

7.04 MIDOSTAURIN, 25 mg Capsule, Rydapt[®], Novartis Pharmaceuticals Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 (Highly Specialised Drugs Program – Public and Private Hospital) listing for midostaurin for the treatment of FMS-like tyrosine kinase-3 (FLT3) mutation positive acute myeloid leukaemia (AML).
- 1.2 This was the second submission for midostaurin for FLT3 positive AML. The first submission was considered by the PBAC in November 2017. The key components of the clinical issue addressed were unchanged from the previous submission and are reiterated in Table 1.

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

Component	Description
Population	Patients with newly diagnosed FLT-3 mutation positive acute myeloid leukaemia eligible for standard intensive remission induction chemotherapy (cytarabine and an anthracycline).
Intervention	Midostaurin, 50 mg twice daily, in combination with chemotherapy for induction and consolidation therapy and as single agent for maintenance therapy.
Comparator	Placebo, 50 mg twice daily, in combination with chemotherapy for induction and consolidation therapy and as single agent for maintenance therapy.
Outcomes	<ul style="list-style-type: none"> • Primary outcome: Overall survival (OS); • Secondary outcomes: Event free survival (EFS), Disease free survival (DFS), Complete remission rate (CRR), Stem cell transplant (SCT) rates and impact on EFS, DFS and OS.
Clinical claim	In newly diagnosed patients with FLT-3 mutation positive acute myeloid leukaemia eligible for standard intensive remission induction chemotherapy (cytarabine and an anthracycline) the addition of midostaurin to standard intensive remission induction chemotherapy, followed by single agent maintenance therapy for relevant patients, is superior to placebo (standard medical management) at increasing complete remission rates, sustaining event free and disease free survival and significantly improving overall survival.

FLT-3 – FMS-like tyrosine kinase-3
Source: Table ES-1, p (ii) of resubmission

2 Requested listing

- 2.1 The resubmission presented a revised restriction, with amendments, following the previous PBAC advice (paragraph 7.4, November 2017 midostaurin Public Summary Document (PSD)). The essential elements of the requested PBS listing are summarised below. Grey shading indicates changes compared with the restriction proposed by the PBAC in its November 2017 consideration. Suggested additions are in italics and deletions are in strikethrough.

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Name, restriction, manner of administration, form	Maximum quantity (Packs)	Number of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
MIDOSTAURIN 25mg capsules, 1x56	1	2	\$10,206.50 (published, public) \$10,253.52 (published, private)	Rydapt® Novartis Pharmaceuticals Pty Ltd
Category / Program:	Section 100 – <i>Highly Specialised Drugs Program</i> (Public and Private hospitals)			
PBS Indication:	Acute myeloid leukaemia (AML)			
Treatment phase:	Induction / Consolidation therapy			
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
Clinical criteria:	<p>Patient must have a diagnosis of acute myeloid leukaemia; AND Patient must not have received a prior line of intensive chemotherapy for acute myeloid leukaemia this condition prior to standard intensive remission induction therapy; AND The condition must be internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation <i>positive before initiating this drug for this condition at diagnosis</i>; AND The condition must not be acute promyelocytic leukaemia AND The treatment must be in combination with undergoing, or considered eligible to receive standard intensive remission induction or consolidation chemotherapy for acute myeloid leukaemia with this drug for this condition</p>			
Prescriber Instructions	<p>A maximum of six cycles will be authorised under this phase restriction in a lifetime.</p> <ul style="list-style-type: none"> • Patients with acute promyelocytic leukaemia are not eligible for treatment. • Evidence of a FLT3 ITD or TKD mutation must be supplied, including the date of the test and the result. • Patients will still be considered eligible despite receiving prior, but essential treatment as follows: <ul style="list-style-type: none"> ○ emergency leukapheresis for hyperleukocytosis; ○ cranial radiation for central nervous system leukostasis; ○ growth factor/cytokine support; or ○ hydroxyurea for hyperleukocytosis. <p>Standard intensive remission induction combination chemotherapy must include cytarabine and an anthracycline.</p> <p>The FLT3 ITD or TKD mutation test result and date of testing must be provided at the time of application.</p> <p>Progressive disease monitoring via a complete blood count must be taken at the end of each cycle.</p> <p>If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.</p>			

	<p>Progressive disease is defined as the presence of any of the following:</p> <ul style="list-style-type: none"> ○ Leukaemic cells in the CSF; ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; ○ Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause; ○ Extramedullary leukaemia. <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p> <p><i>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.</i></p>
Administrative Advice	<p>No applications for increased maximum quantities will be authorised. No applications for increased repeats will be authorised.</p>

Name, restriction, manner of administration, form	Maximum quantity (Packs)	Number of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
MIDOSTAURIN 25mg capsules, 2x56	1	2	\$20,413.00 (published, public) \$20,460.15 (published, private) \$ [REDACTED] (effective, public) \$ [REDACTED] (effective, private)	Rydapt® Novartis Pharmaceuticals Pty Ltd

Category / Program:	Section 100 – Highly Specialised Drugs Program (Public and Private hospitals)
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Maintenance therapy – initial treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must not have experienced disease progression whilst receiving PBS-subsidised treatment with this drug for this condition; AND <i>Patient must have demonstrated complete remission after induction and consolidation chemotherapy plus midostaurin</i> AND Patient must not <i>be undergoing or be planned for, or have undergone or be receiving the conditioning regimen for, a stem cell transplant in first remission;</i> OR Patient must be awaiting a stem cell transplant in first remission. AND <i>The condition must have been internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation positive before initiating this drug for this condition</i></p>
Prescriber	A maximum of 3 cycles will be authorised <i>under this restriction</i> in a lifetime

<p>Instructions</p>	<p>Progressive disease monitoring via a complete blood count must be taken at the end of each cycle.</p> <p>If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.</p> <p>Progressive disease is defined as the presence of any of the following:</p> <ul style="list-style-type: none"> ○ Leukaemic cells in the CSF; ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; ○ Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause; ○ Extramedullary leukaemia. <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p> <p>Authority applications for initial maintenance therapy must be made in writing.</p> <p><i>The authority application must be made in writing and must include:</i></p> <p><i>(1) a completed authority prescription form;</i></p> <p><i>(2) a completed Acute myeloid leukaemia PBS Authority Application - Supporting Information Form; and</i></p> <p><i>(3) a declaration that the patient is not undergoing or has not undergone a stem cell transplant; and</i></p> <p><i>(4) a declaration that the patient does not have progressive disease; and</i></p> <p><i>(5) a copy of a recent bone marrow biopsy report demonstrating that the patient is in complete remission; and</i></p> <p><i>(6) a copy of the pathology test demonstrating that the condition was FMS tyrosine kinase 3 (FLT3) (ITD or TKD) mutation positive prior to commencing midostaurin.</i></p>
<p>Administrative Advice</p>	<p>No applications for increased maximum quantities will be authorised.</p> <p>No applications for increased repeats will be authorised.</p> <p><i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i> <i>Department of Human Services</i> <i>Complex Drugs</i> <i>Reply Paid 9826</i> <i>HOBART TAS 7001.</i></p>

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MIDOSTAURIN 25mg capsules, 2x56	1	21	\$20,413.00 (published, public) \$20,460.15 (published, private)	Rydapt® Novartis

\$ [REDACTED] (effective, public) Pharmaceuticals Pty Ltd
 \$ [REDACTED] (effective, private)

Category / Program:	Section 100 – Highly Specialised Drugs Program (Public and Private hospitals)
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Maintenance therapy - grandfathering treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must have received non-PBS treatment with this drug for this condition prior to [Date to be finalised] AND Patient must be receiving treatment with this drug for this condition at the time of application AND Patient must not have experienced disease progression whilst being treated with this drug for this condition; AND Patient must have demonstrated complete remission after induction and consolidation chemotherapy plus midostaurin AND Patient must not be undergoing or be planned for, or have undergone or be receiving the conditioning regimen for, a stem cell transplant in first remission; OR Patient must be awaiting a stem cell transplant in first remission. AND The condition must have been internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation positive before initiating this drug for this condition</p>
Prescriber Instructions	<p>A maximum of 23 cycles will be authorised <i>under this restriction</i> in a lifetime</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p> <p>For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the maintenance therapy continuing treatment criteria.</p> <p>Progressive disease monitoring via a complete blood count must be taken at the end of each cycle.</p> <p>If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.</p> <p>Progressive disease is defined as the presence of any of the following:</p>

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	<ul style="list-style-type: none"> ○ Leukaemic cells in the CSF ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy ○ Greater than 5% blasts in the marrow not attributable to bone marrow regeneration or another cause ○ Extramedullary leukaemia. <p>Authority applications for initial maintenance therapy must be made in writing. A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p> <p><i>The authority application must be made in writing and must include:</i></p> <p>(1) a completed authority prescription form; (2) a completed Acute myeloid leukaemia PBS Authority Application - Supporting Information Form; and (3) a declaration that the patient is not undergoing or has not undergone a stem cell transplant; and (4) a declaration that the patient does not have progressive disease; (5) a copy of a recent bone marrow biopsy report demonstrating that the patient is in complete remission; and (6) a copy of the pathology test demonstrating that the condition was FMS tyrosine kinase 3 (FLT3) (ITD or TKD) mutation positive prior to commencing midostaurin.</p>
Administrative Advice	<p>No applications for increased maximum quantities will be authorised. No applications for increased repeats will be authorised.</p> <p><i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i> Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001.</p>

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Category / Program:	Section 100 – Highly Specialised Drugs Program (Public and Private hospitals)
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Maintenance therapy – continuing treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic

	<input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously <i>received PBS-subsidised treatment with this drug for this condition under the initial maintenance or the initial maintenance grandfathering treatment restriction.</i> received PBS-subsidised treatment with this drug for this condition; AND Patient must not have developed disease progression whilst being treated with this drug for this condition; AND Patient must not <i>be undergoing</i> be planned for, or have undergone or be receiving the conditioning regimen for, a stem cell transplant in first remission; OR Patient must be awaiting a stem cell transplant in first remission.</p>
Prescriber Instructions	<p>A maximum of 9 cycles will be authorised under this restriction in a lifetime.</p> <p>Progressive disease monitoring via a complete blood count must be taken at the end of each cycle.</p> <p>If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.</p> <p>Progressive disease is defined as the presence of any of the following:</p> <ul style="list-style-type: none"> ○ Leukaemic cells in the CSF ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy ○ Greater than 5% blasts in the marrow not attributable to bone marrow regeneration or another cause ○ Extramedullary leukaemia. <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p>
Administrative Advice	<p>No applications for increased maximum quantities will be authorised. No applications for increased repeats will be authorised.</p>

Source: p13-14 of resubmission.

[^] The resubmission merged induction and consolidation treatment phases, split the maintenance phase into initial and continuing, and proposed corresponding grandfathering treatment phases to accommodate patients receiving midostaurin through the sponsor's ongoing compassionate access program, in contrast with three treatment phases (induction, consolidation and maintenance) requested in the November 2017 submission.

2.2 The resubmission proposed a reduction in the effective price for midostaurin through a Special Pricing Arrangement (SPA). Under the SPA proposed in the resubmission, the sponsor proposed to rebate the Commonwealth Government █% of PBS expenditure on midostaurin use in the maintenance phase of treatment. The impact of this rebate reduced the effective price per pack of midostaurin 25 mg x 112 tablets (used for maintenance) from \$20,413.00 to \$█ in the public hospital setting.

2.3 The pre-PBAC response offered a █% rebate on Commonwealth expenditure on midostaurin in all settings (induction, consolidation and maintenance).

- 2.4 The resubmission made the following changes to the proposed restriction that were consistent with the PBAC's advice from November 2017 (paragraph 7.4, November 2017 midostaurin PSD):
- the induction and consolidation treatment phases were merged and the maintenance phase was split into initial and continuing restrictions;
 - an Authority required (telephone) listing was requested for induction and consolidation treatment, while Authority Required (in writing) and Authority Required (telephone) listings were requested for initial and continuing phases of maintenance therapy, respectively;
 - the number of repeats in each treatment phase was aligned to meet PBAC's advice on the number of cycles that should be dispensed per prescription.
- 2.5 Consistent with the PBAC's previous advice, the resubmission proposed that up to three cycles could be authorised initially in the induction /consolidation phase, with a maximum of six cycles [packs] in total possible under this phase. The Pre-Sub-Committee Response (PSCR) noted that further splitting this phase into initial and continuing restrictions may help ensure that only patients achieving response to induction would be eligible for the consolidation phase. The PSCR further stated that it may also be appropriate for up to two cycles (rather than three) to be permitted on the initial supply and up to four cycles to be prescribed under a continuation restriction (as patients who have not responded after two cycles of induction should not receive a third cycle of treatment). The PBAC considered that the number of induction and consolidation cycles would vary between patients (e.g. many patients will have one cycle of induction and two of consolidation, while some will have two cycles of induction then one cycle of consolidation followed by an allograft). Overall, the PBAC re-iterated its previous advice that up to three cycles could be authorised initially for induction /consolidation, with a maximum of six cycles [packs] in total possible under this phase.
- 2.6 The resubmission stated that the proposed wording for the induction/consolidation phase was intended to enable patients who commenced midostaurin as a public hospital inpatient to access ongoing midostaurin under the PBS (providing they would otherwise meet the required PBS restriction criteria). For example, a patient may receive non-PBS midostaurin in the induction phase (as a public hospital inpatient) then be eligible to commence PBS-subsidised midostaurin in the consolidation phase, or receive their first or a partial induction cycle as a public hospital inpatient then be eligible to commence PBS-subsidised midostaurin for a subsequent induction cycle. Similarly, the resubmission also intended that grandfathered patients would be able to access midostaurin in the induction/consolidation setting (providing they would otherwise meet the required PBS restriction criteria). This intent was reasonable.
- 2.7 The PBAC also reiterated its previous advice from November 2017 (paragraph 7.4) that:

- a telephone authority was appropriate in the induction/consolidation phase where rapid approval was required, noting the low potential for leakage outside the restriction early in treatment;
- for the initial maintenance restriction, the PBAC considered that a written authority was necessary to assist minimising use outside the intended population. The PBAC considered the written authority should include a declaration that the patient is not undergoing or has not undergone a stem cell transplant; proof of complete remission and proof of FLT3 mutation positivity; and
- the Prescriber Instruction regarding evidence of a FLT3 ITD or TKD mutation should specify that the date and result of the test must be supplied.

2.8 The resubmission made the following additional changes to the restriction:

- The resubmission removed ‘fludarabine’ from the definition of ‘standard intensive remission induction chemotherapy’. The ESC had previously advised that in older patients, less intense chemotherapies such as fludarabine-based regimens may be used in place of anthracyclines (paragraph 2.5, November 2017 midostaurin PSD). The resubmission stated that the rationale for removing fludarabine (an antimetabolite rather than an anthracycline) was to align with the TGA indication, the RATIFY trial and the definition applied in the financial estimates for being fit for intensive chemotherapy.
- As a result of merging induction and consolidation phases into one restriction, the resubmission proposed further amendments to the restriction wording to enable patients who received midostaurin induction as an inpatient (but otherwise meet the required PBS restriction criteria) would be eligible to receive consolidation therapy under the PBS. This was appropriate.

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

3 Background

Registration status

- 3.1 The resubmission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, midostaurin was TGA-approved for use in the requested indication and the following documents were available: TGA Delegate’s overview; the Advisory Committee on Medicines (ACM) Minutes; and the TGA approval letter.
- 3.2 The TGA approved indications are:
- ‘in combination with standard anthracycline and cytarabine induction and cytarabine consolidation chemotherapy, followed in patients in complete response by single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive’.
 - ‘for the treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms, or mast cell leukaemia’.

- 3.3 Midostaurin for the treatment of FLT3 positive AML is also approved for use in some international jurisdictions. The main differences across the indications in the pivotal Phase III trial (RATIFY), the U.S. Food and Drug administration (FDA) approval, the European Medicines Agency (EMA) registration, the approved TGA indication and the requested PBS listing, are:
- Midostaurin is not approved as maintenance therapy in the United States
 - the PSCR (argued that although not explicitly stated, single-agent midostaurin for maintenance is not precluded by the FDA registration;
 - however, the ESC noted that the FDA approval of midostaurin was ‘in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation’, i.e. not as single-agent maintenance therapy. The ESC noted that TGA’s assessment (minutes of the Advisory Committee on Medicines (ACM)), also indicated that midostaurin was not approved for single-agent use as maintenance therapy by the FDA.
 - The RATIFY trial, along with the United States FDA approval and the EMA registration, specify the chemotherapy backbone for induction therapy (i.e. daunorubicin and cytarabine), while the TGA indication and proposed PBS restriction refer to ‘standard’ induction with an anthracycline and cytarabine. The ACM stated this would allow prescribers the flexibility to choose the anthracycline component of the regimen, noting that idarubicin is used more commonly than daunorubicin in Australia.

Previous PBAC consideration

- 3.4 This was the second submission for midostaurin for the treatment of FLT3 positive AML. The original major submission was considered by the PBAC in November 2017.
- 3.5 A summary of the outstanding matters of concern to the PBAC are presented in the table below.

Table 2: Summary of outstanding matters of concern

Matters of concern in November 2017	How the resubmission addresses it
Requested PBS listing	
<p>The PBAC considered that the restrictions for induction and consolidation could be combined with a telephone authority, allowing up to three cycles initially, and a maximum of six cycles in total.</p> <p>The PBAC considered that the restriction for use in the maintenance setting should be split into initial and continuing restrictions. The initial restriction should allow for three cycles of treatment and should be an Authority required (in writing) restriction. The restriction for continuing maintenance treatment should allow for a maximum of nine cycles, with a telephone authority. [paragraph 7.4, November 2017 Public Summary Document (PSD)]</p>	<p>The resubmission merged induction and consolidation treatment phases, split the maintenance phase into initial and continuing, and proposed two grandfathering phases (one for initial/consolidation and one for initial maintenance; noting that the former was incorporated into the non-grandfathered restriction), in contrast with three treatment phases (induction, consolidation and maintenance) requested in the November 2017 submission.</p>
<p>In the maintenance setting, the PBAC considered that the restriction should be amended to specify that midostaurin was not approved as maintenance following a stem cell transplant... the clinical criteria should state (among other criteria) that the "Patient must not be planned for, or have undergone, a stem cell transplant in first remission OR Patient must be awaiting a stem cell transplant in first remission". [paragraph 7.4, November 2017 PSD]</p>	<p>The resubmission proposed the following wording for this clinical criterion: "Patient must be undergoing, or considered eligible to receive, standard intensive remission induction or consolidation chemotherapy for acute myeloid leukaemia." The resubmission claimed that this will ensure that maintenance treatment was not administered post-transplant.</p>
<p>The PBAC did not consider it reasonable to restrict use of midostaurin to patients less than 60 years of age. [paragraph 7.4, November 2017 PSD]</p>	<p>The resubmission removed the age-related criterion from the restriction. This was appropriate.</p>
Clinical Evidence	
<p>The ESC and the PBAC had also considered that the use of midostaurin in the maintenance setting represents a departure from current practice for the treatment of FLT3 positive AML (in which maintenance therapy is not used). However, the Committees noted that it was not possible to discern the impact of maintenance therapy on the overall results from the RATIFY trial as patients were not re-randomised before the onset of maintenance therapy in the RATIFY trial. [paragraphs 4.8 and 6.14, November 2017 November 2017 PSD]</p>	<p>The resubmission acknowledged that the effect of maintenance therapy alone could not be explored due to the design of the RATIFY trial, and offered a ■% rebate on the price of maintenance therapy in order to mitigate PBAC's uncertainty about the necessity and efficacy of this treatment phase (increased in the pre-PBAC response to a ■% rebate across all treatment settings). There was neither any new evidence nor any compelling justifications in the resubmission that is likely to necessitate any change to the interpretation of clinical evidence.</p>
Economic Model	
<p>The PBAC advised that the impact of lower comparative effectiveness in the older age group should be adequately incorporated in the economic model. [paragraph 7.10, November 2017 PSD]</p>	<p>The updated economic model presented in the resubmission divided the population into two cohorts (those aged ≥ 60 and those aged < 60 years) to enable the assessment of different comparative efficacies of midostaurin in the two patient groups. This was reasonable.</p>
<p>The PBAC was particularly concerned by the model's inability to assess the impact of the inputs and assumptions related to SCT eligibility, use of maintenance therapy, duration of treatment and, importantly, outcomes for patients aged 60 years and over. [paragraph 7.14, November 2017 PSD]</p>	<p>The updated economic model presented in the resubmission was restructured so that all input parameters for patients aged ≥ 60 could be varied independently of those for patients aged < 60 years. Shorter time horizon, reduced rates of uptake of SCT in patients aged ≥ 60, with corresponding increases in the use of maintenance therapy, were applied in the revised base case.</p>

Matters of concern in November 2017	How the resubmission addresses it
<p>The PBAC considered that additional factors should have been explored in the economic model, such as by reducing the time horizon to better reflect life expectancy in this age group, increasing mortality in the induction phase in both arms, and reducing the SCT rate.</p> <p>The PBAC also considered that the model time horizon of 50 years was not clinically plausible and that more reasonable time horizons would be 25 years in the group of patients aged 60 years and over, and 40 years in the group under 60 years of age. [paragraph 7.15 and 7.17, November 2017 PSD]</p>	<p>The updated economic model presented in the resubmission divided the population into two cohorts (those aged ≥ 60 and those aged < 60 years) and applied a time horizon of 25 years in branches of the model with patients aged ≥ 60, and a time horizon of 40 years in the branches of the model with patients aged < 60 years. This was appropriate.</p>
<p>The PBAC noted alternative published utility values and considered the values used in the submission were not adequately justified...</p> <p>The PBAC recommended that any resubmission should better justify the selection of utility values in the maintenance and post-treatment health states, especially post SCT. [paragraphs 6.37 and 7.16, November 2017 PSD]</p>	<p>The resubmission claimed that the utility weights applied in the publication cited in the PBAC PSD (Cressman 2016) were not relevant, as they were not derived from a utility elicitation study but, instead, were estimates of quality of life data that are derived by application of a mapping technique based on clinical opinion (which is not described) to quality of life data from other studies. Further, the resubmission indicated that this study included patients with myelodysplastic syndrome.</p> <p>The resubmission acknowledged that the utility weights in the maintenance health state and the two post-SCT health states i.e. post-SCT first year and beyond the first year were too high, and adjusted the utility weights for these health states so that the maximum utility applied in any health state was no higher than age-appropriate Australian population norms. However, the evaluation and the ESC considered that the choice of utilities applied in the respecified base case was not adequately justified by the resubmission.</p>
<p>The utility applied ■ assumed that only ■% of patients experience graft-versus host disease, however the PBAC considered the incidence would be higher. [paragraph 6.37, November 2017 PSD]</p>	<p>The updated economic model presented in the resubmission doubled the incidence of chronic graft-versus-host disease to ■%.</p>
<p>...on visual inspection, the extrapolation used in the model appeared to underestimate survival in the placebo arm which would favour midostaurin... paragraph 7.18, November 2017 PSD]</p>	<p>The resubmission argued that the emphasis should not be placed on the comparison of the curves at the tail of the Kaplan-Meier curve of the RATIFY trial.</p>
<p>... Noting that the service volumes for FLT3 testing were likely to modestly increase with the PBS listing of midostaurin, the PBAC advised that it would be appropriate to account for this increase in the economic model. paragraph 7.18, November 2017 PSD]</p>	<p>This issue was not adequately addressed in the resubmission.</p>
<p>The PBAC considered that the ICER presented (\$45,000 - \$75,000 per QALY gained) was unacceptably high, particularly as it was highly uncertain and likely to be an underestimate.</p> <p>The PBAC advised that a reduced drug cost/patient/course and an acceptably cost-effective ICER below \$45,000/QALY - \$75,000/QALY would be more reasonable. [paragraphs 7.18 and 7.20, November 2017 PSD]</p>	<p>After incorporating the revised assumptions and a ■% reduction in the price per pack in the maintenance setting, the resubmission presented a respecified base case of \$45,000/QALY - \$75,000/QALY. The evaluation and the ESC considered that this was likely to be an underestimate, as the proportion of patients assumed to be ≥ 60 years old (32%) was underestimated, and was the biggest driver of the model.</p> <p>The pre-PBAC response revised the proportion of patients assumed to be ≥ 60 years, the utilities applied in some health states, and the rebate offered in all settings.</p>

Matters of concern in November 2017	How the resubmission addresses it
...the model assumed that only █% of patients would receive consolidation treatment as an inpatient. The PBAC considered that a significantly higher proportion of patients were likely to receive consolidation treatment as an inpatient (e.g. closer to 80-90%)... [paragraph 7.18, November 2017 PSD]	The resubmission updated this to █% in the respecified base case. However, for the purposes of the financial estimates, the resubmission maintained that █% of midostaurin used for consolidation cycles will be dispensed through the PBS.
The PBAC advised that a Risk Sharing Arrangement with 100% rebate beyond the agreed subsidisation caps to mitigate the risk of use beyond the proposed restriction and other uncertainties in the financial estimates would be appropriate. [paragraph 7.20, November 2017 PSD]	The resubmission expressed the sponsor's willingness to negotiate a Risk Sharing Arrangement (RSA). The resubmission did not specify any further details of the proposed RSA.

Source: November 2017 PBAC PSD and July 2018 resubmission.

4 Population and disease

- 4.1 AML is a rare (orphan) malignant disorder that is rapidly progressive and frequently fatal, with a five year survival rate of 24%.
- 4.2 FLT3 mutation positive AML is recognised as a distinct subtype of AML that is associated with reduced complete remission rates and higher rates of relapse, accompanied by shorter survival post-relapse than their FLT3 wild type (WT) counterparts.
- 4.3 As in the November 2017 submission, the resubmission indicated that midostaurin was intended to be used in combination with AML induction and consolidation chemotherapy regimens and as a substitute to “watch and wait” for patients who do not undergo a SCT.
- 4.4 In its November 2017 consideration, the ESC and the PBAC had advised that in practice, the use of four cycles of consolidation is reserved for FLT3 positive patients with an accompanying core binding factor (CBF) mutation; the current standard treatment (i.e. without PBS-subsidised access to midostaurin) for other patients is two cycles, and potentially only one if the patient is proceeding to an allograft (paragraph 4.8, November 2017 midostaurin PSD). This may have potentially resulted in the costs of comparator treatments being overestimated in the economic model and financial estimates compared with current clinical practice in Australia, which was not addressed in the resubmission. The ESC and the PBAC noted that the clinical algorithm in the resubmission remained inconsistent with Australian clinical practice, in terms of the number of cycles of consolidation therapy in the current scenario.

5 Comparator

- 5.1 As per the November 2017 submission, the resubmission nominated placebo or no treatment, in combination with cytarabine and an anthracycline in induction therapy; in combination with high dose cytarabine in consolidation therapy; and alone in maintenance (continuing therapy), as the main comparator. This was

reasonable, as the PBAC had previously considered that the nominated comparator was appropriate (paragraph 7.7, November 2017 midostaurin PSD).

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The ESC noted that compared with the November 2017 submission, no new clinical information was presented in the resubmission. As such, only the main clinical data from the November 2017 submission have been presented in the following paragraphs, in order to provide context.

6.4 The November 2017 submission was based on one trial comparing midostaurin 50 mg twice daily versus placebo in the induction, consolidation, and maintenance cycles in the treatment of FLT3 mutation positive AML patients aged ≤ 59 years (RATIFY).

6.5 The November 2017 submission also included one supplementary single arm study of midostaurin treated AML patients of the ITD FLT3 mutation subtype, between the ages of 18 and 70 years (AMLSG-16-10), to support listing for treatment in patients aged 60 years and older.

6.6 Details of the trials and studies presented in the November 2017 submission are provided in the table below.

patients without complete remission, (iii) in those occurring during first complete remission, or (iv) in those having a SCT after relapse.

- 6.10 At its November 2017 consideration of midostaurin, the ESC had advised that the rate of SCTs in the Australian population was likely to be 70-80%, as opposed to that observed in RATIFY, and applied in the economic model and financial estimates (55-60%). While considering the resubmission, the ESC maintained that the rate of SCT was lower than standard Australian clinical practice, especially given that FLT3 positivity indicates that a patient is at poor prognostic risk, and is an indication for transplantation in first remission.

Table 5: Overall survival reported in the RATIFY trial

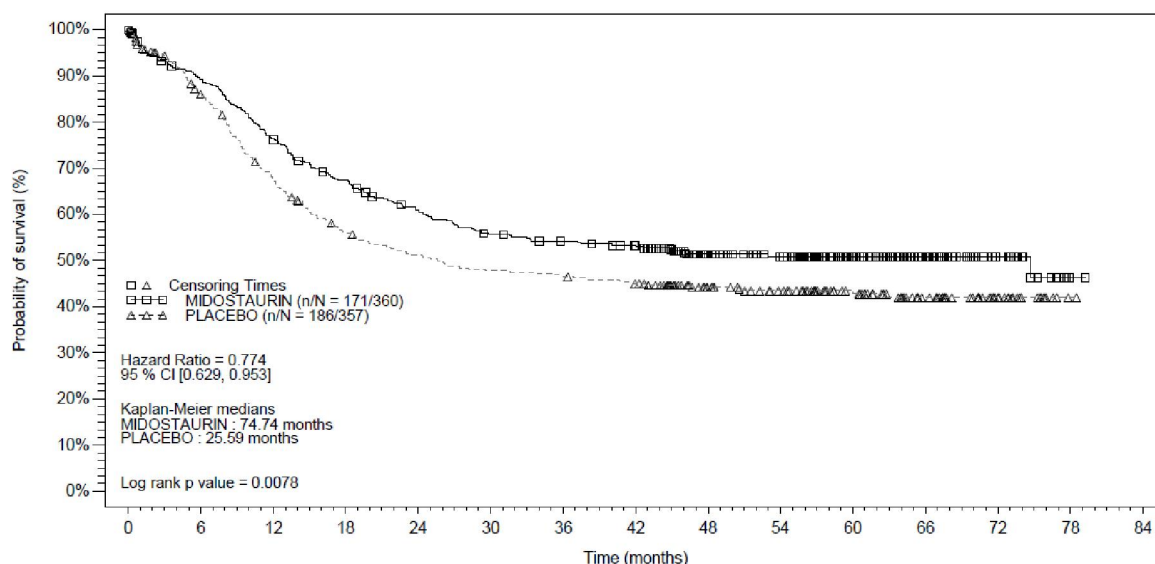
	Midostaurin; N=360	Placebo; N=357	Absolute Difference	Hazard ratio (95% CI)
OS not censored at time of SCT (primary outcome)				
No. deaths, n (%)	171 (47.5)	186 (52.1)	4.6%	0.77 (0.63, 0.95)
No. censored, n (%)	189 (52.5)	171 (47.9)	4.6%	
KM estimates (95% CI)				
At 12 months	██████████	██████████	███%	NR
At 24 months	██████████	██████████	███%	
At 60 months	██████████	██████████	███%	
Median OS, months	74.74 (31.54, NE)	25.59 (18.63, 42.87)	49.1	
OS Censored at time of SCT				
No. deaths, n (%)	71 (19.7)	██████████	███%	0.75 (0.54, 1.03)
No. censored, n (%)	██████████	██████████	███%	
KM estimates (95% CI)				
At 12 months	██████████	██████████	███%	NR
At 24 months	██████████	██████████	███%	
At 60 months	██████████	██████████	███%	
Median OS, months	██████████	██████████	NA	

Source: Tables 2.5-1, p124 and Table 2.5-3, p 128 of the submission.

CI = confidence interval; NA = not applicable; NE = not estimable; OS = overall survival; SCT= stem cell transplant

Bold typography indicates statistically significant differences

Figure 1: Kaplan Meier curve for OS, non-censored at time of SCT



No. of patients still at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
MIDOSTAURIN	360	314	269	234	208	189	181	174	133	120	77	50	22	1	0
PLACEBO	357	284	221	179	163	152	148	141	110	85	71	45	20	1	0

Logrank test and Cox regression model stratified for FLT3mutation strata used in the randomization

Source: Figure 2.5.-1, p125 of the November 2017 submission.

OS = overall survival; SCT = stem cell transplant

- 6.11 The results of the overall survival analysis indicated statistically significant improvement in overall survival, non-censored at time of SCT (HR = 0.77, 95% confidence interval: 0.63, 0.95), with a reported incremental median survival of 49.1 months in patients treated with midostaurin.
- 6.12 In its November 2017 consideration of midostaurin, the PBAC had considered that RATIFY was a mature, well-conducted trial with similar results with and without censoring for SCT. The PBAC had considered that the numerical difference between arms in median OS (not censored at time of SCT) potentially overstated the survival benefit of midostaurin, as the survival curves began to plateau just prior to the time of median OS (paragraph 7.9, November 2017 PSD).
- 6.13 As the RATIFY trial limited enrolment to those aged ≤ 59 years (approximate mean and median age of 45 years and 47 years, respectively), but the requested listing proposed that PBS-subsidised access to midostaurin should not be age-restricted, the November 2017 submission presented results from the AMLGS-16-10 study.
- 6.14 The AMLSG 16-10 study was a Phase II single-arm, study evaluating the efficacy and safety of midostaurin in combination with standard intensive remission induction therapy and as single agent maintenance therapy following allogeneic haematopoietic SCT or high dose cytarabine consolidation in 284 patients aged 18-70 years (68% of patients aged ≤ 59 years and 32% aged ≥ 60 years; with a median age of 54 years) with newly diagnosed FLT3 ITD positive AML.
- 6.15 Results from AMLGS-16-10 indicated:

- Patients aged 60-70 years achieved the same complete remission (CR) rates as patients aged ≤ 59 . Overall response, defined by CR or CR with incomplete platelet recovery (CRi), was 76% in younger patients (≤ 59 years) and 76% in older patients (≥ 60 years).
- Median overall survival in those aged 60-70 years was not significantly worse than younger patients. Median overall survival was 25 months (26 months in the younger population and 23 months in the older population ($p = 0.15$)). Death during induction therapy occurred in 4% of younger patients and 10% of older patients.

6.16 In November 2017, the PBAC and ESC had considered that the overall applicability of the AMLSG-16-10 study to the likely eligible PBS population was unclear as:

- enrolment was limited to those aged 18-70 years;
- enrolment was limited to those who were FLT3 ITD mutation positive, whereas the requested restriction is for both ITD and TKD mutation positive; and
- the ESC considered that the use of midostaurin post-allograft in the AMLGS-16-10 study diminished its applicability to support the use of midostaurin in older patients.

However, notwithstanding the above limitations, the ESC and the PBAC had considered it was not necessary to include an age limit in the proposed PBS restriction, and advised that the effect of age on treatment eligibility would be best left to the discretion of the prescriber (paragraphs 6.18 to 6.20, November 2017 midostaurin PSD).

6.17 No new details of the AMLSG 16-10 study were provided in the resubmission.

Comparative harms

6.18 Compared to the November 2017 submission, no new safety data were presented in the resubmission. The table below summarises the key adverse events of the RATIFY trial presented in the November 2017 submission.

Table 6: Summary of key adverse events in the RATIFY trial, n (%)

Adverse event		Midostaurin; N=345	Placebo; N=335	RD (95% CI)
Nausea (all grades)		284 (82.3%)	246 (73.4%)	0.09 (0.03, 0.15)
Nausea (grade 3 / 4)		20 (5.8%)	34 (10.1%)	-0.04 (-0.09, -0.003)
Stomatitis (all grades)		65 (18.8%)	40 (11.9%)	0.07 (0.02, 0.12)
Exfoliative dermatitis (grade 3 / 4)		47 (13.6%)	26 (7.8%)	0.06 (0.01, 0.11)
Exfoliative dermatitis (grade 3 / 4) Suspected related to study drug		25 (7.2%)	9 (2.7%)	0.05 (0.01, 0.08)
Device related infections (grade 3 / 4)		56 (16.2%)	34 (10.1%)	0.06 (0.01, 0.11)
Skin toxicities: Bleeding events (grade 3 / 4)	Overall	61 (17.7%)	37 (11.0%)	0.07 (0.01, 0.19)
	Induction	51 (14.8%)	30 (9.1%)	0.06 (0.01, 0.11)
	Consolidation	1 (0.4%)	0 (0)	0.003 (-0.003, 0.01)

Source: Table 2.5.3, p 5.10.COM.39, November 2017 midostaurin commentary

CI = confidence interval; RD = risk difference.

Bold typography indicates statistically significant differences

6.19 There were higher rates of nausea (all grades) associated with midostaurin, but higher rates of severe nausea associated with placebo. Additionally there were higher rates of stomatitis, exfoliative dermatitis, device related infections and skin toxicities associated with midostaurin.

Benefits/harms

6.20 A summary of the comparative benefits and harms for midostaurin versus placebo, unchanged from the November 2017 submission¹, is presented in the table below.

¹ The number of patients alive at 60 months is reported as a different value compared with that reported in the Public Summary Document (PSD) for midostaurin for its November 2017 consideration (despite the same trial data being used) as these data were re-calculated using a different method (Kaplan Meier estimates were used in Table 7).

Table 7: Summary of comparative benefits and harms for midostaurin and placebo

Benefits						
Overall survival, non-censored for stem cell transplant (SCT) (median follow up of 60 months)						
Event	Midostaurin	Placebo	Absolute difference (%)	HR (95% CI)		
Number of deaths, n/N (%)	171/360 (47.5%)	186/357 (52.1%)	-	0.77 (0.63, 0.95)		
Alive at 60 months (Kaplan-Meier method), % (95% CI)	51% (45%, 56%)	43% (38%, 49%)	8.0			
Harms						
	Midostaurin n/N	Placebo n/N	RR (95% CI)	Events/100 patients*		RD (95% CI)
				Midostaurin	Placebo	
Exfoliative dermatitis (grade 3 / 4)						
RATIFY	47/345	26/335	1.76 (1.12, 2.76)	13.6	7.8	0.06 (0.01, 0.11)
Device related infections (grade 3 / 4)						
RATIFY	56/345	34/335	1.60 (1.08, 2.38)	16.2	10.1	0.06 (0.01, 0.11)
Skin toxicities (grade 3 / 4)						
RATIFY	61/345	37/335	1.60 (1.10, 2.34)	17.7	11.0	0.07 (0.01, 0.12)

PBO = placebo; RR = risk ratio

Source: Compiled during the evaluation; Table 3-7, p31 of the RATIFY Clinical Study Report ('PKC412 SCE AML RATIFY.pdf', provided with November 2017 submission)

6.21 On the basis of direct evidence presented in the November 2017 submission, and unchanged in the resubmission, for every 100 patients treated with midostaurin in comparison to placebo:

- Approximately 8 additional patients would be alive at 60 months.
- Approximately 6 additional patients would have grade 3 / 4 exfoliative dermatitis, over a median duration of exposure of 42 days.
- Approximately 6 additional patients would have grade 3 / 4 device related infections over a median duration of exposure of 42 days.
- Approximately 6 additional patients would have grade 3 / 4 skin toxicities: bleeding events over a median duration of exposure of 42 days.

Clinical claim

6.22 At its November 2017 consideration, the PBAC considered that the pivotal trial, RATIFY, demonstrated that midostaurin improved overall survival versus placebo in patients aged under 60 years. The PBAC had also considered that while it was biologically plausible for older patients to respond to midostaurin, it was not convinced of the magnitude of incremental benefit in the older patient population due to the absence of a placebo comparison and a higher background mortality (e.g. transplant-related or from causes unrelated to AML) in the older population. While the November 2017 PBAC advised against restricting the use of midostaurin based on age and considered the effect of age on treatment eligibility would be best regulated if left to the discretion of the prescriber, the Committee advised that the impact of lower comparative effectiveness in the older age group should be

adequately incorporated in the economic model (paragraph 7.10, November 2017 PSD).

- 6.23 The November 2017 PBAC considered that midostaurin was inferior in safety compared with placebo but considered that in the context of chemotherapy-induced morbidity and mortality, the additional toxicity with midostaurin treatment was relatively minor (para 7.12, November 2017 PBAC meeting).
- 6.24 In November 2017, the ESC and PBAC had also considered that the use of midostaurin in the maintenance setting represents a departure from current practice for the treatment of FLT3 positive AML (in which maintenance therapy is not used). However, the Committees noted that it was not possible to discern the impact of maintenance therapy on the overall results from the RATIFY trial as patients were not re-randomised before the onset of maintenance therapy (paragraphs 4.8 and 6.14, November 2017 midostaurin PSD). The resubmission acknowledged that the effect of maintenance therapy alone could not be explored due to the design of the RATIFY trial, and offered a ■■■% rebate on the price of maintenance therapy in order to mitigate PBAC's uncertainty about the necessity and efficacy of this treatment phase.
- 6.25 The ESC and the PBAC advised that there was neither any new evidence nor any compelling justifications in the resubmission that changed the previous interpretation of the clinical evidence. Thus, the PBAC re-iterated its previous consideration that:
- the claim of superior comparative effectiveness of midostaurin versus placebo was reasonable, but that the magnitude of the incremental benefit was uncertain particularly in patients aged 60 years and older; and
 - midostaurin was inferior in safety compared with placebo, but considered that in the context of chemotherapy-induced morbidity and mortality, the additional toxicity with midostaurin treatment is relatively minor.

Economic analysis

- 6.26 The ESC and the PBAC noted that as per the November 2017 submission, the resubmission presented a stepped economic evaluation using a cohort-based state transition model, based on results of the RATIFY trial.
- 6.27 The resubmission updated the economic model in order to address a number of concerns raised by the PBAC in its November 2017 consideration of midostaurin. The major difference was structural, i.e. the restructured model presented in the resubmission allowed the input parameters for the cohort of patients ≥ 60 years to be varied independently of those aged < 60 years.
- 6.28 The ESC and the PBAC noted that the differences in input parameters for the older population, compared with those under 60 years of age, were:

- a 2.5 fold higher risk of mortality in patients aged ≥ 60 years without SCT i.e. when undergoing induction and consolidation, after achieving remission, and in the relapsed or refractory health states (unchanged from the previous submission);
- a time horizon of 25 years (revised in the resubmission);
- a ■■■% lower likelihood of SCT (revised in the resubmission);
- a corresponding higher likelihood of receiving maintenance therapy (revised in the resubmission)
- relatively lower utility weights in the remission and post-SCT health states (revised in the resubmission); and
- a higher age-adjusted background mortality rate (corrected in the resubmission).

6.29 The ESC and the PBAC noted that input parameters that were revised in the resubmission that affected both patient populations included:

- proportion of patients having consolidation therapy as hospital inpatients increased from ■■■% to ■■■%; and
- proportion of patients with graft versus host disease (GVHD) in the first year following SCT was increased from ■■■% to ■■■%.

6.30 The economic model assumed that only 32% of the proposed PBS population would be aged ≥ 60 years, based on age distributions in the AMLSG 16-10 study.

- This was inconsistent with assumptions applied in the financial estimates, wherein the resubmission assumed that 57-59% of the eligible population would be aged ≥ 60 years when commencing PBS-subsidised midostaurin. The PSCR stated this was partly due to “simplifying assumptions” that had been made in the financial analysis (i.e. that the proportion of patients with positive FLT-3 mutation status and uptake rates of midostaurin would be identical in the younger and older populations);
- Further, the evaluation noted that PBS utilisation data for idarubicin, an anthracycline routinely used in Australia for induction and consolidation therapy in AML, showed that 70% (112/161) of patients who received a PBS supply of idarubicin in 2017 were ≥ 60 years old and 30% (49/161) were < 60 years old at the time of their first supply. This more closely aligned with the assumptions used in the financial estimates;
- The PSCR questioned the applicability of the PBS utilisation data for idarubicin for the purposes of estimating the proportion of patients aged <60 versus ≥ 60 years (e.g. idarubicin may be used in some patients who would not be eligible to receive midostaurin, such as when idarubicin is used in less intensive induction regimens or in patients with relapsed/refractory AML);
- The ESC advised that an epidemiological approach together with evidence from standard clinical practice be taken into account to estimate the proportion of patients ≥ 60 years who were likely to be treated with midostaurin.

- The ESC considered that it was highly unlikely that patients over the age of 65 years would undergo an SCT, or that patients over the age of 70 years would be fit enough for 7:3 chemotherapy regimen;
- As such, the ESC noted that although AIHW² data indicated that 72% (765/1059) of all patients diagnosed with AML were over 60 at the time of diagnosis, many of these patients would not be fit enough to receive standard intensive induction chemotherapy with cytarabine and an anthracycline (and would thus not be eligible for midostaurin);
- The ESC noted that of all patients who were <70 years old, 43% (224/518) were ≥ 60 years.
- However, the ESC acknowledged that there would be some patients <70 years old who would not be fit for 7:3 chemotherapy regimen, just as there would be a small number of older patients who would be fit enough.
- The PSCR claimed that the proportion of older patients likely to receive treatment with midostaurin would be “less than 50%”, noting that a survey of 20 haematologists estimated that around ■% of AML patients were aged 60 years or over;
- The PSCR also cited evidence that the frequency of FLT3 mutations decreases substantially with increasing age³. However, the ESC considered that there was some ambiguity in this assumption as there was also evidence in the literature that suggested the opposite⁴;
- Considering all of the above evidence, the ESC advised that it would be reasonable to assume that ■-■% of the PBS-eligible population would be aged 60 years or over when commencing midostaurin; and
- The proportion of patients assumed to be aged ≥ 60 years was tested in sensitivity analyses and had a large impact on the cost-effectiveness ratio of midostaurin.
- The pre-PBAC response proposed that an estimate of ■% be used in the economic model.
- The PBAC agreed with the pre-PBAC response, and advised that it was reasonable to assume that ■% of patients in the PBS-eligible population would be aged 60 years or over.

6.31 The resubmission appropriately revised the proportion of patients having consolidation chemotherapy in the inpatient setting from ■% to ■%. In the economic model, this increased the estimated hospitalisation costs in the consolidation health state in both arms, and thus only had a minor impact on the cost-effectiveness of midostaurin. (Note that in the financial estimates the

² Australian Institute of Health and Welfare (AIHW) 2017. Australian Cancer Incidence and Mortality (ACIM) books: Acute myeloid leukaemia (AML). Specific data used were from Table A3.4, Cancer in Australia 2017, Supplementary tables, Chapter 3 Incidence of cancer, February 2017, accessed at: <https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2017/data>

³ Schneider F, Hoster E, Unterhalt M, Schneider S, Dufour A et al. Age-Dependent Frequencies of NPM-1/FLT3-ITD Mutations in Patients with Normal Karyotype AML. *Blood* 2008;112:2531

⁴ Levis M. *Hematology Am Soc Hematol Educ Program*. 2013;2013:220-6. doi: 10.1182/asheducation-2013.1.220.

resubmission assumed that ■% of midostaurin used in consolidation therapy as inpatients would be dispensed through the PBS).

- 6.32 In its November 2017 consideration, the PBAC had considered that the model time horizon of 50 years was not clinically plausible and that more reasonable time horizons would be 25 years in the group of patients aged ≥ 60 years, and 40 years in the group < 60 years of age (paragraph 7.17, November 2017 midostaurin PSD). The resubmission revised the time horizons, consistent with the PBAC's advice. This only had a minor impact on the cost effectiveness of midostaurin as most patients had died within the modelled time horizon.
- 6.33 Compared with the previous submission, the economic model was revised so that patients aged ≥ 60 years had a ■% lower likelihood of receiving SCTs and consequently a higher likelihood of receiving maintenance therapy than the younger cohort. This was appropriate.
- 6.34 In November 2017, the PBAC had considered that the incidence of chronic GVHD was underestimated in patients who were more than one year post-SCT (paragraphs 6.37 and 7.16, November 2017 midostaurin PSD). To address this, the resubmission revised the proportion of patients with chronic GVHD from ■% to ■%. The ESC advised that this was appropriate.
- 6.35 In its November 2017 consideration of midostaurin, the PBAC had considered that the utilities, sourced from an unpublished study by Hensen et al 2017, were not adequately justified and were implausibly high in the maintenance health state and the two post-SCT health states (paragraphs 7.16 and 6.37, November 2017 midostaurin PSD). To address this, the resubmission presented revised utility weights (for some health states) based on expert clinical opinion from a sample of clinicians who were presented with:
- utility weights as reported by Hensen et al 2017 (i.e. those used in the November 2017 submission);
 - alternative utility weights derived based on clinical opinion and applied in the midostaurin National Institute for Health and Care Excellence (NICE) application (no further information was provided on how these were derived); and
 - Australian population norms for utility weights by age based on EQ-5D-3L and EQ-5D-5L scores.
- 6.36 Based on clinical opinion, the resubmission acknowledged that the utility weights applied in the maintenance and post-SCT health states were too high in the November 2017 economic model. The revised utility weights are shown in Table 9, and were based on:
- for 'first year post-SCT' and 'post-SCT after 1st year with complications (GVHD)' the average of Hensen et al 2017 and the NICE estimates were applied, based on clinical opinion; and
 - for 'maintenance' and 'post-SCT after 1st year without complications' the utility

values were lowered so that they were no higher than the age-specific Australian population norms. The resubmission calculated that these were [REDACTED] in patients aged ≥ 60 years and [REDACTED] in patients aged < 60 years.

Table 8: Utility weights applied in the economic model (not all health states are shown)

Health state	Nov 2017	Current resubmission (March 2018)	Method used to derive value in resubmission	Pre-PBAC response ^b
Induction	0.16	0.16	Unchanged from Nov 2017	[REDACTED]
Consolidation	0.57	0.57	Unchanged from Nov 2017	[REDACTED]
Maintenance	[REDACTED]	[REDACTED] for patients aged < 60 [REDACTED] for patients aged ≥ 60	Capped at age-adjusted population norms	[REDACTED]
In remission but not on treatment ^a	[REDACTED]	[REDACTED] for patients aged < 60 [REDACTED] for patients aged ≥ 60	Capped at age-adjusted population norms	[REDACTED]
First year post-SCT	[REDACTED]	[REDACTED]	Midway between Hensen & NICE	[REDACTED]
Post-SCT after 1st year without complications	[REDACTED]	[REDACTED] for patients aged < 60 [REDACTED] for patients aged ≥ 60	Capped at age-adjusted population norms	[REDACTED] if aged < 60 [REDACTED] if aged ≥ 60
Post-SCT after 1st year with complications (GVHD)	[REDACTED]	[REDACTED]	Midway between Hensen & NICE	[REDACTED]
Relapsed refractory disease	[REDACTED]	[REDACTED]	Unchanged from Nov 2017	0.51

Source: Table 6.9, p 46 of the submission.

^a This is a temporary health state designed to reflect the period in which patients are being conditioned to receive SCT or are waiting for haematological recovery before commencing maintenance treatment.

^b Values that were used in the multivariate sensitivity analyses presented in the ESC advice (per Table 12) and accepted in the pre-PBAC response.

6.37 No further information was provided in the resubmission regarding the number of clinicians surveyed, nor whether the utility weights chosen by the clinicians were validated (other than by comparison with Australian population norms). Justifications presented in the resubmission did not provide a clear rationale in relation to why an average of Hensen et al 2017 and NICE utilities were used on some occasions, but not others. Further, the utility weights applied in some states equalled the Australian population norms which may be too high. For example, it may not be clinically plausible to assume that patients on maintenance therapy for AML have the same health as the average Australian of a similar age. The ESC considered that the choice of utility weights applied in the base case was not adequately justified in the resubmission, and the assumption that utility weights in certain health states would be as high as Australian population norms was optimistic. The pre-PBAC response accepted the alternative utility weights proposed by ESC, but claimed that these were selectively chosen and therefore presented a ‘worst-case’ scenario.

6.38 The key drivers of the economic model are presented in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Proportion of patients aged ≥ 60 years	32%, unchanged from previous submission.	High, favours midostaurin Likely underestimated. Inconsistent with assumptions applied in the financial estimates, where █-█% of the eligible population were assumed to be ≥ 60 years. This value was changed to █% in the pre-PBAC response.
Number of cycles of consolidation chemotherapy in the placebo arm	Maximum of 4, unchanged from previous submission.	Unclear, favours midostaurin The November 2017 PBAC had considered that in Australian clinical practice, many patients receive up to 2 cycles of consolidation, rather than up to 4 cycles as assumed in the submission.
Utilities	Per above	Moderate, favours midostaurin

Source: compiled during the evaluation

6.39 The results of the stepped economic analysis are presented in the table below.

Table 10: Stepped economic evaluation – from resubmission

Step	< 60 years			≥ 60 years			Weighted population (32% patients aged ≥ 60 years)		
	Mido	Placebo	Δ	Mido	Placebo	Δ	Mido	Placebo	Δ
Step 1: November 2017 sensitivity analyses with population split into age groups									
Costs	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█
LYs gained	█	█	█	█	█	█	█	█	█
QALYs gained	█	█	█	█	█	█	█	█	█
ICER/LY			\$█			\$█			\$█
ICER/QALY			\$█			\$█			\$█
Step 2: Separation of cohorts by age and correction of errors ^a									
Costs	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█
LYs gained	█	█	█	█	█	█	█	█	█
QALYs gained	█	█	█	█	█	█	█	█	█
ICER/LY			\$█			\$█			\$█
ICER/QALY			\$█			\$█			\$█
Step 3: Application of a time horizon of 40 years in < 60 year olds; 25 years in ≥ 60 year olds (instead of 50 years)									
Costs	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█
LYs gained	█	█	█	█	█	█	█	█	█
QALYs gained	█	█	█	█	█	█	█	█	█
ICER/LY			\$█			\$█			\$█
ICER/QALY			\$█			\$█			\$█
Step 4: Revision of the proportion of patients undergoing consolidation therapy as inpatients (10% to 90%)									
Costs	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█
LYs gained	█	█	█	█	█	█	█	█	█
QALYs gained	█	█	█	█	█	█	█	█	█
ICER/LY			\$█			\$█			\$█
ICER/QALY			\$█			\$█			\$█
Step 5: Revision of the proportion of patients with GVHD post-SCT (█% to █%)									
Costs	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█

Step	< 60 years			≥ 60 years			Weighted population (32% patients aged ≥ 60 years)		
	Mido	Placebo	Δ	Mido	Placebo	Δ	Mido	Placebo	Δ
LYs gained	■	■	■	■	■	■	■	■	■
QALYs gained	■	■	■	■	■	■	■	■	■
ICER/LY			\$■			\$■			\$■
ICER/QALY			\$■			\$■			\$■
Step 6: Incorporation of revised utility weights									
Costs	\$■	\$■	\$■	\$■	\$■	\$■	\$■	\$■	\$■
LYs gained	■	■	■	■	■	■	■	■	■
QALYs gained	■	■	■	■	■	■	■	■	■
ICER/LY			\$■			\$■			\$■
ICER/QALY			\$■			\$■			\$■
Step 7: Incorporation of a lower proportion of SCT and higher likelihood on maintenance in the older population									
Costs	\$■	\$■	\$■	\$■	\$■	\$■	\$■	\$■	\$■
LYs gained	■	■	■	■	■	■	■	■	■
QALYs gained	■	■	■	■	■	■	■	■	■
ICER/LY			\$■			\$■			\$■
ICER/QALY			\$■			\$■			\$■
Step 8: Application of a ■% rebate on the cost of maintenance therapy									
Weighted costs	\$■	\$■	\$■	\$■	\$■	\$■	\$■	\$■	\$■
Weighted LYGs	■	■	■	■	■	■	■	■	■
Weighted QALYs	■	■	■	■	■	■	■	■	■
ICER/LY			\$■			\$■			\$■
ICER/QALY			\$■			\$■			\$■

Source: p52-72 of the resubmission, the 'Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018' workbook, and the 'Midostaurin model FLT3 mutation positive AML July 2018' TreeAge Pro file

GVHD = graft versus host disease; ICER = incremental cost effectiveness ratio; LY = life years; QALY = quality adjusted life years; SCT = stem cell transplant

^a The resubmission identified and rectified several errors in the way in which transition probabilities were applied in the economic model November 2017 submission.

6.40 Based on the cost-effectiveness in the two cohorts, the resubmission presented a weighted ICER for the entire PBS population, assuming that 32% of the patients would be aged ≥ 60 years. The results are presented in the table below.

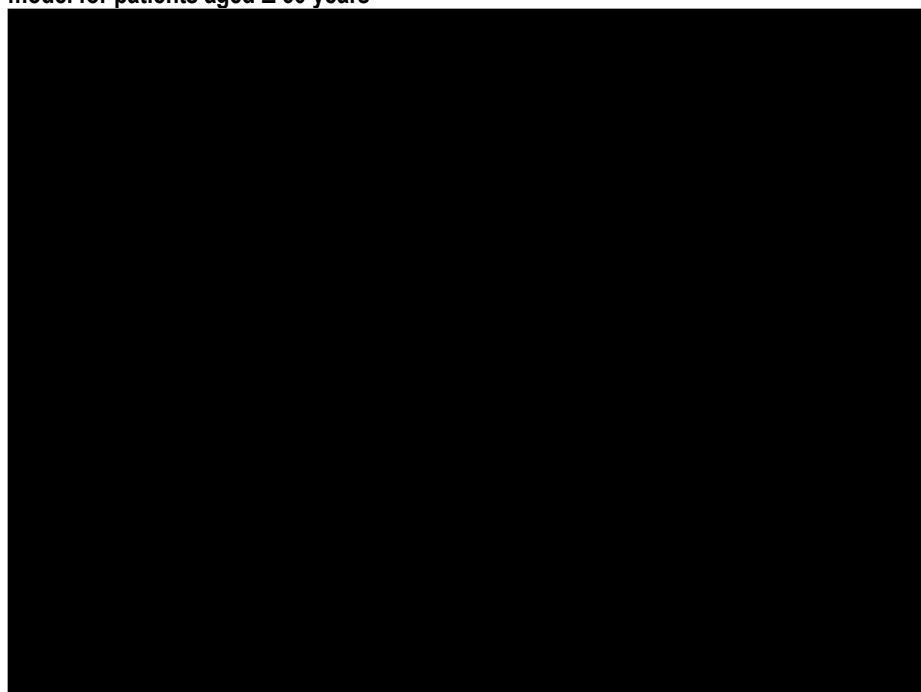
Table 11: Results of the stepped economic evaluation

Step and component	Midostaurin	Placebo	Increment
July 2018 base case – from resubmission (weighted population – 32% patients aged ≥ 60 years)			
Weighted costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Weighted LYs gained	[REDACTED]	[REDACTED]	[REDACTED]
Weighted QALYs gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/LY gained			\$ [REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
November 2017 base case			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs gained	[REDACTED]	[REDACTED]	[REDACTED]
QALYs gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/LY gained			\$ [REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]

Source: Table 3.8-1 of the November 2017 submission and p52-72 of the resubmission and the 'Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018' workbook

6.41 Noting that the PBAC had advised that the impact of lower comparative effectiveness in the older age group should be adequately incorporated in the economic model (paragraph 7.10, November 2017 midostaurin PSD), the resubmission presented a comparison of the modelled survival curves for the older population in the November 2017 submission and the resubmission (Figure 2).

Figure 2: Comparison of modelled survival curves generated by the November 2017 model and the resubmission model for patients aged ≥ 60 years



Source: p52-72 of the resubmission, the 'Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018' workbook

6.42 Sensitivity analyses conducted by the resubmission and during the evaluation are presented in the table below.

Table 12: Results of sensitivity analyses – based on base case proposed in resubmission

	Population aged < 60 years			Population aged ≥ 60 years			Weighted population	
	Δ costs	Δ QALY	ICER	Δ costs	Δ QALY	ICER	ICER	% change
Base case resubmission	\$████	██	\$████	\$████	██	\$████	\$████	N/A
Univariate sensitivity analyses								
Scenario 1: Proportion of patients aged ≥ 60 years (base case = 32%)								
i) Increased to █%	\$████	██	\$████	\$████	██	\$████	\$████	█%
ii) Increased to █%	\$████	██	\$████	\$████	██	\$████	\$████	█%
ii) Increased to █%	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 2: Utility weight in 'maintenance' state (base case = █ for < 60; █ for ≥ 60)								
█ in both cohorts	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 3: Utility weight in 'in remission but not on treatment' state (base case = █ for < 60; █ for ≥ 60)								
█ in both cohorts	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 4: Utility weight in 'in first-year post-SCT' state (base case = █)								
█ in both cohorts	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 5: Utility weight in the 'post-SCT after 1st year with complications i.e., GVHD' stage (base case = █)								
█ in both cohorts	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 6: Utility weight in the 'relapsed of refractory disease' stage (base case = █)								
█ in both groups	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 7: Disutility for additional AEs (base case = 0)								
█ in both groups	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 8: Rebate on cost of maintenance (base case = █%)								
i) Increased to █%	\$████	██	\$████	\$████	██	\$████	\$████	█%
ii) Increased to █%	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 9: Rebate on the cost of induction and consolidation (base case = █%)								
i) Increased to █%	\$████	██	\$████	\$████	██	\$████	\$████	█%
ii) Increased to █%	\$████	██	\$████	\$████	██	\$████	\$████	█%
Multivariate sensitivity analyses								
Scenario 10 (2+3+4+5)	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 11 [1i(█%≥60y)+2+3+4+5]	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 12 [1ii(█%≥60y)+2+3+4+5]	\$████	██	\$████	\$████	██	\$████	\$████	█%
Scenario 13 [1iii(█%≥60y)+2+3+4+5]	\$████	██	\$████	\$████	██	\$████	\$████	█%

Source: p52-72 of the resubmission, the ‘Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018’ workbook, and the ‘Midostaurin model FLT3 mutation positive AML July 2018’ TreeAge Pro file

- 6.43 Varying the utility weights in the post-SCT and maintenance health states to reflect those in the Cressman 2016 study (or midostaurin’s NICE submission) (i.e. scenarios 3 to 6 in the table above) had a moderate impact on the ICER.
- 6.44 The sensitivity analyses indicated that the biggest driver of the cost-effectiveness of midostaurin was the proportion of patients in the older population (resubmission base case = 32%). The ESC considered that this assumption was likely to be a significant underestimate and noted that increasing this proportion to the acceptable range of █-█% increased the weighted ICER to \$45,000/QALY - \$105,000/QALY.
- 6.45 The ESC noted that multivariate analyses (scenarios 11, 12 and 13) incorporating alternative utility weights (in the maintenance, remission and post-SCT health states) and assuming that █, █ and █% patients would be aged ≥ 60 years when commencing PBS-subsidised midostaurin, resulted in weighted ICERs of \$75,000/QALY - \$105,000/QALY, \$75,000/QALY - \$105,000/QALY and \$75,000/QALY - \$105,000/QALY, respectively. Taking into consideration the evidence presented in the resubmission, the ESC advised that the ICER was likely to be in this range, and noted that it was significantly higher than the acceptable cost-effective ICER of approximately \$45,000/QALY - \$75,000/QALY recommended by the PBAC in its November 2017 consideration of midostaurin (paragraph 7.20, November 2017 midostaurin PSD). The rebate required on either the cost of maintenance therapy (resubmission base case = █%) or on the cost of maintenance as well as induction and consolidation therapy (base case = 0%) under scenarios 11, 12 and 13 has been explored in the table below.

Table 13: Results of sensitivity analyses – based on base case proposed in resubmission

Scenario	Weighted ICER	Rebate on cost of maintenance therapy ^a		Rebate on cost of induction, consolidation and maintenance therapy ^b	
		% rebate required	Resultant ICER	% rebate required	Resultant ICER
Scenario 11: MV with █% older patients (1i+2+3+4+5)	\$█	█%	\$█	█%	\$█
Scenario 12: MV with █% older patients (1ii+2+3+4+5)	\$█	█%	\$█	█%	\$█
Scenario 13: MV with █% older patients (1iii+2+3+4+5)	\$█	█%	\$█	█%	\$█

^a In the ‘Inputs’ sheet of the ‘Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018’ workbook, cell B46 was changed to the desired rebate percentage

^b In the ‘Inputs’ sheet of the ‘Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018’ workbook, cell B46 was changed to the desired rebate percentage. Additionally, the same rebate percentage was applied to cell B54.

Source: p52-72 of the resubmission, the ‘Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018’ workbook, and the ‘Midostaurin model FLT3 mutation positive AML July 2018’ TreeAge Pro file

- 6.46 The ESC noted that assuming █-█% of eligible patients were aged above 60 years, and with more realistic utility weights for certain health states, a rebate in the range of █-█% on the on the cost of maintenance therapy, or one in the range of █-█

% on overall cost of therapy, would be required to generate an ICER of approximately \$45,000/QALY - \$75,000/QALY.

- 6.47 The pre-PBAC response noted that when the proportion of eligible patients aged ≥ 60 years was increased from 32% to [redacted] and the revised utility weights applied in the ESC multivariate sensitivity analysis were incorporated, the ICER increased from \$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY. The pre-PBAC response therefore offered a rebate of [redacted] on the overall cost of therapy, which reduced this ICER from \$75,000/QALY - \$105,000/QALY to \$45,000/QALY - \$75,000/QALY, i.e. below \$45,000/QALY - \$75,000/QALY, which the PBAC previously considered would be acceptably cost-effective for this drug in this condition (paragraph 7.20, November 2017 midostaurin PSD).
- 6.48 The table below shows the results of the revised base case proposed in the pre-PBAC response which revised: the proportion of patients assumed to be aged ≥ 60 years (from 32% to [redacted]); the utilities (per Table 8); and the rebate applied (from [redacted] in maintenance to [redacted] in all settings).

Table 14: Results of the stepped economic evaluation proposed in pre-PBAC response

Step and component	Midostaurin	Placebo	Increment
Weighted costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Weighted LYs gained	[redacted]	[redacted]	[redacted]
Weighted QALYs gained	[redacted]	[redacted]	[redacted]
Incremental cost/LY gained			\$ [redacted]
Incremental cost/QALY gained			\$ [redacted]

Source: 'Dynamic links – Midostaurin – July 2018 – pre-PBAC response' workbook

The redacted table shows an ICER in the range of \$45,000/QALY - \$75,000/QALY.

Drug cost/patient

- 6.49 The resubmission estimated an average cost of midostaurin treatment per patient to be \$ [redacted] and \$ [redacted] in patients aged <60 years and those ≥ 60 years, respectively, based on the average number of packs dispensed in the RATIFY trial and the midostaurin price proposed in the resubmission ([redacted] % rebate on maintenance therapy). Maintenance therapy was the biggest component of this cost (\$ [redacted] and \$ [redacted] in patients aged <60 years and those ≥ 60 years, respectively).
- 6.50 Using the higher rebate proposed in the pre-PBAC response ([redacted] % rebate in all treatment settings), the cost of midostaurin treatment per patient was estimated to be \$ [redacted] and \$ [redacted] in patients aged <60 years and those ≥ 60 years, respectively.
- 6.51 The November 2017 submission estimated that the average cost of midostaurin treatment per patient would be \$ [redacted] (costs were not reported by age group in the previous submission).

Estimated PBS usage & financial implications

- 6.52 This resubmission was not considered by DUSC.
- 6.53 As per the November 2017 submission, the resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing midostaurin for the treatment of FLT3 positive AML on the PBS. A number of changes were made to the financial estimates to address the previous concerns raised by the ESC and PBAC.
- 6.54 In its November 2017 consideration of midostaurin, the PBAC had noted that a Western Australian registry of patients with AML⁵ reported that of the █████ patients in the cohort, █████ recorded a positive FLT3 test, equivalent to █████% of the cohort (paragraph 6.48, November 2017 midostaurin PSD). The resubmission argued that this estimate was higher than the rates reported in the literature, which range up to 34%⁶, and was uncertain given the relatively small size of the registry. The resubmission therefore assumed a FLT3 positivity of █████%, i.e. average of 34% and █████%. The PSCR indicated that the sponsor was willing to consider the revision of the financial estimates to account for the assumption that █████%, instead of █████%, of Australian AML patients carried the FLT3 mutation. The ESC also advised that it might be appropriate to apply the Australian estimate of █████% in the financial estimates. However, the PBAC considered that █████% FLT3 positivity was an overestimate, noting that in the RATIFY trial, the proportion of patients who were preregistered for the trial who had a FLT3 mutation was 27% (896/3,277). Therefore, on balance of all the evidence presented, the PBAC advised that the estimates should assume a FLT3 positivity of 34%, i.e. as originally proposed by the November 2017 submission.
- 6.55 The proportion of AML patients, stratified by age, who would be fit for intensive chemotherapy was based on a Swedish AML registry⁷. This was unchanged from the previous submission. While this was a relatively large registry (n = 2,767) with data on AML patients from 1997 to 2005, the data collected were not stratified by FLT3 status, or any other AML subgroups. It was unclear whether the demographic composition of this study population would be applicable to the Australian AML population.
- 6.56 Uptake rates were assumed to be █████% in the first year of listing, increasing to █████% in Year 6 after listing of midostaurin in all patient groups, and were unchanged in the resubmission. Should midostaurin be recommended for listing, it would be a first targeted therapy for FLT3 positive AML on the PBS. As such, it could be expected that the uptake rate would be close to █████%, especially in the first 1-2 years of listing. The PSCR contended that uptake rates of █████%, even in younger patients, are

⁵ Gangatharan SA, Grove CS, P'ng S et al. Acute myeloid leukaemia in Western Australia 1991-2005: a retrospective population-based study of 898 patients regarding epidemiology, cytogenetics, treatment and outcome. *Internal Medicine Journal*. 2013;43(8): 903-911

⁶ Levis and Small 2003, Bacher, Haferlach et al. 2008, Levis 2011, Levis 2013

⁷ Juliusson G, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood* 2009; 113(18):4179-87

highly unlikely given that the likelihood of ongoing trial participation for de novo AML patients. The ESC advised that if the clinical trials are randomised for patients to not receive a FLT3 inhibitor, accrual will likely be low. The only clinical trials likely to recruit would need to have added value (i.e. another novel agent), and when such trials may occur is uncertain. The ESC therefore advised that the financial estimates should assume a [REDACTED] % uptake rate in the first six years of PBS listing. The pre-PBAC response proposed that the uptake rates be revised to [REDACTED] % in Year 1, followed by [REDACTED] in the subsequent years of listing (up to Year 6). The PBAC advised that the proposal in the pre-PBAC response was reasonable and an upper estimate.

- 6.57 The ESC considered that the increase in consolidation therapy to a maximum of four cycles, instead of a maximum of two cycles as per current clinical practice, increased the cost-offset from chemotherapy use in the placebo arm, resulting in an underestimation of the overall PBS expenditure of midostaurin.
- 6.58 The resubmission assumed that [REDACTED] and [REDACTED] grandfathered patients would commence PBS-subsidised midostaurin consolidation (cycle 1) and maintenance (cycle 1), respectively. These estimates were reasonable, based on the incidence (adjusted for 'chemotherapy fitness' as applied in the resubmission, ~[REDACTED]) and mortality-incidence ratio (~[REDACTED]) of FLT3 positive AML in Australia.
- 6.59 As per the November 2017 submission, the resubmission expected that 100% of the cost of induction therapy with midostaurin, and 10% of the cost of consolidation therapy, would be borne by hospital budgets.
- 6.60 The ESC noted that resubmission did not account for an increase in the cost of FLT3 testing, despite the PBAC previously anticipating that the listing of midostaurin would result in a minor increase in the MBS service volumes of FLT3 testing for AML (paragraph 7.6, November 2017 midostaurin PSD). The PSCR contended that the availability of midostaurin on the PBS would have negligible impact on rates of testing for FLT3 mutation.
- 6.61 The financial estimates presented in the resubmission were also revised during evaluation to rectify other errors identified in estimating (i) the number of patients receiving midostaurin in-hospital, and (ii) the cost of patients receiving chemotherapy in the placebo arm.

Table 15: Estimate of number of scripts dispensed and cost to PBS per year – per the resubmission

	2018	2019	2020	2021	2022	2023
Number of patients who will commence treatment with midostaurin	█	█	█	█	█	█
Packs of midostaurin 25 mg x 56 (1 pack per induction and consolidation cycle)	Hospital and PBS	█	█	█	█	█
	PBS only	█	█	█	█	█
Packs of midostaurin 25 mg x 112 (1 pack per maintenance cycle)	Hospital and PBS	█	█	█	█	█
	PBS only	█	█	█	█	█
Total PBS dispensed cost for midostaurin 25 mg x 56 (induction & consolidation) at published DPMQ	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total PBS dispensed cost for midostaurin 25 mg x 112 (maintenance) at published DPMQ	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total dispensed PBS cost for midostaurin (less co-payments)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net PBS expenditure on midostaurin (less █% rebate on maintenance therapy via proposed SPA)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net additional PBS costs for chemotherapy	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total financial implications for PBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total financial implications for PBS (assuming █% FLT3 positivity and █% uptake rate)^a	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Figures in this table were revised during evaluation after rectifying calculation errors in the incorporation of grandfathered patients and the calculation of the incremental cost of chemotherapy. These revisions were accepted in the PSCR.

^a In the 'Inputs' sheet of the 'Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018' workbook, cell B221 was changed to █% and cells B233-238 were changed to █%.

DPMQ = dispensed price per maximum quantity; PBS = Pharmaceutical Benefits Scheme; SPA = Special Pricing Agreement

Source: pp75-80 of resubmission and 'Dynamic links – Midostaurin for newly diagnosed FLT3 mutation positive AML – July 2018' workbook ('Inputs' and 'Financial estimates' sheets)

6.62 The resubmission estimated that less than 10,000 patients would be eligible for midostaurin treatment in the first year of listing, increasing to less than 10,000 by Year 6. The resubmission estimated a net PBS cost of approximately \$20 - \$30 million in the first year of listing, with a total of approximately more than \$100 million in the first six years of listing. The ESC noted that assuming █% FLT3 positivity and █% uptake rate, an estimated less than 10,000 patients would be eligible for midostaurin treatment in the first year of listing increasing to less than 10,000 by Year 6, with a total PBS cost of approximately more than \$100 million in the first six years of listing.

6.63 The pre-PBAC response updated the financial estimates to include: the higher rebate proposed (█% in all treatment settings); █% FLT3 positivity; and uptake rates of █% in Year 1 and █% in Years 2 to 6. The pre-PBAC response also presented an additional analysis that assumed █% of the PBS-eligible population were aged ≥ 60

years, consistent with the assumption applied in the pre-PBAC response's economic evaluation.

- 6.64 The financial estimates were most sensitive to the cost of midostaurin maintenance therapy, followed by the frequency of FLT3 positivity among newly diagnosed AML patients, the uptake rate of midostaurin, and the number of grandfathered patients.
- 6.65 In its November 2017, the ESC considered that there was potential for use of midostaurin as maintenance post-allograft, noting that such use is being explored with other FLT3 inhibitors in clinical trials, and occurred in the AMLSG 16-10 study (paragraph 6.48, November 2017 midostaurin PSD). While the resubmission proposed a written authority in the maintenance setting along with changes to the wording of the restriction to explicitly state that the patient must not have undergone a stem cell transplant, the ESC and PBAC advised that there remained a risk of leakage to the post-SCT population and also to patients with FLT3 wild-type AML.

Quality Use of Medicines (QUM)

- 6.66 No QUM issues were identified in the resubmission.

Financial Management – Risk Sharing Arrangements

- 6.67 In its November 2017 consideration of midostaurin, the PBAC had advised that a Risk Sharing Arrangement (RSA) with 100% rebate beyond the agreed subsidisation caps would be required to mitigate the risk of use beyond the proposed restriction and other uncertainties in the financial estimates (paragraph 7.20, November 2017 midostaurin PSD). The resubmission and the PSCR indicated the sponsor's willingness to enter into a RSA with the Commonwealth, however no details of the proposed RSA were provided in the resubmission.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) Authority Required listing of midostaurin for the treatment of FLT3 mutation positive AML. In reaching this outcome, the PBAC acknowledged the high unmet clinical need in the proposed PBS population and considered that midostaurin treatment improved outcomes in FLT3 positive AML patients. The PBAC noted that the majority of ESC and PBAC's advice at their October 2017 and November 2017 considerations of midostaurin, respectively, were appropriately incorporated by the resubmission. The PBAC also advised that midostaurin was acceptably cost-effective at the reduced price proposed in the resubmission's pre-PBAC response.
- 7.2 The PBAC recommended that the initial maintenance restriction be an Authority Required (in writing) listing and that the grandfather restriction for maintenance also be an Authority Required (in writing) restriction. The PBAC recommended that

induction, consolidation and continuation of maintenance treatment be Authority Required (telephone) benefits.

- 7.3 The PBAC recalled that the November 2017 submission was based on a direct randomised controlled trial comparing midostaurin versus placebo in the induction, consolidation, and maintenance phases of treatment in FLT3 mutation positive AML patients aged ≤ 59 years (RATIFY). The PBAC had considered that RATIFY was a mature, well-conducted trial with similar results with and without censoring for SCT.
- 7.4 The PBAC recalled that it had previously considered that the claim of superior comparative effectiveness of midostaurin versus placebo was reasonable, but that the magnitude of the incremental benefit was uncertain particularly in patients aged 60 years and older. The PBAC also recalled that it had previously considered that midostaurin was associated with inferior comparative safety versus placebo, but had advised that in the context of chemotherapy-induced morbidity and mortality, the additional toxicity with midostaurin treatment is relatively minor (paragraphs 7.8, 7.9 and 7.11 November 2017 midostaurin PSD). The PBAC advised that there was neither any new clinical evidence nor compelling justifications in the resubmission that changed its previous interpretation of the clinical evidence.
- 7.5 The PBAC recalled that at its November 2017 consideration of midostaurin, it had considered that the economic model was not sufficiently flexible to enable relevant sensitivity analyses to be conducted. The PBAC had been particularly concerned by the model's inability to assess the impact of the inputs and assumptions related to SCT eligibility, use of maintenance therapy, duration of treatment and, importantly, outcomes for patients aged 60 years and over. The PBAC was satisfied that the economic model presented in the resubmission addressed a majority of the concerns raised by the Committee at its November 2017 consideration of midostaurin.
- 7.6 The PBAC noted that the restructured model presented in the resubmission allowed the input parameters for the cohort of patients ≥ 60 years to be varied independently of those aged < 60 years. The PBAC advised that this was appropriate, as it allowed the assessment of the impact of various input parameters on the cost-effectiveness of midostaurin in the two age groups. The PBAC also noted that the resubmission assumed (i) a 2.5 fold higher risk of mortality in patients without SCT in the induction and consolidation, post-remission, and relapsed or refractory health states; (ii) a ■■■% lower likelihood of SCT; (iii) a corresponding higher likelihood of receiving maintenance therapy; and (iv) a higher age-adjusted background mortality rate in the older population, compared with those under 60 years of age. The PBAC advised that these changes were appropriate.
- 7.7 The PBAC noted that using the restructured model and more conservative input parameters for the older population, the resubmission presented a weighted ICER (base case = \$45,000/QALY - \$75,000/QALY) across the two populations stratified by age, assuming that 32% of patients in the PBS-eligible population would be ≥ 60 years of age. The PBAC noted that the ESC considered that this was an underestimate, and advised that about ■■■-■■■% of the PBS-eligible population was

likely to be ≥ 60 years of age. The PBAC also noted that this was the biggest driver of the cost-effectiveness of midostaurin. The pre-PBAC response proposed that an estimate of ■% be used in the economic model. The PBAC agreed with the pre-PBAC response, and advised that it was reasonable to assume that ■% of patients in the PBS-eligible population would be over the age of 60 years in the economic model and the financial estimates.

- 7.8 The PBAC noted that the resubmission had appropriately revised the time horizons to 25 years in the group of patients aged ≥ 60 years, and 40 years in the group < 60 years of age.
- 7.9 The PBAC noted ESC's advice regarding revised utility weights for certain health states. The PBAC also noted that the pre-PBAC response accepted the alternative utility weights proposed by ESC, but claimed that these were selectively chosen and therefore presented a 'worst-case' scenario.
- 7.10 The PBAC noted that increasing the proportion of eligible patients aged ≥ 60 years from 32% to ■% and incorporating the revised utility weights recommended by ESC increased the ICER from a base case to \$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY. The PBAC also noted that applying a rebate of ■% on the overall cost of therapy (in all treatment settings), as proposed in the pre-PBAC response, significantly reduced the ICER to a respecified base case of \$45,000/QALY - \$75,000/QALY, i.e. below \$45,000/QALY - \$75,000/QALY which the PBAC previously considered would be acceptably cost-effective for this drug in this condition (paragraph 7.20, November 2017 midostaurin PSD).
- 7.11 The PBAC noted that the resubmission assumed that patients aged ≥ 60 years had a ■% lower likelihood of receiving SCTs than the younger cohort, and consequently a higher likelihood of receiving maintenance therapy. The PBAC noted that assuming the SCT rate would be ■% or ■% lower in the older population (compared with the younger cohort) decreased the ICER from the pre-PBAC base case of \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY. The PBAC therefore advised that midostaurin was likely to be more cost-effective if initial treatment resulted in a greater proportion of SCTs in the older population.
- 7.12 The PBAC noted that the resubmission maintained the use of up to four cycles of consolidation therapy in the placebo arm, despite its previous advice that the current standard treatment (i.e. without PBS-subsidised access to midostaurin) for patients is two cycles, and potentially only one if the patient is proceeding to an allograft (paragraph 4.8, November 2017 midostaurin PSD). The pre-PBAC response argued that there was no rationale to support the suggestion that standard practice in relation to number of cycles of consolidation chemotherapy administered will change as a consequence of availability of midostaurin, apart from the increased use due to higher rates of patients achieving remission after induction, which is already captured in the modelled economic evaluation. The PBAC considered that this assumption was nevertheless a departure from current practice, and could have potentially resulted in the costs of comparator treatments being overestimated in

the economic model and financial estimates. The PBAC acknowledged that this had limited impact on the ICER, and advised that this should be appropriately adjusted for while calculating the cost-offsets from the comparator arm in the financial estimates.

- 7.13 Taking into account all the evidence presented in the resubmission and the reduced price across all treatment settings proposed in the pre-PBAC response, the PBAC advised that midostaurin was acceptably cost-effective at the respecified pre-PBAC base case of \$45,000/QALY - \$75,000/QALY, noting the unmet clinical need in patients with an uncommon disease with high rates of fatality.
- 7.14 The PBAC noted that there was some uncertainty regarding the proportion of Australian AML patients who are FLT3 positive. While the original submission assumed that FLT3 positivity was 34%, based on the literature⁸, the ESC preferred █%, based on a small Australian registry⁹. The PBAC indicated that █% FLT3 positivity was potentially an overestimate, noting that in the RATIFY trial 27% of patients who preregistered for the trial had an FLT3 mutation (896/3,277). Therefore, on balance of all the evidence presented, the PBAC considered that the financial estimates should assume a FLT3 positivity rate of 34%, i.e. as originally proposed by the November 2017 submission.
- 7.15 The PBAC noted ESC's advice that uptake rates were likely to be close to █%, but considered that uptake rates of █% in Year 1, followed by █% in the subsequent years of listing (up to Year 6), as proposed by the pre-PBAC response, were reasonable and an upper estimate.
- 7.16 The PBAC also advised that the financial estimates be revised to take into account cost-offsets from up to two, instead of up to four, cycles of consolidation therapy in the placebo arm. The PBAC further advised that the financial estimates should assume that █% of patients would be aged ≥ 60 years, consistent with the economic model.
- 7.17 The PBAC maintained that there was a high risk of leakage into the post-transplant population, and advised that an RSA with a █% rebate above the subsidisation caps, based on the financial estimates after adjusting for the parameters described above, would be required to mitigate the risk of leakage beyond the PBS-eligible population.
- 7.18 The PBAC advised that the Early Supply Rule should not apply to the listing of midostaurin.
- 7.19 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* midostaurin should not be treated as interchangeable on an individual patient basis with any other drugs.

⁸ Levis and Small 2003, Bacher, Haferlach et al. 2008, Levis 2011, Levis 2013

⁹ Gangatharan SA, Grove CS, P'ng S et al. Acute myeloid leukaemia in Western Australia 1991-2005: a retrospective population-based study of 898 patients regarding epidemiology, cytogenetics, treatment and outcome. *Internal Medicine Journal*. 2013;43(8): 903-911

7.20 The PBAC advised that midostaurin is not suitable for prescribing by nurse practitioners.

7.21 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, restriction, manner of administration, form	Maximum quantity (Packs)	Number of repeats	Proprietary name and manufacturer
MIDOSTAURIN 25mg capsules, 1x56	1	2	Rydapt® Novartis Pharmaceuticals Pty Ltd

Category / Program:	Section 100 – Highly Specialised Drugs Program (Public and Private hospitals)
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Induction / Consolidation therapy
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must not have received a prior line of intensive chemotherapy for this condition prior to standard intensive remission induction therapy; AND The condition must be internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation positive before initiating this drug for this condition; AND The condition must not be acute promyelocytic leukaemia AND The treatment must be in combination with standard intensive remission induction or consolidation chemotherapy for this condition</p>
Prescriber Instructions	<p>A maximum of six cycles will be authorised under this restriction in a lifetime. Standard intensive remission induction combination chemotherapy must include cytarabine and an anthracycline. The FLT3 ITD or TKD mutation test result and date of testing must be provided at the time of application. This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting. Progressive disease monitoring via a complete blood count must be taken at the end of each cycle. If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles. Progressive disease is defined as the presence of any of the following:</p> <ul style="list-style-type: none"> ○ Leukaemic cells in the CSF;

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	<ul style="list-style-type: none"> ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; ○ Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause; ○ Extramedullary leukaemia. <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p>
Administrative Advice	<p>No applications for increased maximum quantities will be authorised.</p> <p>No applications for increased repeats will be authorised.</p>

Name, restriction, manner of administration, form	Maximum quantity (Packs)	Number of repeats	Proprietary name and manufacturer
MIDOSTAURIN 25mg capsules, 2x56	1	2	Rydapt® Novartis Pharmaceuticals Pty Ltd

Category / Program:	Section 100 – Highly Specialised Drugs Program (Public and Private hospitals)
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Maintenance therapy – initial treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition;</p> <p>AND</p> <p>Patient must not have experienced disease progression whilst receiving PBS-subsidised treatment with this drug for this condition;</p> <p>AND</p> <p>Patient must have demonstrated complete remission after induction and consolidation chemotherapy plus midostaurin</p> <p>AND</p> <p>Patient must not be undergoing or have undergone a stem cell transplant</p> <p>AND</p> <p>The condition must have been internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation positive before initiating this drug for this condition</p>
Prescriber Instructions	<p>A maximum of 3 cycles will be authorised under this restriction in a lifetime</p> <p>Progressive disease monitoring via a complete blood count must be taken at the end of each cycle.</p> <p>If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.</p> <p>Progressive disease is defined as the presence of any of the following:</p> <ul style="list-style-type: none"> ○ Leukaemic cells in the CSF; ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; ○ Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration

	<p>or another cause;</p> <ul style="list-style-type: none"> ○ Extramedullary leukaemia. <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form;</p> <p>(2) a completed Acute myeloid leukaemia PBS Authority Application - Supporting Information Form; and</p> <p>(3) a declaration that the patient is not undergoing or has not undergone a stem cell transplant; and</p> <p>(4) a declaration that the patient does not have progressive disease; and</p> <p>(5) a copy of a recent bone marrow biopsy report demonstrating that the patient is in complete remission; and</p> <p>(6) a copy of the pathology test demonstrating that the condition was FMS tyrosine kinase 3 (FLT3) (ITD or TKD) mutation positive prior to commencing midostaurin.</p>
Administrative Advice	<p>No applications for increased maximum quantities will be authorised.</p> <p>No applications for increased repeats will be authorised.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001.</p>

Name, restriction, manner of administration, form	Maximum quantity (Packs)	Number of repeats	Proprietary name and manufacturer
MIDOSTAURIN 25mg capsules, 2x56	1	1	Rydapt® Novartis Pharmaceuticals Pty Ltd

Category / Program:	Section 100 – Highly Specialised Drugs Program (Public and Private hospitals)
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Maintenance therapy - grandfathering treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have received non-PBS treatment with this drug for this condition prior to [Date to be finalised] AND Patient must be receiving treatment with this drug for this condition at the time of application AND Patient must not have experienced disease progression whilst being treated with this drug for

	<p>this condition; AND Patient must have demonstrated complete remission after induction and consolidation chemotherapy plus midostaurin; AND Patient must not be undergoing or have undergone a stem cell transplant; AND The condition must have been internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation positive before initiating this drug for this condition</p>
<p>Prescriber Instructions</p>	<p>A maximum of 2 cycles will be authorised under this restriction in a lifetime A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the maintenance therapy continuing treatment criteria. Progressive disease monitoring via a complete blood count must be taken at the end of each cycle. If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles. Progressive disease is defined as the presence of any of the following:</p> <ul style="list-style-type: none"> ○ Leukaemic cells in the CSF ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy ○ Greater than 5% blasts in the marrow not attributable to bone marrow regeneration or another cause ○ Extramedullary leukaemia. <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) a completed authority prescription form; (2) a completed Acute myeloid leukaemia PBS Authority Application - Supporting Information Form; and (3) a declaration that the patient is not undergoing or has not undergone a stem cell transplant; and (4) a declaration that the patient does not have progressive disease; (5) a copy of a recent bone marrow biopsy report demonstrating that the patient is in complete remission; and (6) a copy of the pathology test demonstrating that the condition was FMS tyrosine kinase 3 (FLT3) (ITD or TKD) mutation positive prior to commencing midostaurin.
<p>Administrative Advice</p>	<p>No applications for increased maximum quantities will be authorised. No applications for increased repeats will be authorised.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826</p>

	HOBART TAS 7001.
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Name, restriction, manner of administration, form	Maximum quantity (Packs)	Number of repeats	Proprietary name and manufacturer
MIDOSTAURIN 25mg capsules, 2x56	1	2	Rydapt® Novartis Pharmaceuticals Pty Ltd
Category / Program:	Section 100 – Highly Specialised Drugs Program (Public and Private hospitals)		
PBS Indication:	Acute myeloid leukaemia (AML)		
Treatment phase:	Maintenance therapy – continuing treatment		
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined		
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition under the initial maintenance or the initial maintenance grandfathering treatment restriction;</p> <p>AND</p> <p>Patient must not have developed disease progression whilst being treated with this drug for this condition;</p> <p>AND</p> <p>Patient must not be undergoing or have undergone a stem cell transplant</p>		
Prescriber Instructions	<p>A maximum of 9 cycles will be authorised under this restriction in a lifetime.</p> <p>Progressive disease monitoring via a complete blood count must be taken at the end of each cycle.</p> <p>If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.</p> <p>Progressive disease is defined as the presence of any of the following:</p> <ul style="list-style-type: none"> ○ Leukaemic cells in the CSF ○ Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy ○ Greater than 5% blasts in the marrow not attributable to bone marrow regeneration or another cause ○ Extramedullary leukaemia. <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p>		
Administrative Advice	<p>No applications for increased maximum quantities will be authorised.</p> <p>No applications for increased repeats will be authorised.</p>		

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Novartis is pleased with this recommendation by the PBAC. This is an important outcome for patients with this rare condition.