to severe
PBS Indication: Moderate to severe chronic graft versus host disease (cGVHD)
Treatment phase: Grandfather
Restriction type: ☒ Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative advice: No increase in the maximum number of repeats may be authorised.
Clinical criteria:

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Patient must have received non-PBS-subsidised treatment with this drug for this PBS-indication prior to [insert date of PBS listing]
AND
Clinical criteria:
Patient must have received prior systemic steroid treatment prior to initiation of this drug for this condition
AND
Clinical criteria:
Patient must be one of the following (i) refractory to steroid treatment, (ii) dependent on steroid treatment, (iii) intolerant to steroid treatment
AND
Clinical criteria:
Patient must have responding disease at 24 weeks compared with baseline, demonstrated by either a: (i) partial response, (ii) complete response
Treatment criteria:
Must be treated by a medical practitioner who is either (i) a haematologist, (ii) an oncologist with allogeneic bone marrow transplantation experience, (iii) a medical practitioner working under the direct supervision of one of the afore mentioned specialist types
AND
Treatment criteria:
Patient must be undergoing treatment with this drug following allogenic haematopoietic stem cell transplantation
Prescriber instructions: Steroid-refractory disease is defined as: (a) A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent) OR (b) Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent). Steroid-dependent disease is defined as an increased prednisone dose to > 0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent). Steroid intolerance is defined as patient developing an intolerance of a severity necessitating treatment withdrawal. Details of prior steroid use should be documented in the patient's medical records.
Prescriber instructions: Response is defined as attaining a complete or partial response as defined by the <i>National Institutes of Health</i> (NIH) criteria (Lee et al., 2015). Note that response is relative to the assessment of organ function affected by cGVHD prior to commencing initial treatment with ruxolitinib. (a) Complete response is defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without initiation or addition of new systemic therapy. (b) Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, initiation or addition of new systemic therapies. The assessment of response must be documented in the patient's medical records.
Prescriber instructions: Tapering the dose of corticosteroids should be considered in patients with responding disease. Following successful tapering of corticosteroids, tapering the dose of ruxolitinib can be initiated.
Administrative advice: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting
Administrative advice: Special Pricing Arrangements apply

Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
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This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

19 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

20 Sponsor's Comment

The sponsor had no comment.