

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

1 Purpose of Application

- 1.1 The submission requested for a Section 100 (Efficient funding of Chemotherapy - Public and Private hospital) listing for midostaurin for treatment of FMS-like tyrosine kinase-3 (FLT3) mutation positive acute myeloid leukaemia (AML).

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 (usually cytarabine and an anthracycline).
Intervention	Midostaurin (Rydapt [®]), 50 mg BID (plus chemotherapy)
Comparator	Placebo (chemotherapy alone)
Outcomes	<ul style="list-style-type: none"> • Overall survival (OS) • 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 is superior to placebo (standard medical management) at increasing complete remission rates, sustaining event free and disease free survival and significantly improving overall survival.

Source: Table 1.1-1, p4 of the submission

2 Requested listing

- 2.1 The requested listing is presented below. Changes to the requested listing following PBAC's advice are added in italics and crossed out with strikethrough.

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Name, restriction, manner of administration, form	Maximum quantity	No. of repeats initial	No. of repeats cont.	Dispensed price for maximum quantity		Proprietary name and manufacturer
				Public	Private	
INDUCTION / CONSOLIDATION Midostaurin, capsules, 25 mg	56 capsules	4	0 2	██████	██████	Rydapt® Novartis Pharmaceuticals Pty Ltd
CONSOLIDATION Midostaurin, capsules, 25 mg	56 capsules	4	3 (2)	██████	██████	
MAINTENANCE - INITIAL Midostaurin, capsules, 25 mg	112 capsules	4	3 (2)	██████	██████	
MAINTENANCE - CONTINUING Midostaurin, capsules, 25 mg	112 capsules	4	3 (8)	██████	██████	
Category / Program:	Section 100 – Public and Private hospitals					
PBS Indication:	Acute myeloid leukaemia (AML)					
Treatment phase:	Induction / Consolidation					
Restriction:	Authority required – In Writing Telephone					
Clinical criteria:	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; AND Condition must be FMS tyrosine kinase 3 (FLT3) mutation positive at diagnosis; AND Patient must be considered eligible for standard intensive remission induction chemotherapy; AND Patient must be aged ≤50 years					
Prescriber Instructions	<ul style="list-style-type: none"> • Up to 2 3 cycles will be authorised <i>initially, with a maximum of six in total possible under this phase.</i> • Patients with acute promyelocytic leukaemia are not eligible for treatment. • Evidence of a FLT3 ITD or TKD mutation must be supplied, <i>including the date of the test and the result.</i> • 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. • Standard intensive remission induction combination chemotherapy must include cytarabine and an anthracycline; or cytarabine and fludarabine for patients unable to tolerate an anthracycline. 					

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Category / Program:	Section 100—Public and Private hospitals
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Consolidation
Restriction:	Authority required—In Writing
Clinical criteria:	<p>Patient must have a diagnosis of acute myeloid leukaemia; AND Condition must be FMS tyrosine kinase 3 (FLT3) mutation positive at diagnosis; AND Patient must have received standard intensive remission induction combination chemotherapy for the treatment of AML as initial treatment; AND Patient must have received midostaurin therapy in the induction treatment phase as a hospital inpatient; AND Patient must have demonstrated complete remission or complete remission with incomplete haematologic recovery after up to two cycles of induction chemotherapy plus midostaurin; AND Patient does not have progressive disease.</p>
Prescriber Instructions	<ul style="list-style-type: none"> ● Up to 4 cycles will be authorised. ● Patients with acute promyelocytic leukaemia are not eligible for treatment. ● FLT3 mutation status includes patients with an ITD or TKD mutation. ● Standard intensive remission induction combination chemotherapy must include cytarabine and an anthracycline or cytarabine and fludarabine for patients unable to tolerate an anthracycline. ● A complete remission and complete remission with partial haematologic recovery is defined as a bone marrow blast count of $\leq 5\%$ with or without platelet level recovery to at least $100 \times 10^9/L$. ● Progressive disease is defined as the presence of: <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 ○ $>5\%$ blasts in the marrow not attributable to marrow regeneration or another cause ○ Extramedullary leukaemia.

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Category / Program:	Section 100 – Public and Private hospitals
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Continuation therapy (Maintenance therapy) – Initial
Restriction:	Authority required – In Writing
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must not have progressive disease; AND Patient must be ineligible for a stem cell transplant not be planned for, or have undergone, a stem cell transplant in first remission; OR Patient must be awaiting a stem cell transplant <i>in first remission.</i>
Prescriber Instructions	<ul style="list-style-type: none"> • Up to 12-3 cycles of treatment will be authorised. • 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 of midostaurin therapy. • Progressive disease is defined as the presence of any of the following: <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 ○ >5% blasts in the marrow not attributable to bone marrow regeneration or another cause ○ Extramedullary leukaemia.

Category / Program:	Section 100 – Public and Private hospitals
PBS Indication:	Acute myeloid leukaemia (AML)
Treatment phase:	Continuation therapy (Maintenance therapy) – Continuing
Restriction:	Authority required – Telephone
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must not have progressive disease; AND Patient must not be planned for, or have undergone, a stem cell transplant in first remission.
Prescriber Instructions	<ul style="list-style-type: none"> • Up to 3 cycles of treatment will be authorised initially, with a maximum of 9 cycles allowed under this restriction. • 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 of midostaurin therapy. • Progressive disease is defined as the presence of any of the following: <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 ○ >5% blasts in the marrow not attributable to bone marrow regeneration or another cause ○ Extramedullary leukaemia.

2.2 A Section 100 (Efficient Funding of Chemotherapy – Public and Private hospital) listing was requested for midostaurin. Induction therapy is provided to patients in the inpatient setting, therefore funding of midostaurin utilised in the induction

setting is expected to fall within the budget of the hospitals, not the Commonwealth. However, the submission requested that the PBAC consider funding midostaurin in the inpatient setting. A similar request had previously been made for blinatumomab; however in July 2016 the PBAC had considered that "... PBS subsidised blinatumomab should not be provided to public hospital inpatients" (Blinatumomab Public Summary Document (PSD), July 2016). The ESC and PBAC noted that currently patients with AML receive induction and consolidation therapy in the hospital inpatient setting.

- 2.3 Midostaurin 50 mg twice daily is proposed to be used:
- in combination with cytarabine and an anthracycline in induction therapy (days 8-21 of the chemotherapy cycle) for up to two cycles;
 - in combination with high dose cytarabine in consolidation therapy (days 8-21 of the chemotherapy cycle) for up to four cycles; and
 - as monotherapy as maintenance therapy for up to 12 cycles (daily) in those who:
 - maintain complete remission following consolidation therapy;
 - do not show signs of progression; and
 - do not undergo stem cell transplant (SCT).
- 2.4 The ESC noted that the submission requested an Authority Required (streamlined) listing for the induction therapy, as a rapid turn-around of approval process would be required, given that FLT3 mutation testing can take 2-3 working days and treatment can rarely wait to start. The ESC considered that this was a reasonable request, and advised that this could be achieved by either a telephone or streamlined authority.
- 2.5 Induction therapy with cytarabine and anthracycline is consistent with the current Australian clinical practice for the treatment of AML (these are the current regimens recommended on eviQ). The ESC advised that in older patients, less intense chemotherapies such as fludarabine-based regimens may be used in place of anthracyclines.
- 2.6 Acknowledging that there was an inclusion criteria of less than 60 years of age in the RATIFY trial, the submission proposed two alternative sets of restriction criteria, with and without an age restriction. The submission and the Pre-Sub-Committee-Response (PSCR) (p1) argued that there was a clinical need for extending the listing to patients aged ≥ 60 years. The ESC agreed, and considered that it was not appropriate to limit treatment to patients younger than 60 years of age on grounds of equity and access, however the comparative benefit in the older subgroup remained unclear (see paragraphs 6.19 and 6.41).
- 2.7 The pre-PBAC Response (p3) acknowledged the potential for use of midostaurin outside the intended restriction as maintenance therapy following a stem cell transplant and proposed the restriction clarify that use in this setting (post stem cell transplant) was not permitted.

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

3 Background

- 3.1 TGA status at the time of PBAC consideration: The submission was made under TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, no TGA documents were available. The submission indicated that the first round clinical evaluation report was expected to be received in September 2017. No update on the TGA regulatory status was provided prior to the PBAC meeting. The PBAC noted that the TGA Delegate's overview is due in March 2018.
- 3.2 The PBAC noted that the registered indication for midostaurin differed in the United States compared with that in Europe and proposed in Australia in that use in the maintenance setting was not approved¹. The PBAC further noted that as no documents relating to the TGA's assessment of midostaurin were available it was unknown if the TGA is likely to approve maintenance therapy.
- 3.3 Midostaurin has not been previously considered by the PBAC.

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

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 FLT3 mutations are considered to be activating in nature and present as:
 - internal tandem duplications (FLT3 ITD) in or near the juxtamembrane domain of the receptor (present at diagnosis in approximately 23-34% of adult AML patients and 10-17% of paediatric AML patients); and
 - missense point mutations resulting in single amino acid substitutions occurring within the activation loop of the tyrosine kinase domain (FLT3 TKD) (incidence of 5-10%, and most frequently involving mutations of the D835 residue of a TKD).
- 4.4 The ESC noted that the type of FLT3 mutation, ITD or TKD, is itself prognostic for survival in patients with AML. Further, TKD mutations are associated with better OS than ITD. Recently, new data have emerged which indicate that the presence of a TKD mutation together with a nucleophosphomin (NPM1) mutation is a highly favourable prognostic indicator in AML patients.² The ESC advised that while assessment of NPM1 status is routine in the treatment of AML patients in Australian clinical practice, and

¹https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

² Boddu, P., Kantarjian, H., Borthakur, G., Kadia, T., Daver, N., Pierce, S., Andreeff, M., Ravandi, F., Cortes, J., & Kornblau, S. M. (2017). Co-occurrence of FLT3-TKD and NPM1 mutations defines a highly favorable prognostic AML group. *Blood Advances*, 1(19), 1546-1550. Accessed October 06, 2017.

was used in a propensity matched analysis discussed in the PSCR (p1); its potential interaction with treatment effects observed for midostaurin is as yet unknown.

- 4.5 Testing for *FLT3* mutations is currently subsidised on the MBS (item numbers 73314, 73315) and is routinely conducted as the general “work-up” for patients diagnosed with AML. The ESC noted that *FLT3* testing is done for prognostic purposes and to stratify patients for future allograft. Correspondence from MSAC indicated “... as long as the provision of midostaurin does not change the intent of *FLT3* testing currently reimbursed utilising the MBS item code 73314 (i.e. no change to the treatment population or service volumes) then there is no requirement for an application to the MSAC process.” As *FLT3* testing is currently being undertaken as the general “work-up” for patients with AML, there is likely to be no change to the treatment population or the service volumes, however the intent of testing would evolve from one of prognostication, including selection for SCT to now include determining eligibility for a specific PBS-listed therapy. The PBAC advised that *FLT3* mutation testing is routinely conducted as standard clinical practice for most patients diagnosed with AML who are suitable for intensive induction therapy. In some centres, it is not performed when cytogenetics indicated a favourable or unfavourable prognosis (as opposed to an intermediate prognosis, where the presence of *FLT3* mutations has the most utility as a prognostic indicator), but increasingly it is becoming uniform in line with international guidelines that antedate FDA approval of midostaurin. As such, the PBAC foreshadowed that while the PBS listing of midostaurin may result in a minor increase in the service volumes of *FLT3* testing, the overarching purpose of testing, i.e. to guide management, has not changed.
- 4.6 The ESC considered that while it was reasonable to assume that the PBS listing of midostaurin would not alter the intent or the population of the current MBS listing for *FLT3* testing, the current evidence for the use of midostaurin in *FLT3* AML has been informed by studies conducted in *FLT3* positive patients alone. As such, in the absence of data comparing the effect of midostaurin in *FLT3* positive as well as *FLT3* negative/wild type subgroups, it was unclear whether *FLT3* mutation status was a treatment effect modifier.
- 4.7 Midostaurin is 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.
- 4.8 The ESC considered that the treatment algorithm presented by the submission did not accurately reflect current practice in Australia for *FLT3* positive AML. In particular, the submission assumed patients would undergo four cycles of consolidation chemotherapy, and that midostaurin would be used in the maintenance setting (post consolidation, for up to 12 months). Currently, patients with AML do not receive maintenance therapy. In addition, the use of four cycles of consolidation is reserved for *FLT3* positive patients with an accompanying core binding factor (CBF) mutation; the standard is two cycles, and potentially only one if the patient is proceeding to an allograft. The PBAC agreed with ESC, and considered that this would have an impact on the proposed restriction and the financial estimates.
- 4.9 Additionally, the ESC noted that the proposed clinical algorithm presented in the submission did not include the use of midostaurin post-allograft, but only as use in

consolidation or maintenance pre-allograft. While midostaurin was used post-allograft in the AMLGS-16-10 study, the PBAC noted it was not used post-allograft in the RATIFY trial. The pre-PBAC Response (p3) stated that the intent of the restriction was to limit use to patients who had not undergone an allograft, consistent with the RATIFY trial.

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

5 Comparator

- 5.1 The submission nominated placebo for 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. The ESC agreed that this was the appropriate comparator.

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

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 submission was based on one trial comparing midostaurin versus placebo in the induction, consolidation, and maintenance phases of treatment of FLT3 mutation positive AML patients aged ≤ 59 years (RATIFY).
- 6.4 The 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.
- 6.5 Details of the trials and studies presented in the submission are provided in Table 2.

Table 2: Trials/studies and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trial		
RATIFY (A2301)	<p>A Phase III, randomised double-blind study of induction (daunorubicin and cytarabine) and consolidation (high-dose cytarabine) chemotherapy + midostaurin (PKC412) or placebo in newly diagnosed patients less than 60 years of age with FLT-3 mutated acute myeloid leukaemia (AML).</p> <p>Stone, R.M., et al., CALGB 10603 (RATIFY): A randomized phase III study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy combined with midostaurin or placebo in treatment-naive patients with FLT3 mutated AML.</p> <p>Stone, R.M., et al., The multi-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (ind), high-dose c consolidation (CONSOL), and as maintenance (MAINT) therapy in newly diagnosed acute myeloid leukemia (AML) patients (PTS) age 18-60 with FLT3 mutations (MUTS): An international prospective randomized (RAND) P-controlled double-blind trial (calgb 10603/ratify [alliance]).</p>	<p>July 2016.</p> <p>Journal of Clinical Oncology, 2011. 29(15).</p> <p>Blood, 2015. 126(23): p. 6.</p>
Supplementary study		
AMLSG 16-10	<p>Schlenk, R.F., et al., Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: Interim-analyses of the AMLSG 16-10 trial.</p> <p>Schlenk, R., et al., Midostaurin in combination with intensive induction and as single agent maintenance therapy after consolidation therapy with allogeneic hematopoietic stem cell transplantation or high-dose cytarabine (NCT01477606).</p>	<p>Blood, 2016. 128(22).ASH abstract 2016</p> <p>Blood, 2015. 126 (23): p. 322.</p>

Source: Table 2.2.-1, p88-89 of the submission.

6.6 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence, midostaurin versus placebo

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
RATIFY	717	R, DB, MC 5 years	Low	Newly diagnosed FLT3 mutation positive AML, aged ≤59 years	Overall survival Event-free survival Complete remission	Yes (■)

DB=double blind; ■; MC=multi-centre; R=randomised.

Source: compiled during the evaluation

Comparative effectiveness

6.7 Table 4 presents the results of overall survival (OS; non-censored and censored at the time of SCT) and Figure 1 presents the Kaplan-Meier curve for OS non-censored for SCT (the primary outcome of the RATIFY trial).

6.8 Overall, 59.4% and 55.2% of patients treated with midostaurin and placebo underwent an SCT, respectively. No statistically significant differences in the rates of SCTs were observed between the treatment groups (i) overall, (ii) in those occurring in patients without complete remission, (iii) in those occurring during first complete remission or (iv) in those having an SCT after relapse.

Table 4: Overall survival reported in the RATIFY trial

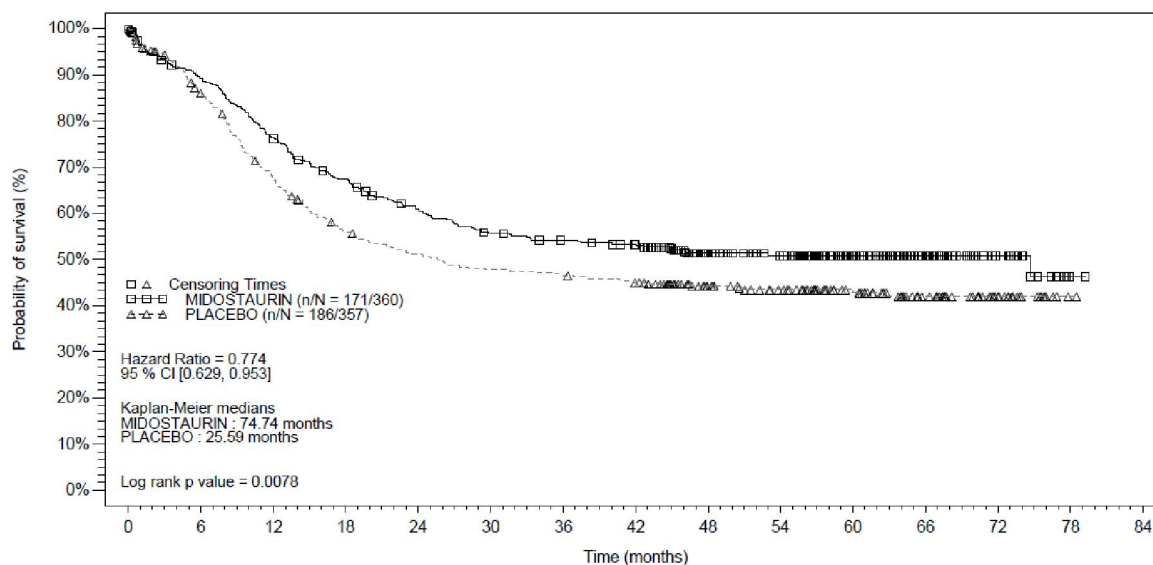
	Midostaurin; N=360	Placebo; N=357	Absolute Difference	Hazard ratio (95% CI)
OS not censored at time of SCT (primary outcome)				
No. deaths, n (%)	171 (47.5)	186 (52.1)	4.6%	0.774 (0.629, 0.953)
No. censored, n (%)	189 (52.5)	171 (47.9)	4.6%	
KM estimates (95% CI)				
At 12 months	██████████	██████████	██████	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 (%)	██████████	██████████	██████	██████████
No. censored, n (%)	██████████	██████████	██████	
KM estimates (95% CI)				
At 12 months	██████████	██████████	██████	NR
At 24 months	██████████	██████████	██████	
At 60 months	██████████	██████████	██████	
Median OS, months	██████████	██████████	██████	

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 submission.

OS = overall survival; SCT = stem cell transplant

6.9 The results from the RATIFY trial indicated statistically significant improvement in OS, non-censored at time of SCT (HR=0.774), with a reported incremental median survival of 49.1 months in patients treated with midostaurin. The RATIFY CSR (p138) stated

that

It is also not known whether the difference in median OS between the two treatment arms was statistically significant (although this was unlikely, as the 95% CIs overlapped).

6.10 The PBAC considered that RATIFY was a mature, well-conducted trial with similar results with and without censoring for SCT. The PBAC 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.

6.11 Exploratory analyses conducted for the RATIFY trial

6.12 The ESC noted that in the analyses of survival outcomes stratified by type of FLT3 mutation (ITD or TKD), although the point estimates were more favourable in TKD patients, none of the mutation specific subgroups achieved statistical significance with respect to OS.³ However, the ESC noted that the study was not powered for subgroup analysis.

6.13 Patients treated with midostaurin also demonstrated improved event-free and disease-free survival and complete remission rates and remission duration compared with placebo.

6.14 The ESC 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, 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. The PBAC further noted that a recent publication that discussed the impact of maintenance therapy with midostaurin stated that "... More than half of midostaurin-treated patients (59%) underwent allogeneic transplant, and, per protocol, therefore did not receive maintenance therapy. The lack of further separation of the survival

³ Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *New England Journal of Medicine*. 2017;377(5):454-464.

curves after the first few months of therapy attests to the fact that either midostaurin does not work as maintenance or that few patients were taking midostaurin, either because they had been transplanted or because of some other reason.... Midostaurin administered as maintenance therapy after allogeneic transplant is currently under active study, although it is too early to draw any conclusions about tolerability or efficacy in this setting”⁴.

- 6.15 The RATIFY trial limited enrolment to those aged ≤ 59 years (approximate mean and median age of 45 years and 47 years, respectively), but the submission proposed that PBS-subsidised access to midostaurin should not be age-restricted, citing evidence from the AMLGS-16-10 study in support of this proposal.
- 6.16 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.
- 6.17 Results from AMLGS-16-10 indicated:
- Patients aged 60-70 years achieved similar complete remission (CR) rates as patients aged ≤ 59 . Overall response, defined by CR or CR with incomplete platelet recovery (Cri), was 76% in both younger patients (≤ 59 years) and older patients (≥ 60 years).
 - Median overall survival in those aged 60-70 years was not significantly worse than younger patients. Median overall survival was 26 months in the younger population and 23 months in the older population ($p=0.15$). Death occurred in 4% of younger patients and 10% of older patients.
- 6.18 As the AMLGS-16-10 study was non-comparative it is unknown whether the incremental benefit observed in patients aged ≤ 59 years in this study was comparable to that reported in the RATIFY trial. Consequently, it was not known whether the “comparable” effects observed between those aged ≤ 59 years and 60-70 years in the AMLSG 16-10 study could be used to conclude the effects observed in RATIFY would also be observed in those aged ≥ 60 years.
- 6.19 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;
 - the PSCR (p1) stated that chronological age is no longer a reason to deny a patient access to intensive chemotherapy. For patients aged ≥ 60 years, a clinical judgement of fitness should be made taking into consideration factors including performance status, the presence or absence of adverse features and the presence or absence of comorbid conditions;

⁴ Levis, M. (2017). Midostaurin approved for FLT3-mutated AML. *Blood*, 129(26), 3403-3406. Accessed November 06, 2017.

- the ESC agreed with the PSCR, noting that changes in SCT methodologies allowed older patients to be eligible for transplant. While the magnitude of benefit of midostaurin treatment in the older population was difficult to determine from the evidence presented, it was likely that the uptake of midostaurin in the older population suitable for intensive therapy would be similar to that in the younger age groups;
- the ESC considered that biologically, there was no reason why patients who are older patients would not respond in the same way to midostaurin as those <59 years; and
- additionally, the ESC and the PBAC considered that given that PBS-subsidised treatment would be limited to patients having high dose induction chemotherapy, it is unlikely that many patients over the age of 70 would be included in this group.
- enrolment was limited to those who were FLT3 ITD mutation positive, where the requested restriction is for both ITD and TKD mutation positive; and
- the use of midostaurin in Study AMLSG-16-10 appeared to differ to that in RATIFY. It appeared that patients undergoing SCT (n=146) in Study AMLSG-16-10 could proceed to maintenance therapy with midostaurin, whereas in RATIFY: "In the event a patient having received SCT directed against their leukaemia, midostaurin/placebo therapy was not to be resumed". 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.

6.20 Despite the above limitations, the ESC and the PBAC 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 regulated if left to the discretion of the prescriber.

Comparative harms

6.21 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 and harms

6.22 A summary of the comparative benefits and harms for midostaurin versus placebo is presented in Table 5.

Table 5: 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 n/N (%)	Placebo n/N (%)	RD	HR (95% CI)		
Number alive, n (%)	189/360 (52.5)	171/357 (47.9)	0.05	0.774 (0.629, 0.953)		
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)

Abbreviations: PBO = placebo; RD = risk difference; RR = risk ratio

Source: Compiled during the evaluation

6.23 On the basis of direct evidence presented by the submission, for every 100 patients treated with midostaurin in comparison to placebo:

- Approximately 5 additional patients alive over a median duration of follow-up of 60 months.
- Approximately 6 additional patients would have grade 3 / 4 exfoliative dermatitis.
- Approximately 6 additional patients would have grade 3 / 4 device related infections.
- Approximately 7 additional patients would have grade 3 / 4 skin toxicities.

Clinical claim

6.24 The submission considered that midostaurin 50 mg BID with standard intensive remission induction and consolidation therapy followed by 1 year of single agent maintenance therapy was superior to placebo at prolonging overall survival. This was achieved by improved disease control (numerically increased remission rate and prolonged disease-free and event-free survival). The submission also considered that midostaurin had a good tolerability profile.

6.25 In patients aged ≤59 years, for which RATIFY trial results were representative, the claim of superior effectiveness was supported. Treatment with midostaurin demonstrated improvement in OS compared to placebo when patients were non-censored for SCT (the primary outcome), which was supported by improved event-free survival and a greater proportion of patients achieving remission after a single induction cycle (which is associated with a better prognosis). Nevertheless, several factors made it difficult to assess the size of comparative effect in the expected treatment population. Specifically:

- OS in patients censored at the time of SCT was characterised by wide confidence intervals, which though statistically significant, verged on insignificance. This suggested that the size of effect in patients who did not receive SCT might not be

as substantial, or that the analysis was underpowered. Uncensored overall survival would be most valid if SCT rates in the Australian setting were expected to be similar to that of the RATIFY trial.

- The trial limited enrolment to patients with an allelic ratio of >0.05 for ITD, which is not a proposed criteria for PBS eligibility. The PSCR (p4) stated that the restriction inherently assumed that an allelic ratio of 0.05 would be applied as the cut-off for FLT3 ITD mutation positivity, as this is commonly recognised as the standard cut-off. The ESC and the PBAC advised that this allelic ratio is the standard criteria for determining ITD positivity.
- Subgroup analyses presented by the submission indicated a differential effect in OS based on gender that was not fully explained by imbalances in observable variables.
- Differences in OS were also noted by FLT3 mutation subtype, but a lack of statistically significant difference may have been driven by the smaller proportion of patients in the trial having the TKD mutation. The potential impact of this was unclear without knowledge of the likely proportion of the Australian population having the TKD mutation.

6.26 The ESC and the PBAC considered that the submission's claim of superior efficacy against placebo was reasonable in patients aged ≤ 59 years.

6.27 In patients aged 60 years and older, the claim of superiority was based on results of the AMLSG 16-10 study, a single arm study with a sample size of 284. Given that the point estimate of risk of death (10% in older population versus 4% in younger population) was 250% higher in the older group (exceeding the improvement in survival of midostaurin over placebo from RATIFY), it was impossible to infer reliably whether any benefit of midostaurin over placebo could be expected in the older population. The ESC and the PBAC concluded that a treatment effect in favour of midostaurin in older patients was plausible; however, in the absence of a placebo comparison and other applicability issues, the size of its comparative benefit in the older population was difficult to determine.

6.28 In terms of safety, the submission did not make an explicit claim of non-inferiority or inferiority compared to placebo but stated that midostaurin had 'a good tolerability profile.' The submission stated that 'The safety profile was comparable between midostaurin and placebo', implying a claim of non-inferiority.

6.29 The ESC disagreed with this claim on the basis of the observed toxicities (notably rash or desquamation) in the RATIFY trial and considered that a reasonable claim would have been one of inferior safety, as the addition of midostaurin to an AML treatment regimen was associated with statistically significant increases in a number of severe adverse events. However, the ESC considered that these AEs were not clinically significant enough to warrant inclusion of associated disutilities in the economic analysis.

6.30 The pre-PBAC Response (p1) amended the safety claim to one of inferior safety versus placebo.

6.31 The PBAC 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.

6.32 The 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 is relatively minor.

Economic analysis

6.33 The submission presented a stepped economic evaluation, based on a direct randomised trial and implementing a modelled economic evaluation. This is consistent with the clinical claim made by the submission.

6.34 The submission excluded the costs of FLT3 mutation testing, and the costs and health outcomes associated with patients who are false negatives and false positives.

- The PSCR (p2) contended that if midostaurin were available, false negatives would be treated in the same way as they would be if midostaurin was not available, with the same costs and benefits. Additionally, the PSCR stated that false positives will occur in the same proportion of patients, and as they were included in the midostaurin arm of the RATIFY trial, they were implicitly included in the model estimates of efficacy.
- While the ESC agreed with the PSCR that the inclusion of these costs is not likely to be incrementally significant, it would have been appropriate to include testing in the economic evaluation, given that the availability of midostaurin impacts on the costs and outcomes associated with false positive and false negative patients.

Table 6: Summary of model structure and rationale

Component	Description; Comments
Type of analysis	Cost-utility analysis
Outcomes	Quality-adjusted-life-years (QALYs) Base-case analysis uses QALYs, however previous steps model life years (LYs)
Time horizon	Lifetime (50 years) Extrapolated from a median follow-up of approximately 5 years in the RATIFY trial. As the average age of patients in RATIFY was approximately 45 years and there is a possibility of a cure, the evaluation considered that a time horizon of 50 years may be reasonable to ensure all relevant costs and benefits are captured. However, the PBAC noted that the age of patients treated in clinical practice would be higher than in a clinical trial setting, and also that a group of patients aged 60 and over were included in the model. Further, extrapolation of trial data with a median follow-up of 5 years to a 50-year time horizon is associated with uncertainty. The time-horizon was varied in sensitivity analyses, and the results indicated that the ICER remained comparable at 30 and 40 year durations as very few patients survive to age 95 years.
Methods used to generate results	Cohort expected value analysis
Health states	The model consists of 13 health states. Patients in the model spend most of their time in one of two post-SCT health states (i) while in first remission and (ii) while not in first remission. Patients remain in post-SCT health states or transition to dead. Survival in post-SCT health states are taken from RATIFY trial [REDACTED], and a 100% excess mortality rate is used when extrapolating transitions from these health states. These health states are appropriate.
Cycle length	28 days (except for induction and consolidation health states), which was appropriate. However, the model allows for up to four cycles of consolidation therapy whereas current practice in Australia is for two cycles of consolidation therapy.
Transition probability	Sourced from analysis of [REDACTED] from the RATIFY trial The source of transition probabilities was appropriate, however there was likely to be a great deal of uncertainty around many of these probabilities (see 6.32).
Software package	TreeAge Pro Healthcare 2017 with dynamic links to Excel 2013

Source: Table 3.1-1, p172 of the submission

6.35 Although during the evaluation a life-time horizon (50 years) was considered reasonable, it was noted this required extrapolation of RATIFY trial data with a median follow-up of approximately 5 years and is therefore subject to a degree of uncertainty. Additionally, the difference in survival at 5 years is assumed to be maintained for a long period of time.

- The PSCR (p2) claimed that the application of a life-time horizon is appropriate in the context of AML;
- The ESC advised that a life-time horizon in itself was not unreasonable, given that the 5-year conditional relative survival for patients alive 5 years post diagnosis of AML in Australia is 89.3%⁵;
- However, the ESC considered that given the average age of Australian AML patients at diagnosis was [REDACTED], a 50 year time horizon was implausible.

⁵ <https://canceraustralia.gov.au/affected-cancer/cancer-types/leukaemia/acute-myeloid-leukaemia-statistics>

- Moreover, the ESC considered that extending to a 50 year horizon would result in a ten-fold extrapolation of the existing RATIFY trial data, hence increasing the uncertainty associated with the resulting estimates of cost-effectiveness.
- The ESC therefore advised that a 30 year time-horizon would better reflect the natural history of this disease and provide a more informative basis for decision making. However, the ESC acknowledged that altering the time horizon to 30 years did not have a significant impact on the cost-effectiveness of midostaurin.
- The PBAC noted that, in the group of patients aged 60 years and over, the modelled time horizon of 50 years would exceed life expectancy. While noting that almost all patients aged 60 and over had died by Year 25 in the model, the PBAC considered that a time horizon of 25 years would have been more clinically plausible in this age group.
- For the group of patients aged less than 60 years, the PBAC considered that a time horizon of 50 years was also optimistic.

6.36 The utility values used in the economic model are shown in Table 7.

Table 7: Utility values used in the economic evaluation using a scenario-based method using time-trade off technique with the UK general public's preferences (reported by Hensen et al)

Health state or event	Mean utility
Induction health state	0.16
Consolidation health states	0.57
Maintenance health states	█
In remission but not on treatment health states	█
Post-SCT health states: 1 st year	█
Post-SCT health states: beyond 1 st year	█
Relapsed or refractory disease health state	0.51
Disutility for additional AEs observed in the midostaurin-treated patients in RATIFY	█

Source █

AE = adverse event; SCT = stem cell transplant

^a Utility value is assumed by the submission to represent a proportion of patients who had no SCT complications and were living in a post-SCT health state after 1 year (█) and a proportion of patients who suffered from graft-versus host disease after their SCT and were living in a post-SCT health state after 1 year (█).

6.37 The PBAC considered that the utilities were implausibly high in the maintenance health state and the two post-SCT health states (i.e. post-SCT first year and beyond the first year). The post-SCT health state beyond the first year represented a proportion of patients without complications █ and a proportion with graft-versus host disease █. The utility applied █ assumed that only █% of patients experience graft-versus host disease, however the PBAC considered the incidence would be higher. Further, the PBAC considered the utility value used for patients without graft-versus host disease █ was over-estimated as it implied that patients would return to almost full health one year post-transplant, which did not seem clinically reasonable. Overall, the utility applied in the post-SCT health state beyond the first year █ did not seem plausible when compared with the utility applied in the maintenance health state █. Sensitivity analyses conducted during the evaluation demonstrated that the ICER was highly sensitive to these utility values.

The PBAC noted alternative published utility values⁶ and considered the values used in the submission were not adequately justified.

- 6.38 The model assumed that ██████% 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 (closer to 80-90%), for example as a consequence of being admitted for fever, infection or other complications. However, the PBAC noted that this assumption had only a minor impact on the ICER. Table 8 summarises the key drivers of the model.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Utilities	Utility values for maintenance, remission and post-SCT health states were consistent with general population norms which may not reflect the course of AML.	High, favours midostaurin
Discount Rate	5% for costs and outcomes used in base-case	High
Extrapolations	Different assumptions are applied to the various health states in which patients remained at the end of the RATIFY trial. To extrapolate past the time horizon of the RATIFY trial, the submission assumes that no further SCTs occur in these patients, the rate of death at cycle 52 applies to all cycles subsequent to cycle 52 and background mortality (with a 100% excess mortality rate assumption) applies to all cycles past cycle 60.	As the majority of health gains come from the extended life of those cured, the extrapolations naturally increase the cost-effectiveness of midostaurin significantly. Consideration is required as to whether the extrapolations for each health state are appropriate.

Source: compiled during the evaluation

- 6.39 Table 9 presents the results of the stepped economic evaluation.

⁶ Economic impact of genomic diagnostics for intermediate-risk acute myeloid leukaemia. Br J Haematol. 2016 Aug; 174(4): 526–535.

Table 9: Presentation of the stepped derivation of the base case economic evaluation from the clinical study data

Data	Costs			Health outcomes			ICER
	Mido	PBO	Increment	Mido	PBO	Increment	
Step 1: Trial-based analysis Setting: RATIFY trial Data: [REDACTED] from RATIFY Costs: Drug and drug administration costs as per RATIFY trial & costs of treating AEs Time horizon: 5 years (median follow-up in RATIFY)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Step 2: Analysis extrapolated to a lifetime time horizon Setting: RATIFY trial Data: [REDACTED] from RATIFY + extrapolation Costs: As per Step 1 plus costs of monitoring, costs of treating relapsed/refractory disease, costs of SCT & costs of palliation Time horizon: 50 years	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Step 3: application of discounting to future costs and benefits Setting, data, costs and time horizon as per Step 2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Step 4: extension of the population to include patients aged ≥60 years Data: incorporates increased death rates while undergoing treatment from the AMLSG 16-10 trial and adjusts background mortality to account for older population. Costs and time horizon as per Step 3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Step 5 (base case economic evaluation): outcome of life years transformed to QALYs Setting, data, costs and time horizon as per Step 4	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Table 3.8-1 of the submission

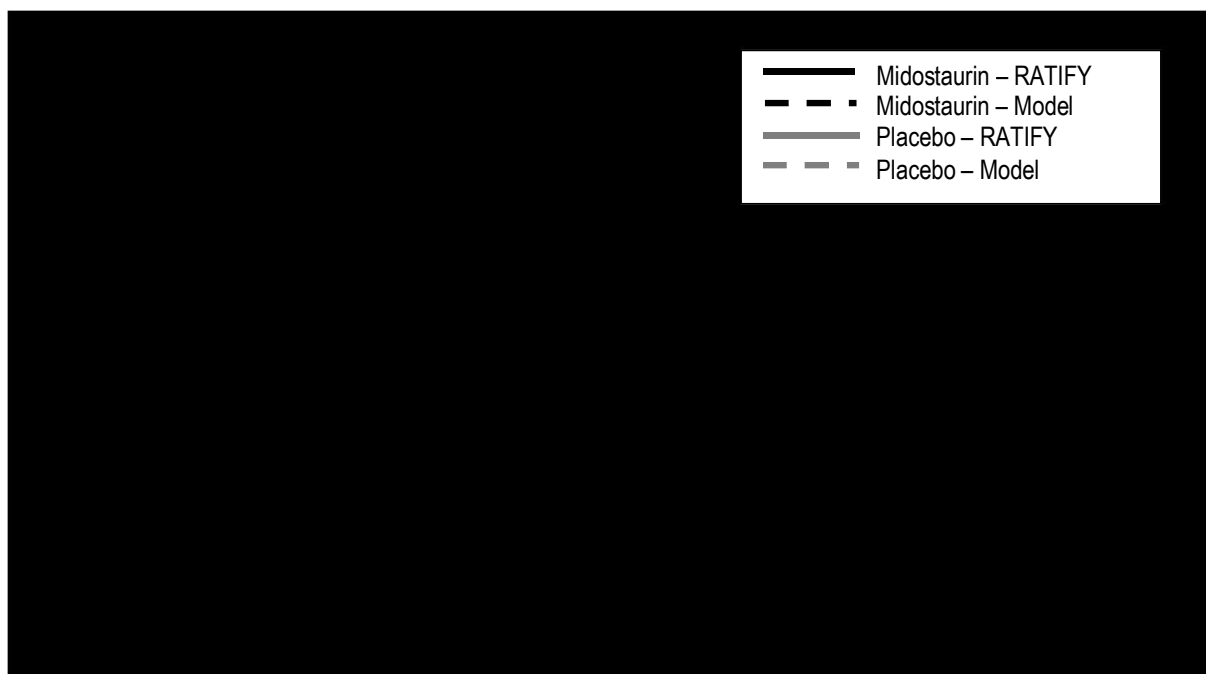
6.40 While the use of [REDACTED] is appropriate for the generation of an economic evaluation, there are some limitations to the approach in that some of the transitions are derived from small patient numbers ([REDACTED] for some transitions) in later cycles, which introduces some uncertainty. Given the use of [REDACTED] in the model (as opposed to applying a hazard ratio to a placebo curve), it was not possible to provide sensitivity analyses around the treatment effect, other than for the excess mortality in patients surviving more than 5 years after remission who have been consolidated by an SCT.

6.41 Moreover, the ESC considered that given that the data used were drawn from the RATIFY trial, they do not represent the experience of AML and its treatment in patients aged ≥ 60 years. While the model adjusted mortality (for all health states other than SCT) for the proportion of AML patients in Australia assumed to be ≥ 60 years (32%), no changes were made to other outcomes or health care use (such as the

proportion receiving SCT, or the extent or length of midostaurin maintenance). Adjusting the mortality only resulted in the model being largely insensitive to the proportion of older patients included. Further, the structure of the model was not flexible enough to test the effect of these changes on the cost-effectiveness of midostaurin. The ESC advised that it would have been useful for the impact of age on treatment and outcomes to be explored in more detail in the cost-effectiveness analysis.

6.42 Figure 2 presents the Markov trace of the model compared with the RATIFY trial data.

Figure 2: Comparison of KM overall curves from RATIFY with overall survival curves generated by the model used to conduct the economic evaluations presented in the submission



6.43 The PBAC considered that, based on visual inspection of Figure 2, the model's extrapolations appeared to underestimate survival in the placebo arm which would favour midostaurin.

6.44 The submission presented univariate sensitivity analyses. These analyses demonstrated the ICER was sensitive to the discount rate applied (0% leading to a decreased cost/ Quality adjusted life year [QALY] gained), proportion of older patients (fewer older patients led to a decreased cost/QALY gained), and reducing the excess mortality in patients surviving more than 5 years after remission consolidated by SCT (leading to a decreased cost/QALY gained). Univariate sensitivity analyses conducted during the evaluation demonstrated that the ICER was also sensitive to the utilities applied to the post-SCT and relapsed/refractory health states.

6.45 The ESC noted that although the structure of the economic model and the use of [redacted] to construct the model was reasonable, the model was sufficiently inflexible such that no sensitivity analyses were presented or could be conducted during to evaluation to test variations in important prognostic factors including, but not limited to, FTL3 subtype, SCT and gender, nor to test variations in the health state transition probabilities, or the numbers of consolidation

cycles and extent of maintenance, including if the older population differed in midostaurin use compared with the modelled treatment course.

Drug cost/patient/course

6.46 The submission estimated a cost of \$ [REDACTED], with \$ [REDACTED] of this cost incurred during hospitalisation and the remaining \$ [REDACTED] incurred in an outpatient setting (assuming [REDACTED]% of induction and [REDACTED]% of consolidation treatments are administered in hospital and based on the average number of packs dispensed in the RATIFY trial). The ESC considered that the proportion of AML patients who would receive consolidation treatment in the inpatient setting would be closer to 90%.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC.

Table 10: Estimated use and financial implications

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use							
Number of patients treated		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Packs of midostaurin 25 mg x 56 (1 pack per induction and consolidation cycle)	Hospital and PBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	PBS only	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Packs of midostaurin 25 mg x 112 (1 pack per maintenance cycle)	Hospital and PBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	PBS only	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of midostaurin							
Cost to PBS/RPBS		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Co-payments		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less co-payments		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications for chemotherapy for patients with FLT3 mutation positive AML							
Cost to PBS/RPBS		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net financial implications							
Net cost to PBS/RPBS		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

^a Assuming [REDACTED]% of induction and [REDACTED]% of consolidation packs are dispensed in hospital. Number of packs for induction, consolidation and maintenance based on RATIFY

Source: Table 4.2.6, pp241-242; Table 4.3.1, pp244-245; Table 4.4.1, pp246 of the submission

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 - \$20 million per year.

6.48 The accuracy of the estimates depended on:

- the proportion of AML patients with a FLT3 mutation (assume 34% in the estimates, however one Australian estimate suggests [REDACTED]%, based on a relatively small number of patients (n=[REDACTED]) with a median age of [REDACTED] years);
- the uptake rate (assumed to be [REDACTED]%) applied equivalently to all age groups. The ESC considered that while there might be some differences in uptake based on age, overall the uptake of midostaurin would be high across all age groups.

However, the ESC advised that since fewer patients from the older population would be eligible for allografts, it was likely that a higher proportion of the older population would be eligible for maintenance therapy with midostaurin;

- the assumption that the dose and number of cycles of midostaurin would be the same as the mean dose and number of cycles in the RATIFY trial. The ESC considered that this was likely to be largely dependent on the rate of SCTs in the Australian population which is likely to be 70-80%, as opposed to that observed in RATIFY (55-60%);
- the proportion assumed to have consolidation therapy in hospital, which the ESC noted was more likely to be 90% rather than █% assumed by the submission (with the caveat that some patients may access midostaurin in an outpatient setting between the induction and consolidation periods for use as a hospital inpatient during the consolidation period). The pre-PBAC response (p3) stated that patients undergoing consolidation with cytarabine in hospital would be likely to be “discharged after completion of (cytarabine) treatment, around Days 5-7 of the consolidation cycle. As midostaurin is prescribed sequentially following cytarabine consolidation on Day 8 ... the majority of patients will receive midostaurin consolidation and maintenance therapy in the outpatient setting”. The PBAC considered that most patients would receive consolidation chemotherapy with cytarabine as hospital inpatient, but then access midostaurin consolidation therapy under the PBS;
- that there is no or limited risk of use beyond the restriction, for example, use post-SCT as maintenance therapy or among FLT3 wildtype patients. The ESC considered that there was potential for use of midostaurin as maintenance post-allograft and noted that this is being explored with other FLT3 inhibitors in clinical trials and occurred in AMLSG 16-10; and
- the number of cycles of consolidation used in clinical practice. In Australian clinical practice, many patients receive two cycles of consolidation, rather than the four cycles assumed in the submission (see paragraph 4.8). The PBAC considered that this assumption might overestimate use of midostaurin.

6.49 The ESC noted that induction is expected to occur in hospital and that the submission proposed that this be covered by the PBS; the financial estimates would be affected by changed assumptions for use and PBS coverage for induction and consolidation therapy.

6.50 The inappropriate exclusion of costs to treat adverse events was likely to have underestimated the expected costs.

Quality Use of Medicines

6.51 The submission considered that the following two issues needed to be considered with respect to quality use of medicines:

- A requirement for midostaurin treatment to be commenced on Day 8 of the induction and consolidation cycles. To ensure supply, the submission suggests that midostaurin should be dispensed under the Section 100 (Highly Specialised Drugs Program); and

- Consistency in the use of midostaurin in conjunction with standard intensive remission induction and consolidation regimens driven by patient tolerability across Australia. The sponsor would endeavour to help facilitate the introduction of standardised guidelines for treatment, and educational materials/protocols for clinicians and treatment centres and patients, including a patient support program with tools such as dosing reminders.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend midostaurin for the treatment of FLT3 mutation positive acute myeloid leukaemia. In reaching this outcome, the PBAC acknowledged the high unmet clinical need in this population and demonstrated increase in overall survival in the clinical trial. However, it noted that TGA input was required regarding the role of midostaurin as maintenance therapy and considered that, at the price proposed by the submission, the cost effectiveness of midostaurin was unacceptably high and uncertain, particularly in the population over the age of sixty years.
- 7.2 The PBAC acknowledged that there was an unmet clinical need for new effective therapies for AML.
- 7.3 The PBAC noted that midostaurin would not be PBS subsidised for hospital inpatients.
- 7.4 The PBAC advised that significant changes be made to the proposed restriction. In doing so the PBAC acknowledged that further consideration via a future major resubmission would be required once the TGA-registered indication was known.
- The PBAC did not consider it reasonable to restrict use of midostaurin to patients less than 60 years of age. The PBAC noted that, while the clinical trial limited use based on chronological age, this does not reflect current clinical practice in Australia.
 - The PBAC considered that a telephone authority was appropriate in the induction setting where rapid approval was required, noting the low potential for leakage outside the restriction early in treatment.
 - The PBAC considered that the restrictions for induction and consolidation could be combined given the parallels in doses and duration of treatment across the two settings. The combined restriction could be a telephone authority (per above), with a Treatment Phase of "Induction/consolidation", and Prescriber Instructions enabling "up to three cycles to be authorised initially, with a maximum of six cycles [packs] in total possible under this phase".
 - The PBAC considered that 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.
 - 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 PBAC considered that the restriction for use in the maintenance setting should be split into initial and continuing restrictions.

- For the initial maintenance restriction, the PBAC considered that a written authority was necessary to prevent assist minimising use outside the intended population. For this restriction, the PBAC considered that up to three cycles could be authorised, and 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”.
- 7.5 For the continuing maintenance restriction, the PBAC considered that a telephone authority was appropriate, with up to three cycles authorised initially with a maximum of nine cycles allowed under this restriction. The PBAC considered that this restriction should state that the “Patient must not be planned for, or have undergone, a stem cell transplant in first remission” and the following statement should be removed “OR Patient must be awaiting a stem cell transplant”.
- 7.6 The PBAC advised that FLT3 mutation testing is routinely conducted as standard clinical practice for most patients diagnosed with AML who are suitable for intensive induction therapy. In some centres, it is not performed when cytogenetics indicated a favourable or unfavourable prognosis (as opposed to an intermediate prognosis, where the presence of FLT3 mutations has the most utility as a prognostic indicator), but increasingly it is becoming uniform in line with international guidelines that antedate FDA approval of midostaurin. As such, the PBAC foreshadowed that while the PBS listing of midostaurin may result in a minor increase in the service volumes of FLT3 testing, the overarching purpose of testing, i.e. to guide management, has not changed.
- 7.7 The PBAC considered that placebo was the appropriate comparator.
- 7.8 The PBAC noted that the 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).
- 7.9 The PBAC considered that RATIFY was a mature, well-conducted trial with similar results with and without censoring for SCT. The PBAC 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.
- 7.10 The PBAC considered that the pivotal trial, RATIFY, demonstrated that midostaurin improved overall survival versus placebo in patients aged under 60 years. The PBAC noted that the RATIFY trial only enrolled patients aged ≤ 59 years, and the presented evidence from the the single arm AMLSG 16-10 study, to support midostaurin’s effectiveness in the aged ≥ 60 years. The PBAC 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 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.

- 7.11 Further, the PBAC noted that midostaurin was used post-allograft in the AMLGS-16-10 study, but not in the RATIFY trial. The PBAC noted that on being asked to clarify this matter by ESC, the pre-PBAC Response (p3) stated that the intent of the restriction was to limit use to patients who had not undergone an allograft, consistent with the RATIFY trial.
- 7.12 The pre-PBAC Response (p1) amended the safety claim to one of inferior safety versus placebo. The 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 is relatively minor.
- 7.13 The PBAC noted that the submission presented a stepped economic evaluation, based on a direct randomised trial and implementing a modelled economic evaluation.
- 7.14 The PBAC considered that the economic model was not sufficiently flexible to enable relevant sensitivity analyses to be conducted. 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.
- 7.15 The PBAC noted that the economic model adjusted background mortality (for all health states other than SCT) for the proportion of AML patients in Australia assumed to be 60 years or over (32%). However, the PBAC was concerned that no changes were made to other outcomes or health care use (such as the reduced likelihood of receiving a SCT, or differences in the use of maintenance therapy). 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. Agreeing with ESC's advice on this matter, the PBAC considered that it would have been useful for the impact of age on treatment and outcomes to be explored in more detail in the cost-effectiveness analysis.
- 7.16 The PBAC considered that the utility values applied in the maintenance (██████████) and post-SCT health states (first year post-SCT = ██████; beyond the first year post-SCT = ██████) were high. In particular, the PBAC considered that the utility value applied beyond the first year post-SCT ██████ was overestimated because it was based on (i) an underestimated incidence of graft-versus host disease; and (ii) an assumption that patients without complications would return to almost full health within one year post-transplant. 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.
- 7.17 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. The PBAC acknowledged this would have minimal impact on the cost-effectiveness as death due to causes other AML had been incorporated in the model.

7.18 The PBAC further considered that the following should be accounted for in the economic model:

- the model assumed that ██████% 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%), for example as a consequence of being admitted for fever, infection or other complications.
- that, on visual inspection, the extrapolation used in the model appeared to underestimate survival in the placebo arm which would favour midostaurin (see paragraph 6.43).
- 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.

7.19 Overall, the PBAC considered that the ICER presented (\$45,000/QALY - \$75,000/QALY gained) was unacceptably high, particularly as it was highly uncertain and likely to be an underestimate.

7.20 Acknowledging that midostaurin has clinical benefit in an area of unmet need, the PBAC advised that any future major resubmission should be based on the use of midostaurin as defined by the TGA and include:

- amendments to the restriction considering the PBAC's suggestions (see paragraph 7.4) and any future advice from the TGA;
- a revised economic model that addresses the issues identified in paragraphs 7.14 to 7.19, particularly the flexibility of the model to enable further exploration of the impact of age on treatment and outcomes, and the clinical plausibility of the utility values;
- a reduced drug cost/patient/course and an acceptably cost-effective ICER below \$45,000/QALY - \$75,000/QALY;
- 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.

7.21 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Novartis are pleased with the PBAC's acknowledgement of the high clinical need for an effective treatment in this patient population. Novartis are committed to working with the PBAC to achieve agreement on sustainable PBS listing conditions for midostaurin at the earliest opportunity.