

6.03 MIDOSTAURIN, Capsule 25 mg, Rydapt[®], NOVARTIS PHARMACEUTICALS AUSTRALIA PTY LTD.

1 Purpose of submission

- 1.1 The Category 2 submission requested Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for midostaurin for treatment of adult patients with advanced systemic mastocytosis (AdvSM).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus supportive care (i.e., standard of care [SOC]). The key components of the submission are shown in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with advanced systemic mastocytosis, i.e. aggressive systemic mastocytosis, systemic mastocytosis with an associated haematological neoplasm, or mast cell leukaemia.
Intervention	Midostaurin 100 mg orally twice daily (available in 25 mg capsules).
Comparator	There is no appropriate PBS-listed comparator for this indication ^a
Outcomes	ORR based on modified Valent criteria, DoR, TTR and OS, safety
Clinical claim	In adult patients with advanced systemic mastocytosis, midostaurin has superior efficacy to standard of care based on ORR and OS, and non-inferior safety.

Source: Table 1.1, p13 of the submission

DoR = duration of response; ORR = overall response rate; OS = overall survival; TTR = time to response

^a Despite this, the submission included peginterferon alpha-2a and cladribine in standard of care in the economic model and financial estimates

2 Background

Registration status

- 2.1 Midostaurin was designated orphan drug status on 22 June 2016 and approved by the TGA on 17 May 2018 for the following indications:
- For the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
 - 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 more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
MIDOSTAURIN						
midostaurin 25 mg capsule, 112	NEW (HSD Private) NEW (HSD Public)	\$38,784.72 published \$1 effective	2	224	4 2	Rydapt
Restriction Summary [new1] / Treatment of Concept: [new1A]						
Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload						
Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)						
Administrative Advice: No applications for increased maximum quantities will be authorised. No increase in the maximum quantity or number of units may be authorised.						
Administrative Advice: No applications for increased repeats will be authorised. No increase in the maximum number of repeats may be authorised.						
Episodicity: [blank]						
Severity: Advanced						
Condition: Advanced Systemic Mastocytosis (AdvSM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-Ahn) and mast cell leukaemia (MCL). Systemic mastocytosis						
Indication: Treatment of adult patients with advanced systemic mastocytosis (AdvSM) including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL) Advanced systemic mastocytosis (AdvSM)						
Treatment Phase: Initial treatment						
Clinical criteria:						
Patient must have a diagnosis of The condition must be advanced systemic mastocytosis including: (i) aggressive mastocytosis (ASM), (ii) systemic mastocytosis with an associated haematological neoplasm (SM-AHN), (iii) mast cell leukaemia (MCL).						
AND						
Clinical criteria:						
Patient must not have received prior treatment with this drug for this condition.						
Population criteria:						
Patient must be at least 18 years of age.						
Prescribing Instructions: The pathology and bone marrow biopsy reports including the date and details of the patient's measurable C-findings at baseline (prior to initiation of treatment with this drug) must be documented in the patient's medical record. Measurable C-findings at baseline will be used to assess if patient has developed progressive disease.						

Public Summary Document - March 2025 PBAC Meeting

	<p>Prescribing Instructions: Progressive disease monitoring via a complete blood count (CBC) testing must be assessed taken at the end of the initial 8 weeks of treatment (i.e. after the first 2 cycles). If abnormal blood counts, suggest the potential for relapsed advanced systemic mastocytosis AdvSM. 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>Prescribing Instructions: Progressive disease is defined as a worsening of more than 20% >20% worsening of one or more C-findings compared to the last C-findings value measured prior to treatment initiation before the start of PBS subsidised treatment with this drug for this condition. Measurable C-findings include any of the following:</p> <ul style="list-style-type: none"> (i) Bone marrow dysfunction manifested by 1 or more cytopenia(s) (i.e. <i>Absolute Neutrophil Count (ANC) less than $<1.0 \times 10^9/L$, haemoglobin (Hgb) level less than $<10 \text{ g/dL}$, or platelets count less than $<100 \times 10^9/L$</i>) but with no obvious non-mast cell hematopoietic malignancy; (ii) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; (iii) Skeletal involvement with large osteolytic lesions and/or pathological fractures; (iv) Palpable splenomegaly with hypersplenism; (v) Malabsorption with weight loss due to gastrointestinal mast cell infiltrate.
	<p>Prescribing Instructions: A patient who has developed progressive disease when <i>while being</i> treated with this drug is no longer eligible for PBS-subsidised treatment with this drug for this condition.</p>
	<p>Prescribing Instructions: The authority application must be made in writing and must include:- 1) a completed authority prescription form; 2) a completed AdvSM advanced systemic mastocytosis PBS Authority Application – Supporting Information Form; and 3) a declaration that the patient does not have progressive disease. The authority application must be made in writing and must include: (a) details of the proposed prescription(s); and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice);</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

Public Summary Document - March 2025 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIDOSTAURIN						
midostaurin 25 mg capsule, 112	NEW (HSD Private) NEW (HSD Public)	\$38,784.72 published \$1 effective	2	224	2	Rydapt
Restriction Summary [new2] / Treatment of Concept: [new2A]						
Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload)						
Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)						
Administrative Advice: No applications for increased maximum quantities will be authorised. No increase in the maximum quantity or number of units may be authorised.						
Administrative Advice: No applications for increased repeats will be authorised. No increase in the maximum number of repeats may be authorised.						
Episodicity: [blank]						
Severity: <i>Advanced</i>						
Condition: Advanced Systemic Mastocytosis (AdvSM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-Ahn) and mast cell leukaemia (MCL). <i>Systemic mastocytosis</i>						
Indication: Treatment of adult patients with advanced systemic mastocytosis (AdvSM) including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL) <i>Advanced systemic mastocytosis (AdvSM)</i>						
Treatment Phase: Continuing treatment						
Clinical criteria:						
Patient must have previously received PBS-subsidised treatment with this drug for this condition under the initial treatment or grandfathering treatment restriction <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition;</i>						
AND						
Clinical criteria:						
Patient must not have experienced disease progression whilst receiving PBS-subsidised treatment with this drug for this condition. <i>Patient must not have developed disease progression while receiving treatment with this drug for this condition.</i>						
Prescribing Instructions: Progressive disease monitoring via a complete blood count (CBC) testing must be assessed taken at the end of each 28-day cycle. If abnormal blood counts, suggest the potential for relapsed advanced systemic mastocytosis AdvSM . A bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.						
Prescribing Instructions:						

Public Summary Document - March 2025 PBAC Meeting

	<p>Progressive disease is defined as a worsening of more than 20% >20% worsening of one or more of C-findings compared to the last C-findings value measured prior to treatment initiation before the start of PBS-subsidised treatment with this drug for this condition at baseline.</p> <p>Measurable C-findings include any of the following:</p> <ul style="list-style-type: none"> (i) Bone marrow dysfunction manifested by 1 or more cytopenia(s) (Absolute Neutrophil Count (ANC) less than $\leq 1.0 \times 10^9/L$, haemoglobin (Hgb) less than ≤ 10 g/dL, or platelets less than $\leq 100 \times 10^9/L$) but with no obvious non-mast cell hematopoietic malignancy; (ii) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; (iii) Skeletal involvement with large osteolytic lesions and/or pathological fractures; (iv) Palpable splenomegaly with hypersplenism; (v) Malabsorption with weight loss due to gastrointestinal mast cell infiltrate.
	<p>Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug for this condition.</p>
	<p>Prescribing Instructions: The authority application must be made in writing and must include:-</p> <ul style="list-style-type: none"> 4) a completed authority prescription form; 5) a completed AdvSM advanced systemic mastocytosis PBS Authority Application – Supporting Information Form; and 6) a declaration that the patient does not have progressive disease. <p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> (a) details of the proposed prescription(s); and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice); and (c) date and details of the CBC and bone marrow biopsy reports (if applicable) confirming that the patient does not have progressive disease as assessed by the treating clinician.
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
	<p>Treatment Phase: Grandfathering treatment Transitioning from non-PBS to PBS-subsided treatment - Grandfather arrangements</p>
	<p>Clinical criteria:</p>
	<p>Patient must not have received non-PBS subsidised treatment with this drug for this PBS condition prior to [date to be finalised] Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [date of listing]</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must be receiving treatment with this drug for this condition at the time of application</p>
	<p>AND</p>
	<p>Clinical criteria:</p>

Public Summary Document - March 2025 PBAC Meeting

	<i>The condition must be advanced systemic mastocytosis including: (i) aggressive mastocytosis (ASM), (ii) systemic mastocytosis with an associated haematological neoplasm (SM-AHN), (iii) mast cell leukaemia (MCL).</i>
	AND
	Clinical criteria:
	Patient must not have experienced <i>developed</i> disease progression whilst <i>while</i> being treated with this drug for this condition.
	Population criteria:
	<i>Patient must be at least 18 years of age.</i>
	Prescribing Instructions: <i>The pathology and bone marrow biopsy reports including the date and details of the patient's measurable C-findings at baseline (prior to initiation of treatment with this drug) must be documented in the patient's medical record. Measurable C-findings at baseline will be used to assess if patient has developed progressive disease.</i>
	Prescribing Instructions: Progressive disease monitoring via a complete blood count (CBC) testing must be assessed taken at the end of the initial 8 weeks of treatment (i.e. after the first 2 cycles). If abnormal blood counts, suggest the potential for relapsed advanced systemic mastocytosis AdvSM . A bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.
	Prescribing Instructions: Progressive disease is defined as a worsening of more than 20% <i>>20% worsening</i> of one or more C-findings compared to the last <i>C-findings value measured prior to treatment initiation before the start of PBS-subsidised treatment</i> with this drug for this condition. Measurable C-findings include <i>any of the following</i> : (i) Bone marrow dysfunction manifested by 1 or more cytopenia(s) (i.e. <i>Absolute Neutrophil Count (ANC) less than <math>\leq 1.0 \times 10^9/L</math>, haemoglobin (Hgb) level less than <math>\leq 10 \text{ g/dL}</math>, or platelets count less than <math>\leq 100 \times 10^9/L</math>) but <i>with</i> no obvious non-mast cell hematopoietic malignancy; (ii) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; (iii) Skeletal involvement with large osteolytic lesions and/or pathological fractures; (iv) Palpable splenomegaly with hypersplenism; (v) Malabsorption with weight loss due to gastrointestinal mast cell infiltrate.</i>
	Prescribing Instructions: A patient who has developed <i>developed</i> progressive disease when <i>while</i> being treated with this drug is no longer eligible for PBS-subsidised treatment with this drug for this condition.
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a g-Grandfathered <i>Continuing treatment continuation</i> patient must qualify under the therapy <i>continuation</i> criteria.
	Prescribing Instructions: The authority application must be made in writing and must include: 7) a completed authority prescription form; 8) a completed AdvSM advanced systemic mastocytosis PBS Authority Application – Supporting Information Form; and 9) a declaration that the patient does not have progressive disease. <i>The authority application must be made in writing and must include:</i> (a) <i>details of the proposed prescription(s); and</i> (b) <i>a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice); and</i> (c) <i>if applicable, details of the CBC and/or bone marrow biopsy reports confirming that the patient does not have progressive disease as assessed by the treating clinician.</i>
	Administrative Advice: <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>
	Administrative Advice:

<p>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
--

- 3.1 For the requested indication of AdvSM the effective ex-manufacturer price (EMP) for a 56 pack of 25 mg capsules is \$| and for a 112 pack is \$|. For the maximum dispensed quantity of 224 capsules the effective EMP is \$| which allows for 28-day supply at the recommended dosage of 100 mg midostaurin twice daily. The pre-PBAC response offered a price reduction resulting in an EMP for a 56 pack of 25 mg capsules of \$|. For the maximum dispensed quantity of 224 capsules the pre-PBAC response effective EMP was \$|. The pre-PBAC response noted that a generic for midostaurin was recently registered and acknowledged that if it were listed on the PBS this would result in an additional 25% discount on the price proposed.
- 3.2 Midostaurin is PBS-listed for the treatment of AML. For AML the maximum dispensed quantity is 112 capsules (effective price of \$|) which allows for 28-day supply at the recommended dose of 50 mg midostaurin twice daily.
- 3.3 The requested restriction did not specify criteria for diagnosing AdvSM patients. The presentation of AdvSM patients can be non-specific and heterogeneous and the World Health Organisation (WHO) 2022 diagnostic criteria for systemic mastocytosis could be included in the restriction to systematically identify eligible patients (see paragraph 4.3). The ESC considered that inclusion of the WHO 2022 diagnostic criteria for systemic mastocytosis in the restriction was not required.
- 3.4 Under the WHO 2022 diagnostic criteria for SM, genetic testing to identify KIT 816 mutations was a minor criterion (see paragraph 4.3). Specifically, *KIT D816V* mutations are common in >80% of AdvSM patients and a high allele burden in the bone marrow may be associated with a worse prognosis.^{1,2} In the primary studies in this submission (D2201 and A2213), genetic testing was not a requirement but was conducted in most patients, suggesting that genetic testing may be common practice in the diagnostic

¹ Reiter, A, et al. (2020) New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis, *Blood*, Volume 135, Issue 16, Pages 1365-1376, ISSN 0006-4971, <https://doi.org/10.1182/blood.2019000932>. (<https://www.sciencedirect.com/science/article/pii/S0006497120620997>)

² Jawhar, M, et al. (2017) Response and progression on midostaurin in advanced systemic mastocytosis: *KIT D816V* and other molecular markers. *Blood* 2017; 130 (2): 137–145. doi: <https://doi.org/10.1182/blood-2017-01-764423>

pathway. There are currently four pathology items listed under the MBS for next-generation sequencing (NGS) gene panel testing for genetic variants associated with haematological malignancies (MBS item 73445, 73446, 73447, and 73448). KIT-activating KIT point mutations would be covered by these MBS items for AdvSM if it is included in the panel of at least 25 genes. The Pre-Sub-Committee Response (PSCR) proposed that the restriction include a requirement for KIT D816V mutation testing to limit use to those who have a confirmed mutation. The ESC disagreed with the PSCR, noting that testing for KIT D816V mutation was not an eligibility requirement in the key studies informing the submission. As such, the ESC advised that the restriction should not include a requirement for KIT D816V mutation testing.

- 3.5 Patients in the D2201 and A2213 trials were required to have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status of 0-3, as well as specific parameters when it comes to cardiac, liver and kidney functions. These were not included in the proposed restriction.
- 3.6 The requested restriction allowed the continuation of treatment with midostaurin based on the absence of disease progression and this was consistent with the discontinuation rules in D2201. However, this was different to the A2213 study, the economic model, and the financial estimates where patients stopped treatment after the first two cycles of treatment if they did not respond to treatment. Requiring patients to have demonstrated a response to treatment after the first two cycles of treatment may decrease the time on treatment compared to the approach taken in the requested restriction. The PSCR proposed updating the restriction to include confirmed major or partial response within two months of treatment initiation. The PSCR stated that such a change would require patients to stop treatment after the first two cycles if they do not respond. The PSCR did not provide revised restriction criteria outlining its proposed change. The ESC considered the appropriateness of this proposed change, given that the data upon which effectiveness and cost effectiveness depends on (mainly D2201), remained an issue. The pre-PBAC response stated that data from A2213 informed the PSCR proposed updates to the restriction. The pre-PBAC response argued that amending the restriction to ensure that non-responding patients discontinue midostaurin after 2 cycles removed the likelihood of such patients receiving unnecessary treatment at an unnecessary cost as well as reduced the risk of potential adverse events.
- 3.7 The ESC considered that restricting use to patients that are at least 18 years of age was reasonable. The ESC advised that paediatric mastocytosis is a benign condition and true AdvSM in this population is extremely rare.
- 3.8 The submission requested a grandfathering restriction to account for nine patients on a patient access program.

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

4 Population and disease

- 4.1 Mastocytosis is a rare group of heterogenous diseases characterised by excess mast cells. It includes AdvSM, which is a severe form of the disease that has three distinct subtypes: ASM is typically the least severe subtype, followed by SM-AHN, then MCL (median survival reported for the subtypes was 6.7 years, 4.4 years, and 0.8 years, respectively).³ The ESC noted the symptoms of AdvSM are broad and can be debilitating with a significant impact on quality of life (QoL). They include cutaneous (e.g., urticaria), gastrointestinal (e.g., diarrhoea, nausea), musculoskeletal (e.g., joint pain, osteoporosis), and constitutional (e.g., fatigue, chills) symptoms, as well as anaphylaxis, organopathy and bone marrow insufficiency in severe cases.
- 4.2 Although the exact disease mechanism remains unknown, over 80% of AdvSM patients have an activating mutation in the *KIT* gene (most commonly the *KIT D816V* mutation) resulting in abnormal mast cell growth and proliferation. *KIT D816V* mutations are associated with worse survival. Other prognostic factors associated with worse survival include male gender, age (> 60 years), thrombocytopenia (< 150 x 10⁹/L), anaemia (levels below sex-adjusted normal), elevated alkaline phosphatase (ALP), and mutations in the *SRSF2/ASXL1/RUNX1* genes.^{4, 5, 6}
- 4.3 Diagnosis of AdvSM is not straightforward due to its rare nature and nonspecific and heterogenous symptoms. Under the WHO 2022 diagnostic criteria, systemic mastocytosis is diagnosed when one major and one minor criterion or ≥ 3 minor criteria are met. AdvSM is diagnosed when additional “C-finding(s)” criteria are met. C-findings assess organ dysfunction and/or bone marrow insufficiency due to mast cell infiltration. In brief, a diagnosis of ASM is made when ≥1 C-finding(s) is present; SM-AHN is diagnosed if the criterion for an associated haematologic neoplasm is met; and a diagnosis of MCL is made when bone marrow smears show ≥20% mast cells.
- 4.4 There are no targeted therapies available to treat AdvSM in Australia and current management involves symptom control (e.g., anti-mediator drug therapy including antihistamines, anti-leukotriene agents, and oral or topical corticosteroids) and off-label use of cytoreductive therapies for mast cell debulking (e.g., cladribine, hydroxyurea and peginterferon alpha-2a). These therapies have limited efficacy and do not address underlying pathology. In a historical control group of AdvSM patients

³ Cohen SS, et al. (2014) Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol*. 2014 Aug;166(4):521-8. doi: 10.1111/bjh.12916. Epub Apr 25. PMID: 24761987.

⁴ Pardanani A, et al. (2018) Mayo alliance prognostic system for mastocytosis: clinical and hybrid clinical-molecular models. *Blood Adv*; 2 (21): 2964–2972. doi: <https://doi.org/10.1182/bloodadvances.2018026245>

⁵ Jawhar M, et al. (2019) MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis. *J Clin Oncol*. 2019 Nov 1;37(31):2846-2856. doi: 10.1200/JCO.19.00640. Epub Sep 11. PMID: 31509472; PMCID: PMC6823885.

⁶ Jawhar, M, et al. (2017) Response and progression on midostaurin in advanced systemic mastocytosis: *KIT D816V* and other molecular markers. *Blood* 2017; 130 (2): 137–145. doi: <https://doi.org/10.1182/blood-2017-01-764423>

not treated with midostaurin, the median survival was 19.5 months.⁷ In addition to these therapies, the National Comprehensive Cancer Network (NCCN) 2019 guidelines indicate imatinib (in patients with FIP1L1-PDGFR α fusion gene and KIT D816V mutation-negative) and allogeneic haematopoietic cell transplant (HCT) were recommended therapies for the treatment of AdvSM.

- 4.5 Midostaurin is a multitargeted tyrosine kinase inhibitor (TKI) that competitively inhibits several receptor tyrosine kinases (i.e., SCFR [also known as KIT], FLT3, PDGFR and VEGFR2) and all major isoforms of protein kinase C. Inhibition ultimately reduces mast cell signalling and proliferation, in turn reducing mast cell burden. The dosage of midostaurin for AdvSM is 100 mg orally twice daily (i.e., 8 x 25 mg capsules per day) with the TGA approved Product Information stating that treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

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

5 Comparator

- 5.1 The submission nominated supportive care (i.e., SOC) as the main comparator. The submission stated this to include cladribine, peginterferon alpha-2a and hydroxyurea.
- 5.2 The submission, as per the economic model and financial estimates, only considered cladribine and peginterferon alpha-2a despite other recommended treatments for AdvSM (see paragraph 4.4). The submission stated hydroxyurea was reserved for the palliative setting and therefore these patients would not be candidates for midostaurin. While hydroxyurea was noted to be reserved for the palliative setting, all SOC therapies had been described as palliative measures for AdvSM by the submission. In addition, the submission stated that imatinib is PBS-listed for patients with ASM with eosinophilia who carry the FIP1L1-PDGFR α fusion gene and therefore the eligible population would not include these patients. The requested restriction for midostaurin did not exclude patients with the FIP1L1-PDGFR α fusion gene, thus there may be overlap with the eligible population.⁸ However, it is acknowledged that imatinib may not be recommended for patients who carry the KIT D816V mutation and given >80% of AdvSM patients carry the KIT D816V mutation, this overlap may be small. The ESC considered the SOC therapy listed by the submission were consistent with Australian practice and appeared reasonable.

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

⁷ Reiter, A., et al. (2017). Pooled Survival Analysis Of Midostaurin Clinical Study Data (D2201+A2213) In Patients With Advanced Systemic Mastocytosis Compared With Historical Controls. *Haematologica*.

⁸ <https://www.pbs.gov.au/medicine/item/5444M-9179D-9177B-9175X-9173T-9124F-9116T-9114Q-9112N>

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the difficulty in diagnosing this rare disease, the debilitating symptoms that arise due to mast cell overactivity and the resulting profound impact on patient quality of life. The clinician also discussed the impact of the condition on a patient's family due to the symptom burden. The clinician noted the limited treatment options available for AdvSM and argued there was an unmet for new treatments for this condition. The clinician described how midostaurin would be used in practice if it were to be recommended and emphasised that reducing symptom burden was likely to reduce health care resource use. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from the Leukaemia Foundation via the Consumer Comments facility on the PBS website. The comments described the poor prognosis for AdvSM and the need for new treatment options in this rare disease. The comments noted that the only drug on the PBS for systemic mastocytosis (imatinib) was not suitable for the large proportion of AdvSM patients who carry the *KIT D816V* mutation (see paragraph 5.2). The comments also described a range of benefits of treatment with midostaurin including reducing end-organ damage, decreasing bone marrow mast cell burden and improving overall survival.

Clinical studies

- 6.3 The submission was based on two single arm studies of midostaurin (D2201, N=116; A2213, N=26) and supplemented by two historical control studies (Reiter 2017, N=131; CEREMAST, N=72), of which Reiter 2017 was only available as an abstract/poster presentation. The A2213 single arm study is ongoing.
- 6.4 Details of the studies presented in the submission are provided in Table 2.

Public Summary Document - March 2025 PBAC Meeting

0262898888

Trial ID	Protocol title/ Publication title	Publication citation
D2201 NCT00782067	A single arm, Phase II, open-label study to determine the efficacy of 100 mg twice daily oral dosing of midostaurin administered to patients with aggressive systemic mastocytosis or mast cell leukemia +/- an associated haematological clonal non-mast cell lineage disease Clinical study report: primary analysis data cut 01 December 2014; final analysis data cut 24 August 2017 Gotlib J, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis Hartmann K, et al. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis	April 2018 <i>New England journal of medicine</i> 374(26): 2530-2541 <i>Journal of Allergy and Clinical Immunology</i> 146(2): 356-366.e354.
A2216 NCT00233454	A single arm, Phase II, open-label study to determine the efficacy of twice daily oral dosing of PKC412 administered to patients with aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL) +/- haematological clonal non-mast cell lineage disease Clinical study report: follow up analysis, data cut 01 March 2017 DeAngelo DJ, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial	September 2015 <i>Leukemia</i> 32(2): 470-478
Reiter 2017	Reiter et al. Pooled survival analysis of midostaurin clinical study data (D2201+A2213) in patients with advanced systemic mastocytosis compared with historical controls (abstract and poster presentation S788).	<i>Haematologica</i> 102: 321-322.
CEREMAST	Chandesris MO., et al. Midostaurin in Advanced Systemic Mastocytosis. Chandesris MO, et al. Clinical potential of midostaurin in advanced systemic mastocytosis.	June 2016 <i>New England journal of medicine</i> 374(26): 2605-2607 June 2017 <i>Blood and Lymphatic Cancer: Targets and Therapy</i> 7: 25-35.

Source: Table 2.3, pp40-41 of the submission

6.5 The key features of the studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design Median follow up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Single arm studies of midostaurin						
D2201	116 FAS 89 PEP	P2, SA, OL, MC 43 months/76 months ^a	High	AdvSM (ASM or MCL +/- AHN)	ORR, OS, PFS, TTR, DoR, PROs, safety	ORR, OS, PROs, safety
A2213	26 FAS	P2, SA, OL, MC 73 months/124 months ^a	High	AdvSM (ASM or MCL +/- AHN)	ORR, OS, PFS, TTR, DoR, safety	ORR, safety
Historical control studies of midostaurin-treated pts vs midostaurin-naive historical registry controls						
Reiter 2017	89 mido 42 control	Pooled D2201 and A2213 vs German registry controls 79.5 months/84.2 months ^b	High	AdvSM ^d	OS	OS used in a sensitivity analysis
CEREMAST	28 mido 44 control	Mido-treated French pts vs French registry controls 18.5 months/NR ^{b, c}	High	AdvSM	ORR ^e , OS	ORR, OS

Source: D2201 CSR primary analysis; Gotlib 2016; A2213 CSR primary analysis; DeAngelo 2018; Reiter 2017 poster presentation; Chandesris 2016/2017 (CEREMAST).

AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; DB = double blind; DCO = data cutoff; FAS = full analysis set; MC = multi-centre; MCL = mast cell leukaemia; mido = midostaurin; NR = not reported; OL = open label; OS = overall survival; PFS = progression-free survival; PEP = primary efficacy population; PROs = patient reported outcomes; pts = patients; P2 = phase 2; SA = single arm; SM-AHN = systemic mastocytosis with an associated haematological neoplasm; TTR = time to response.

^a read as: "median follow up at primary analysis / median follow up at final or follow up analysis"

^b read as: "median follow up in midostaurin-treated group / median follow up in control group"

^c the French midostaurin-treated patients were from a compassionate access program

^d patients from D2201 and A2213 with a known date of diagnosis were included in Reiter 2017

^e CEREMAST only reported ORR for the midostaurin-treated group and not the control group

Notes:

D2201: FAS was all patients to whom study treatment has been assigned according to the ITT principle. PEP was all patients who had measurable C-findings considered related to SM as per the study steering committee.

6.6 D2201 and A2213 were non-randomised, single-arm, open-label, phase II studies with small sample sizes. Reiter 2017 included patients from D2201 and A2213 with a known date of diagnosis. While Reiter 2017 and CEREMAST compared midostaurin to historical control arms, the treatments used in the historical control groups were highly heterogeneous.

6.7 The risk of performance and detection bias was high for subjective outcomes (e.g., overall response rate [ORR], patient reported outcomes [PROs], and safety) in both D2201 and A2213. In D2201 the concordance in the assessment of best overall response between Investigators and the Study Steering Committee (SCC) was modest (66% [49/74]) and suggested potential reporting bias. In A2213, the outcomes overall survival (OS), progression free survival (PFS), time to response (TTR), and duration of response (DoR) were not pre-specified in the protocol.

6.8 Treatment discontinuation rules differed between D2201 and A2213. D2201 treated patients continuously until disease progression, intolerable toxicity, or withdrawal due to any cause. This was aligned with the requested restriction. In comparison, A2213 additionally required that patients discontinued treatment if a major response (MR) or partial response (PR) to midostaurin was not achieved in the first two cycles.

- 6.9 Baseline characteristics potentially indicated patients had a more severe disease in A2213 compared to D2201; and in the German historical control group compared to the midostaurin-treated group in Reiter 2017. In CEREMAST the inferences were not clear. The observed differences are summarised below but are caveated by the relatively small sample sizes:
- There was a greater proportion of patients in A2213 compared to D2201 with a worse European Cooperative Oncology Group (ECOG) performance status (PS) (ECOG PS of 3: 15% [4/26] vs 8% [7/89]), with more than two C-findings (88.5% [23/26] vs 65% [58/89]), and who had received prior anti-neoplastic regimens (69.2% [18/26] vs 36% [32/89]).
 - In Reiter 2017, patients in the control group compared to the midostaurin-treated group were diagnosed at an older age (71% [30/42] vs 42% [37/89] diagnosed after 65 years), had a higher proportion of patients with KIT D816V mutation (93% [39/42] vs 82% [73/89]), a longer duration of disease (7.3 vs 2.3 months) and were treated with a greater number of therapies (33% [15/46] vs 24% [21/89]).
 - In CEREMAST, there was a greater proportion of patients in the midostaurin-treated group compared to the control group who were male (85% [24/28] vs 61% [27/44]), and had the KIT D816V mutation (96.5% vs 84%), and despite matching for disease subtype there was a greater proportion who had the MCL subtype (11% [5/28] vs 5% [2/44]) which may have indicated more severe disease in the midostaurin-treated group. In contrast, there was a greater proportion of patients in the control group previously treated with steroids (41% vs 21%), cladribine (49% vs 21%), and TKIs (other than midostaurin; 18% vs 0%) potentially suggesting more severe disease in the control group.
- 6.10 The primary endpoint of ORR was measured differently between D2201 and A2213 in terms of the response criteria used, the timepoint of measurement, and the assessor of response. A2213 used the Valent criteria to assess response. In comparison, D2201 used a modified Valent/Cheson criteria that additionally assessed response in patients with transfusion dependent (TD) anaemia or TD thrombocytopenia. Response was assessed by the SCC after six cycles of treatment in D2201 compared to response being assessed by investigators after two cycles of treatment in A2213. In CEREMAST, the authors noted to apply the same response criteria as in D2201. The ESC advised that both the Valent and Valent/Cheson criteria were standard response criteria used in the management of AdvSM.

Comparative effectiveness

- 6.11 Results for D2201 and A2213 will be presented alongside Reiter 2017 and CEREMAST where applicable and at the latest DCO available.
- 6.12 The ORR from D2201, A2213, and CEREMAST are presented in Table 4. Reiter 2017 did not report ORR.

Table 4: Results of ORR across D2201, A2213, and CEREMAST

	D2201		A2213	CEREMAST
	PEP N=89	FAS N=116	FAS N=26	Midostaurin N=28
Overall response rate (ORR=MR+PR), n (%)	53 (59.6)	53 (47.5)	19 (73.1)	~20 (71)
95% CI	48.6, 69.8*	36.4, 55.2	52.2, 88.4	-
Two-sided p-value	<0.001**	<0.001	NR	-
Best overall response, n (%)				
Major response (MR)	40 (44.9)	40 (34.5)	13 (50)	~16 (57)
Complete remission	0	0	0	-
Incomplete remission	19 (21.3)	19 (16.4)	5 (19.8)	-
Pure clinical response	15 (16.9)	15 (12.9)	8 (30.8)	-
Unspecified	6 (6.7)	6 (5.2)	0	-
Partial response (PR)	13 (14.6)	13 (11.2)	6 (23.1)	~4 (14)
Good partial response	11 (12.4)	11 (9.5)	4 (15.4)	-
Minor response	2 (2.2)	2 (1.7)	2 (7.7)	-
Unspecified	0	0	0	-
Stable disease (SD)	11 (12.4)	11 (9.5)	6 (23.1)	-
Progressive disease (PD)	10 (11.2)	10 (8.6)	1 (3.8)	-
Not evaluable	15 (16.9)	42 (36.2)	0	-

Source: Table 2.13, p55 of the submission

ASM = aggressive systemic mastocytosis; CI = confidence intervals; FAS = full analysis set; MCL = mast cell leukaemia; NR = not reported; PEP = primary efficacy population, RBC = red blood cell

* Exact (Clopper-Pearson) confidence interval

** Exact two-sided p-value, null hypothesis, ORR ≤30%

Bold text indicates a statistically significant result

- 6.13 The ESC noted that in D2201, at the time of primary data cut (01 December 2014), response rate after six cycles of treatment for the PEP was 59.6% (95% CI 48.6, 69.8) and was statistically significantly greater than the prespecified 30% threshold ($p < 0.001$). ORR in the PEP comprised of 40/89 (44.9%) patients with a major response (MR) and 13/89 (14.6%) patients with a partial response (PR). Response in the FAS was slightly lower in comparison (ORR = 47.5%, 95% CI 36.4, 55.2).
- 6.14 In A2213, at the time of primary data cut (03 December 2012), the ORR was 73.1% (95% CI 52.2, 88.4) in the first two cycles and comprised 13/26 (50%) with a MR and 6/26 (23.1%) with a PR. At the follow-up analysis (DCO 01 March 2017), the ORR for the first 12 cycles was 69% (95% CI 50, 88), of which 13/26 (50%) had a MR, 5/26 (19%) had a PR. The submission stated that the ORR did not change with follow-up beyond 12 cycles.
- 6.15 CEREMAST reported the ORR in the midostaurin-treated group to be 71% (MR in 57% and PR in 14% of patients) but response in the historical control group was not reported.

6.16 The OS results from D2201, A2213, Reiter 2017 (including the propensity score matched analysis) and CEREMAST are presented in Table 5.

Table 5: Summary of OS results in D2201 (PEP and FAS), A2213 (PEP/FAS), Reiter 2017, and CEREMAST

Study (analysis set, sample size)	Median follow up, months, analysis type	OS events, n/N (%)	Median OS, months (95% CI)		OS HR (95% CI; p-value)
			Midostaurin-treated	Historic control	
Single arm midostaurin studies					
D2201 (PEP, N=89)	43 months, primary	54/89 (60.7)	26.8 (17.6, 34.4)	NE	NE
	76 months, final	64/89 (71.9)			
D2201 (FAS, N=116)	43 months, primary	67/116 (57.7)	28.7 (20.3, 38)		
	76 months, final	80/116 (69)			
A2213 (N=26)	76 months, primary	11/26 (42.3)	40 (19.2, NE)		
	124 months, follow up	22/26 (84.6)	40 (27.3, 52.7)		
Historical control studies					
Reiter 2017, primary unadjusted (n=89 vs 42)	79.5 months, midostaurin	56/89 (62.9)	41.4 (31, 49.1)	19.5 (13, 35.3)	0.50 (0.33, 0.76; 0.0007)^a
	84.2 months, control	36/42 (85.7)			
Reiter 2017, propensity score matched (n=42 vs 42) ^b	79.5 months, midostaurin	31/42 (73.8)	27.8 (19.3, 44.6)	19.5 (13.0, 35.3)	0.64 (0.33, 1.24; NE)
	84.2 months, control	36/42 (85.7)			
CEREMAST (n=28 vs 44) ^c	18.5 months ^d	NA	NR ^e	~39 months ^e	2.2 (1.08, 4.47; 0.02)^f

Source: Table 11-17, p126 D2201 CSR primary analysis; Table 11-2, p25 D2201 final analysis; Table 11-8, p81 A2213 CSR; Reiter 2017 poster presentation; Section 2.6.3.2, pp84-6 of the submission

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NA = not available; NE = not evaluable; NR = not reached; OS = overall survival; PEP = primary efficacy population

^a one-sided p value

^b In Reiter 2017 the propensity score matched analysis was based on age group at diagnosis, type of disease (ASM/MCL/SM-AHM), prior lines of treatment, and sex with the effective sample size reduced to 42 for the midostaurin population after matching.

^c In CEREMAST, the midostaurin-treated and control groups were matched based on age at diagnosis and disease subtype.

^d median follow up in the control group was noted to be similar to Midostaurin (see Chandesris 2017)

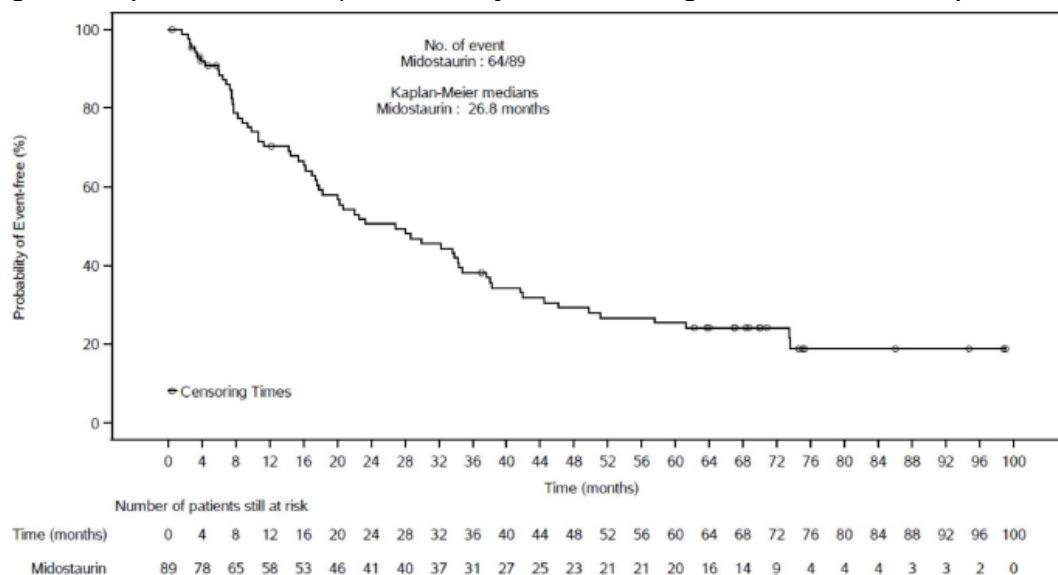
^e median OS was not formally reported in Chandesris 2017 hence values are based on visual inspection of KM plots during the evaluation

^f CEREMAST reported the HR in order of the historical control vs midostaurin i.e., the HR of 2.2 indicated the risk of death was 2.2 times greater in the control group compared to the midostaurin group. The inverse of this HR was 0.45.

Bold indicates a statistically significant result

6.17 The OS Kaplan Meier (KM) plots for midostaurin in D2201 and the A2213 are presented in Figure 1 and Figure 2.

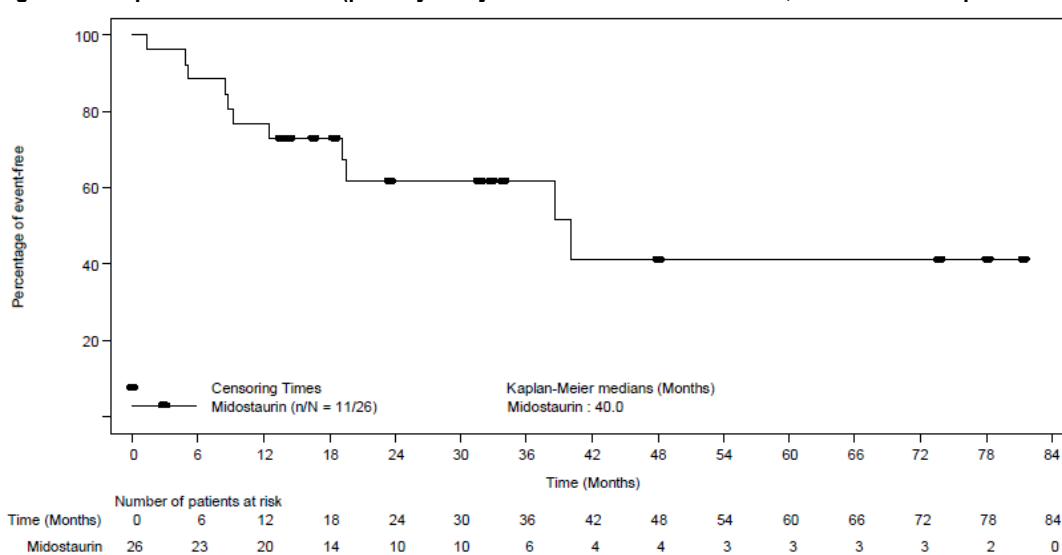
Figure 1: KM plot of OS in D2201 (PEP, final analysis at DCO 27 August 2018 median follow up 76 months)



Source: Figure 2.3, p56 of the submission

DCO = data cut off; KM = Kaplan-Meier; OS = overall survival; PEP = primary efficacy population.

Figure 2: KM plot of OS in A2213 (primary analysis at DCO 3 December 2012, median follow up 73 months)



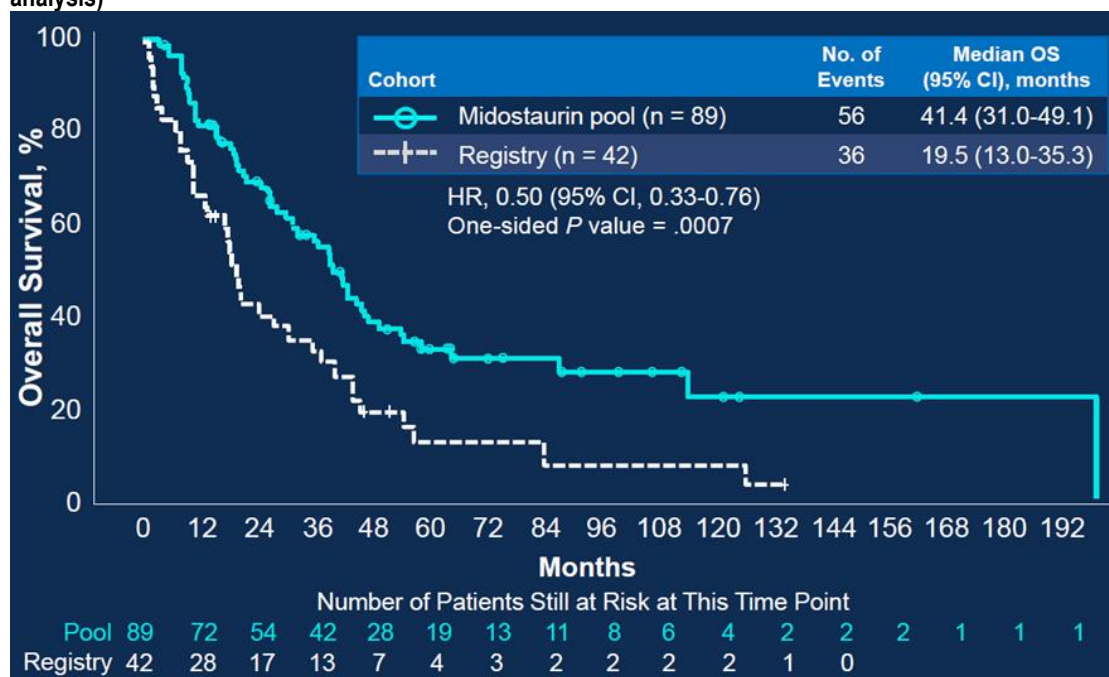
Source: Figure 2.4, p57 of the submission

DCO = data cutoff; FAS = full analysis set; KM = Kaplan-Meier; OS = overall survival.

6.18 In D2201 (PEP), over a median follow up of 76 months, 64/89 (71.9%) patients died, and the median OS was 26.8 months (95% CI 17.6, 34.4). The probability of being alive after five years was 25.5%. The OS results in the FAS were similar to the PEP (median OS 28.7 months). In comparison, in A2213 there were 22/26 (84.6%) midostaurin-treated patients who died over the median follow up of 124 months, and the median OS was notably longer (40 months, 95% CI 27.3, 52.7).

6.19 The OS KM plots comparing the midostaurin-treated groups to the historical control groups in the primary analysis, and the propensity score matched analysis of Reiter 2017, and CEREMAST are presented in Figure 3, Figure 4, and Figure 5, respectively.

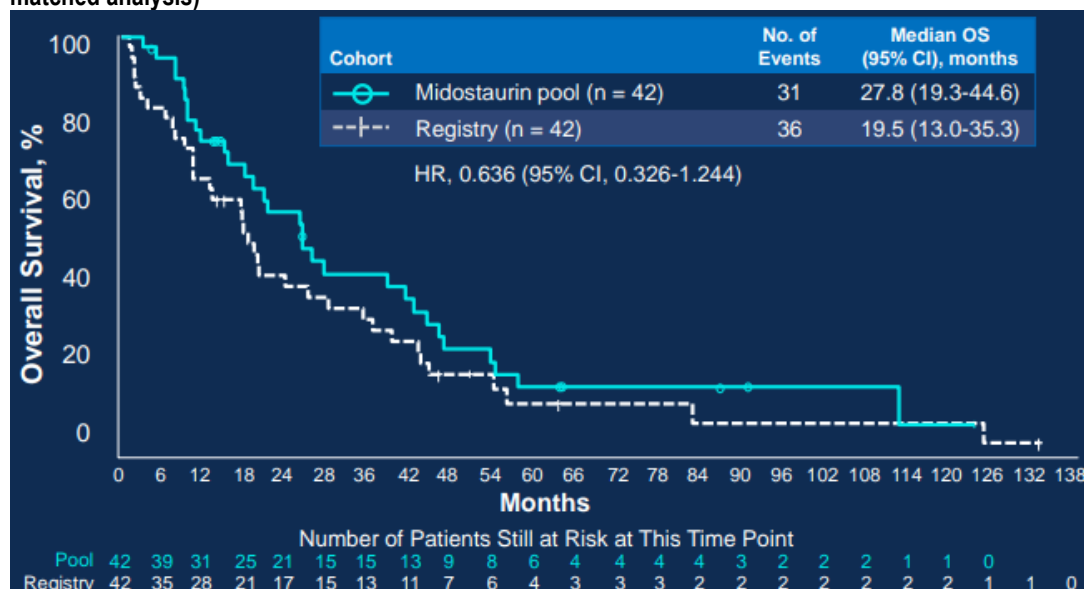
Figure 3: KM plot of OS comparing midostaurin to German historical control group in Reiter 2017 (primary unadjusted analysis)



Source: Figure 2.16, p83 of the submission

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival

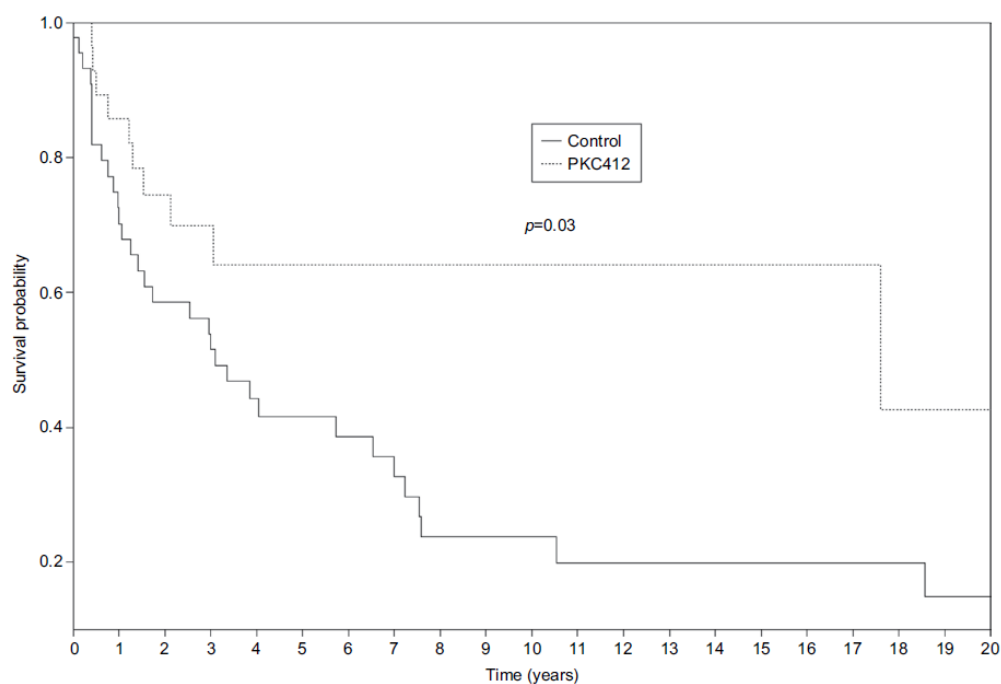
Figure 4: KM plot of OS comparing midostaurin to German historical control group in Reiter 2017 (propensity score matched analysis)



Source: Reiter 2017 poster presentation

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival

Figure 5: Survival curves among patients treated with midostaurin and French historical control in CEREMAST



Source: Figure 2.17, p86 of the submission
 PKC412 = midostaurin-treated group

Notes:

Survival curves at last follow-up in April 2015
 Number of patients at risk were not provided in CEREMAST

- 6.20 In Reiter 2017, the primary (unadjusted) analysis significantly favoured the midostaurin-treated group compared to the historical control group (OS HR = 0.5, 95% CI 0.33, 0.76; $p=0.0007$; median OS 41.4 vs 19.5 months, respectively). However, after adjusting for age group at diagnosis, type of disease (ASM/MCL/SM-AHN), prior lines of treatment, and sex in the propensity score matched analysis, a significant OS HR was not observed (HR = 0.64, 95% CI 0.33, 1.24; median OS 27.8 vs 19.5 months in the midostaurin-treated group and control group, respectively).
- 6.21 In CEREMAST, a significantly superior OS rate was reported in the midostaurin-treated group (42.7%, 95% CI 18.1, 100) compared to the control group (14.9%, 95% CI 6.1, 36) ($p=0.03$). The historical control group showed a statistically significant risk of death twice that of the midostaurin-treated group (OS HR = 2.2, 95% CI 1.08, 4.47; $p=0.02$; of note the historical control group was the reference in this analysis).
- 6.22 The inverse OS HR in CEREMAST was 0.45 and was more favourable than that observed in Reiter 2017 (OS HR = 0.50 [primary unadjusted] and 0.64 [propensity score matched]). The evaluation considered the propensity score matched results from Reiter 2017 provided a more reliable estimate than the primary results as it adjusted for a greater number of prognostic factors that potentially confounded OS. Based on the propensity score matched results there was potentially no difference in OS between patients treated with midostaurin and patients not treated with midostaurin. The PSCR argued that the details in Reiter 2017 were limited and hence a complete

evaluation of these analyses could not be performed increasing uncertainty. The PSCR claimed that CEREMAST was a more reliable estimate for OS. The ESC acknowledged that details in Reiter 2017 were from an abstract/poster presentation but noted that the study comprised of patients from D2201 and A2213 and both studies were well documented. In addition, the ESC noted that CEREMAST was a smaller study (N=72 vs 131) with shorter follow up compared to Reiter 2017 (18.5 months vs 79.5/84.2 months). The ESC noted that even after propensity score matching, Reiter 2017 (n=84) was still larger than CEREMAST. The pre-PBAC response stated there were differences between the propensity score matched analyses reported in the abstract versus that reported in the poster. Noting the limitations of using abstract and poster data, the pre-PBAC response proposed using a Reiter 2017 multivariate analyses which reported a HR of 0.517 (95% CI 0.319, 0.839). The pre-PBAC response argued this was a more conservative estimate of OS than the submission base case, while adjusting for additional covariates included and measured in the Reiter 2017 study.

- 6.23 PFS was immature at the D2201 primary analysis and A2213 follow up analysis (50.6% [45/89] and 38.5% [10/26] PFS events occurred, respectively). Similarly observed with OS, the median PFS was notably longer in A2213 compared to D2201 (41 vs 17 months) but should be considered alongside the small sample size and PFS not being prespecified in A2213.
- 6.24 The median TTR in D2201 (PEP) was 0.3 months (range: 0.1, 3.7) at the primary analysis (median follow up 76 months); and in A2213 the median TTR was 0.95 months (range: 0.85, 1.87) at the primary analysis (median follow up 76 months).
- 6.25 The median DoR in D2201 was 31.4 months (median 43 months follow up) in 53 responders; and in A2213 was 132 months (median 124 month follow up) in 18 responders. DoR results in A2213 should be interpreted with caution since the analysis was stated to be based on 18 patients, but the DoR KM plot was only based on 12 patients; and visual inspection of the KM plot showed the median was reached after ~37 months despite stating the formal median DoR was at 132 months.
- 6.26 PROs were only reported in D2201 and included the Short Form 12 Health Survey Questionnaire (SF-12v2) and Memorial Symptom Assessment Scale (MSAS). There were improvements from baseline in QoL after 36 cycles of midostaurin treatment as measured by the SF-12v2 and MSAS. However, these outcomes should be interpreted with caution as were exploratory outcomes in D2201 and there was a notable amount of incomplete data (e.g. only 53/89 [59.5%] patients had evaluable SF-12v2 scores at baseline and had assessments for at least 168 days). In addition, the QoL improvements in comparison to SOC therapies was unknown given D2201 was a single arm study.

Comparative harms

6.27 A summary of adverse events (AEs) from D2201 and A2213 based on the safety analysis set (SAS) are presented in Table 6. CEREMAST only reported AEs in the midostaurin-treated group and Reiter 2017 did not report AEs, though it is acknowledged Reiter 2017 comprised patients from D2201 and A2213.

Table 6: Summary of key AEs in the D2201 at the final analysis (median follow up 76 months) and A2213 at the primary analysis (median follow up 76 months)

	D2201 SAS (N=116), n (%)		A2213 SAS (N=26), n (%)	
Any AE	116 (100.0)		26 (100.0)	
Grade 3/4	105 (90.5)		16 (61.5)	
Suspected to be study drug-related	108 (93.1)		25 (96.2)	
Any serious AE	88 (75.9)		12 (46.2)	
Grade 3/4	83 (71.6)		11 (42.3)	
Suspected to be study drug-related	26 (22.4)		4 (15.4)	
AEs leading to discontinuation	35 (30.2)		4 (15.4)	
Suspected to be study drug-related	16 (13.8)		1 (3.8)	
AEs leading to dose adjustment or interruption	-		-	
AE leading dose reduction	53 (45.7)		11 (42.3)	
AE leading to dose interruption	52 (48.8)		11 (42.3)	
AE requiring additional therapy ^a	116 (100)		NR	
All deaths	80 (69)		4 (15.4)	
On-treatment deaths	25 (21.6)		4 (15.4)	
Most common AEs (≥10%) of patients	Any grade	Grade 3/4	Any grade	Grade 3/4
Nausea	94 (81.0)	8 (6.9)	24 (92.3)	0
Vomiting	77 (66.4)	8 (6.9)	19 (73.1)	0
Diarrhoea	65 (56.0)	9 (7.8)	8 (30.8)	0
Anaemia	42 (36.2)	33 (28.4)	9 (34.6)	4 (15.4)
Thrombocytopenia	23 (19.8)	15 (12.9)	8 (30.8)	3 (11.5)
AEs suspected to be study drug-related				
Nausea	85 (73.3)	7 (6.0)	24 (92.3)	0
Vomiting	71 (61.2)	7 (6.0)	19 (73.1)	0
Diarrhoea	34 (29.3)	2 (1.7)	7 (26.9)	0
Lipase increased	11 (9.5)	6 (5.2)	3 (11.5)	2 (7.7)
Thrombocytopenia	9 (7.8)	4 (3.4)	4 (15.4)	1 (3.8)
Anaemia	8 (6.9)	4 (3.4)	4 (15.4)	2 (7.7)
Serious AEs regardless of study drug relationship				
Pneumonia	11 (9.5)	9 (7.8)	2 (7.7)	2 (7.7)
Sepsis	10 (8.6)	10 (8.6)	2 (7.7)	2 (7.7)
Anaemia	8 (6.9)	7 (6.0)	0	0
Diarrhoea	8 (6.9)	4 (3.4)	0	0

Source: Table 2.17, p68; Table 2.18, pp69-70; Table 2.20, p72-3 of the submission; Table 12-3, p32 D2201 CSR final analysis; Table 12-5, p149 of D2201 CSR primary analysis

AE = adverse event; CI = confidence interval; n = number of participants reporting data; N = total participants in group; PEP = primary efficacy population; SAS = safety analysis set.

^a Reported at primary analysis only Table 12-5, D2201 CSR primary analysis

No risk difference or relative risk calculations could be conducted during the evaluation due to the absence of a comparator arm

6.28 In D2201, serious AEs were reported in 75.9% (88/116) patients, of which 71.6% (83/116) were Grade 3 or 4 and this included pneumonia (9.5% [11/116]), sepsis and anaemia (8.6% [10/116] for both). There were 22.4% (26/116) serious AEs suspected to be drug related. AEs that led to discontinuation occurred in 30.2% (35/116), of

which 13.8% (16/116) were suspected to be drug related. There were 45.7% (53/116) and 48.8% (52/116) of patients who experienced AEs leading to dose reduction or dose interruption, respectively. All patients experienced an AE that required additional therapy. There were 25 deaths (21.6%) that occurred while on-treatment. This included 12 deaths due to disease progression and 13 deaths due to 'other causes' (cardiac disorders [n=5], multiple organ dysfunction syndrome [n=3], sepsis [n=3], pneumonia [n=1], and acute myeloid leukaemia [n=1]), although the CSR noted that no deaths were related to midostaurin (D2201 CSR final analysis).

- 6.29 In comparison, in A2213 serious AEs were reported in 46.2% (12/26) of patients, of which 42.3% (11/26) were Grade 3 or 4 and this also included pneumonia and sepsis (7.7% [2/26] for both). There were 15.4% (4/26) were suspected to be drug related. AEs leading to discontinuation occurred in 15.4% (4/26) of patients of which 3.8% (1/26) was suspected to be drug related. There were 42.3% (11/26) of patients who experienced AEs leading to both dose reduction or interruption. There were four deaths (15.4%) and all occurred on-treatment (systemic mastocytosis [n=1], multi-organ failure [n=1], and sepsis [n=2]).
- 6.30 The most common AEs of special interest (AESIs) in D2201 included severe infections (66.4% [77/116] any grade; 31.9% [37/116] Grade 3 or 4), leukopenia (22.4% [26/116] any grade; 18.1% [21/116] Grade 3 or 4), and pulmonary toxicity (13.8% [16/116] any grade; 4.3% [5/116] Grade 3 or 4). In A2213 the most frequent clinically notable AEs⁹ of any grade and regardless of study drug relationship were gastrointestinal events (e.g., nausea, vomiting, diarrhoea) (100% [26/26]), infections (61.5% [16/26]); haematologic events (e.g., anaemia and thrombocytopenia; 57.7% [15/26]), and hepatic events (e.g., hepatosplenomegaly; 34.6% [9/26]).
- 6.31 CEREMAST reported AEs of any grade (and Grade 3 and/or 4 events) in the midostaurin-treated group but not the historical control group. The following events were reported (only percentages reported): nausea (89% any grade and 39% Grade 3 and/or 4); vomiting (25% any grade and 3.5% Grade 3 and/or 4); photosensitivity (25% any grade); fatigue (14% any grade and 3.5% Grade 3 and/or 4); diarrhoea (10.5% any grade); drug-induced taxidermy (3.5% any grade and 3.5%); peripheral oedema (3.5% any grade); lymphopenia (67% any grade); cytolytic hepatitis (7% any grade); and 10% discontinued due to AEs.
- 6.32 No comparative evidence was presented for midostaurin compared to SOC therapies to support the claim of non-inferior safety. The PSCR stated that although there are no randomised controlled trials in midostaurin for AdvSM, the safety of midostaurin is demonstrated in two single-arm, open label studies.

⁹ In A2213, clinically notable AEs were defined as those that were previously identified or that were determined to be potential risks of study drug therapy

Benefits/harms

- 6.33 Given the absence of a comparator arm in the two single arm studies and limited inferences of the comparator arm in the two historical control studies, this did not allow for quantitative comparison of the benefits and harms of midostaurin and SOC. Accordingly, the benefits/harms table has not been presented.

Clinical claim

- 6.34 The submission described midostaurin as superior in terms of effectiveness compared with SOC. The evaluation considered this claim was not adequately supported. The key issues were:
- D2201 and A2213 could not inform the comparative ORR and OS benefit of midostaurin vs SOC given they were single arm, open-label studies with small sample sizes.
 - Although Reiter 2017 and CEREMAST compared the OS in patients treated with midostaurin compared to patients not treated with midostaurin, a key limitation was that the therapies in which midostaurin was being compared against were not clear. There were also limitations in both Reiter 2017 (e.g. patients in the control group appeared to have more severe disease compared to the midostaurin-treated group; and included the biases from D2201 and A2213) and CEREMAST (e.g., heterogenous sample, small study and short follow up) and details were limited in both studies.
 - It is acknowledged that AdvSM is a rare condition, and the available evidence is inherently limited, with no randomised controlled trials expected in the near future. With this in mind, the propensity score matched result from Reiter 2017 was considered the more reliable estimate of comparative OS as it adjusted confounding factors. The propensity score matched results indicated there was potentially no difference in OS between patients treated with midostaurin and patients not treated with midostaurin (OS HR 0.64, 95% CI 0.33, 1.24).

The PSCR argued that like other rare diseases, clinical studies in AdvSM are inherently limited to single-arm studies increasing the uncertainty. In the absence of a direct comparison, the PSCR argued that the historical control studies (CEREMAST, Reiter 2017) provided supportive evidence for OS in relation to current SOC. The ESC acknowledged the difficulty of obtaining data in this rare disease. The ESC noted that in D2201, ORR after 6 cycles of treatment was 59.6% (95% CI 48.6, 69.8) and statistically significantly greater than the prespecified 30% threshold. The ESC also agreed with the PSCR that the historical control studies provided supportive evidence for OS in favour of midostaurin. The ESC noted that in both the Reiter 2017 primary unadjusted and the CEREMAST comparisons a significantly superior OS rate was reported in the midostaurin-treated group. The ESC noted that the increase in OS was no longer statistically significant for the Reiter 2017 analysis when the propensity score matching was used and this reflected the wider 95% confidence interval for the

matched analysis, however the point estimate for the increase in OS remained numerically in favour of midostaurin. Overall, the ESC considered that while there is significant uncertainty due to the limitations in the evidence in this rare disease it is likely that midostaurin was superior in terms of effectiveness compared to SOC.

- 6.35 The submission described midostaurin as non-inferior in terms of safety compared to SOC. The evaluation considered this claim was not supported. The submission informed the safety claim with the single arm studies, D2201 and A2213, and no comparative safety evidence was presented. The ESC again acknowledged the limitations of the data in this rare disease and considered that midostaurin is likely to be non-inferior compared to SOC however this is uncertain.
- 6.36 The PBAC considered that, while there was significant uncertainty due to the limitations in the evidence, the claim of superior comparative effectiveness was reasonable in this rare disease.
- 6.37 The PBAC considered that there was a lack of comparative data to support a claim of non-inferiority. However, the PBAC advised that the toxicities were as expected and agreed with the ESC that in this rare disease it was uncertain but likely that midostaurin was non-inferior in safety compared with SOC.

Economic analysis

- 6.38 The submission presented a stepped, modelled economic evaluation based on non-randomised studies. The type of economic evaluation presented was a cost-utility analysis.

6.39 The key components of the economic evaluation are presented in Table 7.

Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Midostaurin vs SOC (comprising of cladribine and peginterferon alpha-2a)
Time horizon	20 years in the model base case vs. median follow up of 76 months and median OS of 26.8 months in D2201
Outcomes	LYG, QALYs gained
Methods used to generate results	PSM
Health states	PF response, PF without response, PD, death.
Cycle length	28 days
Allocation to health states	<ul style="list-style-type: none"> OS in the midostaurin arm was informed by OS data from D2201. OS in the SOC arm was derived using a PH modelling approach using the OS HR from CEREMAST applied to the OS curve of midostaurin. PFS in the midostaurin arm was informed by ToT data from D2201. PFS in the SOC arm was informed by a ratio of ($ORR^{midostaurin} / ORR^{SOC}$) applied to the ToT curve for midostaurin. <ul style="list-style-type: none"> Initial occupation of the PF response and PF without response health states in the midostaurin arm were informed by pooled ORR from D2201, A2213, and CEREMAST (64.3%) and in the SOC arm were informed by pooled ORR from Barete 2015 and Valent 2003 (52.2%). The model assumed that after the first two cycles of treatment, responders will occupy the PF response state and non-responders will occupy the PF without response state. Occupation of the PD health state was the difference between OS and PFS (ToT) curves.
Extrapolation method	<p>A single extrapolation was used in this model i.e., OS for the midostaurin arm. A PH modelling approach was used to derive the OS and PFS (ToT) curves in the SOC arm.</p> <p>For midostaurin, OS KM data from D2201 was used up to 46 months and then extrapolated using the generalised gamma function. Convergence was not assumed in the model but may have been appropriate given the substantial uncertainty in the comparative benefit between midostaurin and SOC.</p> <p>ToT data from D2201 was mature therefore no extrapolation was applied.</p> <p>In the midostaurin arm, 41% of LYG, 39% of QALY gains, and 7% of costs occur in the extrapolated period (16.2 years extrapolated).</p> <p>In the SOC arm, 13% of LYG, 13% of QALY gains, and 5% of total costs occur in the extrapolated period (16.2 years extrapolated). It is acknowledged that a PH approach was used to model SOC and none of the modelled benefits and costs were based on observed KM data for SOC.</p>
Health related quality of life	<p>Utility values were direct from the SF-12v2 in D2201 and mapped to the EQ-5D using the Sullivan and Ghuschyan 2006 algorithm. AE frequency based on pooled data from D2201 and A2213. AE utility decrement was based on the NICE TA400 and NICE TA500.</p> <ul style="list-style-type: none"> PF response = 0.85 PF without response = 0.80 PD = 0.75 AE utility decrement = -0.0084 (midostaurin) and -0.0187 (SOC) once off Utility decrement associated with injections = -0.02 for administration of IV cladribine/SC peginterferon alpha-2a per 28-day cycle for SOC arm
Healthcare resource use and costs	<p>Healthcare resource use included:</p> <ul style="list-style-type: none"> Treatment costs (midostaurin = \$████ per month [30.4 days]; SOC = \$883.54 per month [30.4 days]). An RDI of 87% was applied to both arms. <ul style="list-style-type: none"> SOC market share = 65% peginterferon alpha-2a and 35% cladribine AE management costs (midostaurin = \$9,039.94; SOC = \$18,428.83 once off cycle 1) Disease management costs (pre-progression: midostaurin = \$230.53 and SOC = \$429.82 per 28-day cycle; post-progression both arms = \$226.27 per 28-day cycle)

Component	Summary
	<ul style="list-style-type: none"> Terminal care costs (\$52,291.45 once off upon death).

Source: Table 3.1, p92; Table 3.6, p101; Table 3.7, p103; Table 3.8, p103; Table 3.9, p109; Table 3.12, p107; Table 3.14, p109; and Table 3.15, p110; and p111 of the submission

AE = adverse event; SC = subcutaneous; EQ-5D = EuroQol 5-Dimension questionnaire; LYG = life years gained; HR = hazard ratio; NICE = National Institute for Health and Care Excellence; QALY = quality adjusted life years; ORR = overall response rate; OS = overall survival; PD = progressed disease; PF = progression free; PFS = progression free survival; PH = proportional hazards; PSM = partitioned survival model; QALY = quality adjusted life year; RDI = relative dose intensity; SF-12v2 = 12-Item Short-Form Health Survey version 2; SOC = standard of care; TA = Technical Appraisal; ToT = time on treatment

- 6.40 The submission adopted a four-health state partitioned survival model (PSM; (i) progression free [PF] with response, (ii) PF without response, (iii) progressed disease [PD], and (iv) death) to model the cost and benefits (life years gained [LYG] and quality adjusted life years [QALY] gained) of midostaurin compared to SOC in patients with AdvSM over a 20-year time horizon.
- 6.41 Patients entered the model progression free and initiated treatment with midostaurin or SOC. Patients initially occupied either the PF with response or PF without response health states based on their response to midostaurin or SOC treatment. Patients then either remained in the PF health states (with or without response), or experienced disease progression and entered the PD state, or died (absorbing health state). Transitions to PD were based on the difference between OS and PFS (i.e., ToT). Patients accrued the associated costs and benefits according to time spent in the PF with response or PF without response, PD, or death health states.
- 6.42 The model assumed that patients who responded to midostaurin in the first two cycles would continue treatment in the PF with response health state and patients who did not respond would discontinue midostaurin and occupy the PF without response health state. The treatment discontinuation rules in the model did not align with the requested restriction, which was predicated on experiencing disease progression and not a lack of response to treatment. Treating to response in the model led to a smaller proportion of patients on midostaurin treatment and likely underestimated total costs compared to what may be expected in clinical practice based on the restriction. Furthermore, separating the PF health state according to response meant that the ORR in the midostaurin arm was a driver in the model due to its impact on midostaurin treatment costs which were substantially higher than SOC costs.
- 6.43 In the midostaurin arm, the submission pooled ORR data from D2201, A2213, and CEREMAST. In the SOC arm, ORR was pooled from Barete 2015 (n=32) and Hauswirth 2004¹⁰ (N=5) with these studies representing cladribine and peginterferon alpha 2a respectively. The ORR inputs had substantial transitivity issues and were considered uncertain. ORR in the midostaurin arm had a considerable impact on the incremental cost effectiveness ratio (ICER) whereas ORR in the SOC arm had a minor impact on the

¹⁰ Hauswirth AW, et al. (2004) Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: report of five cases and review of the literature. *Leuk Res.* Mar;28(3):249-57. doi: 10.1016/s0145-2126(03)00259-5. PMID: 14687620. The submission appeared to incorrectly cite this study as Valent 2023.

ICER given the substantially lower treatment costs compared to midostaurin. If treatment costs were included for non-responders in the model as per the restriction, the ICER increased by +|% (see Table 12). The PSCR agreed with the evaluation that the treatment discontinuation rules in the model did not align with the requested restriction and proposed changing the restriction to be consistent with the economic model (see paragraph 3.5). The ESC agreed with the evaluation that the evidence did not reliably inform a separation of the PF health state into 'PF with response' and 'PF without response'. The pre-PBAC response argued that if the PSCR proposed changes to the restriction were accepted then condensing the PF health states would contradict this as it would allow non-responders to continue therapy.

- 6.44 The submission applied a 20-year time horizon. A 20-year time horizon was considered optimistic when compared to the median OS of 26.8 months in D2201 (which informed the model). Although the base case 20-year time horizon appeared to capture most downstream costs and benefits (i.e., <8% of patients alive in the midostaurin arm and <1% alive in the SOC arm), this was based on the favourable OS modelling of midostaurin (i.e., generalised gamma extrapolation) and the absence of convergence. When more conservative OS extrapolations were applied, shorter time horizons appeared reasonable (e.g., under the log normal [best statistical fit] 6.8% of patients were alive at 15 years and increased the ICER +|%; and under the exponential [most conservative] 6.9% of patients were alive at 10 years and increased the ICER +|%). The ESC considered that a 20-year time horizon was optimistic for AdvSM which is an aggressive disease in patients with a median age of diagnosis of 59 years.¹¹ The ESC advised that a 10-year time horizon would be more reasonable. The pre-PBAC response accepted a 10-year time horizon.
- 6.45 The base case used OS KM data from D2201 up to 46 months then applied the generalised gamma extrapolation to model midostaurin survival. The truncation point was selected according to methodology from GebSKI 2018.¹² Of note, it appeared the KM data in the model was more favourable towards midostaurin compared to the actual OS data reported in D2201 (median OS in the model was ~30 months vs 26.8 months in PEP and 28.7 months in FAS in D2201). The reason for this discrepancy could not be identified.
- 6.46 The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics and modelled extrapolations are presented in Table 8 and Figure 6.

¹¹ Gleixner KV, et al. (2018) Treatment of Patients with Aggressive Systemic Mastocytosis, Mast Cell Leukemia and Mast Cell Sarcoma: A single centre experience. *Blood*. Nov;132(Supplement 1): 1769. <https://doi.org/10.1182/blood-2018-99-116465>

¹² GebSKI V, et al. (2018) Data maturity and follow-up in time-to-event analyses. *Int J Epidemiol*. Jun 1;47(3):850-859. doi: 10.1093/ije/dyy013. PMID: 29444326.

Table 8: AIC and BIC statistics – OS in midostaurin arm

Standard parametric models	OS	
	AIC	BIC
Exponential	623.15	625.63
Weibull	624.93	629.91
Log-logistic	617.93	622.91
Log-normal	615.87	620.85
Gompertz	621.61	626.59
Generalised gamma	616.65	624.12

Source: Table 3.5, p100 of the submission

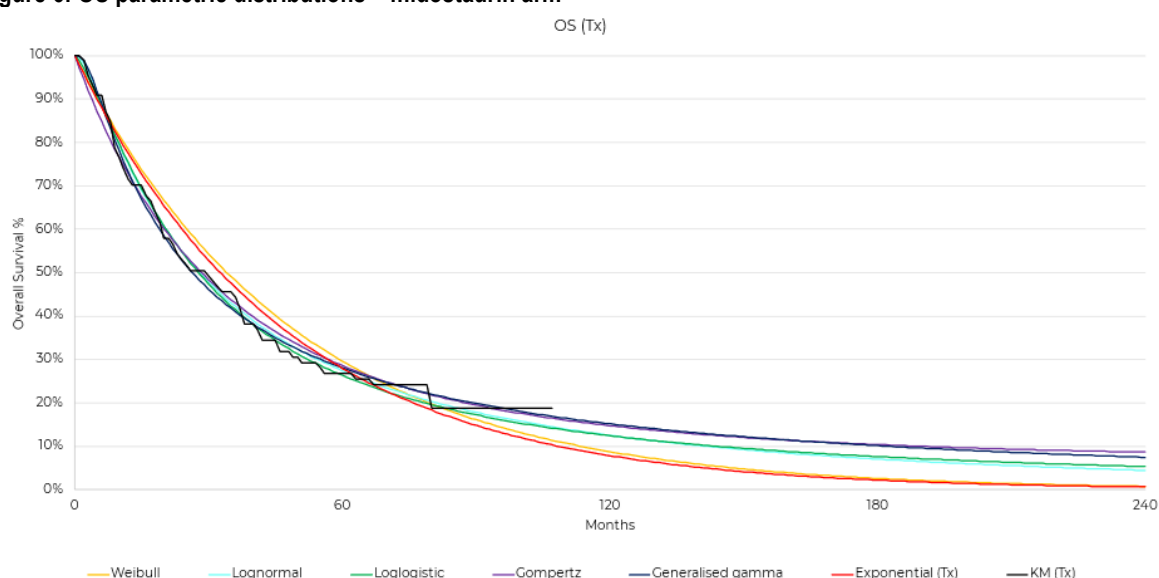
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival

Bold text indicates the best AIC or BIC fit

Grey shaded indicates the extrapolation selected in the base case

6.47 The submission stated that selection of the generalised gamma function was based on the statistical fit, visual fit, and clinical plausibility. The submission stated the log normal was the best fitting AIC and BIC function but was not compatible with the proportional hazards (PH) model. The justification for selecting the generalised gamma function was not reasonable and it appeared to be the most optimistic extrapolation after the observed period. The log normal function produced plausible OS estimates and was compatible with the model (increased the ICER by +1%). The PSCR argued that log-normal distributions are not appropriate for PH models. The ESC considered that the PSCRs reasoning was not applicable to the model as the submission had ‘forced’ the assumption of PH in order to generate the SOC survival curves and hence the shape of the hazard function (i.e. monotonic or non-monotonic) in the context of the PH assumption was irrelevant to the model. The ESC agreed with the evaluation that the log-normal function was appropriate. The pre-PBAC response accepted the use of the log-normal function.

Figure 6: OS parametric distributions – midostaurin arm

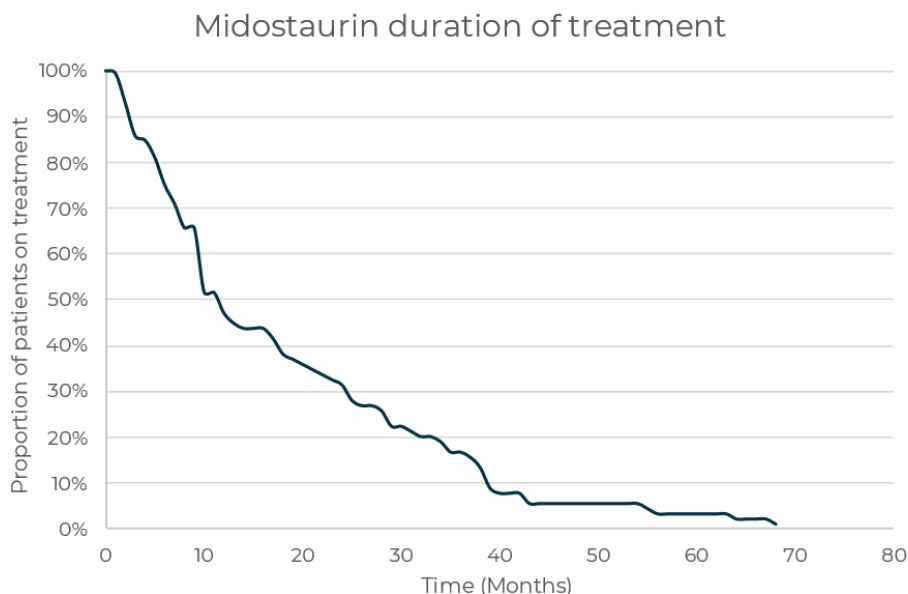


Source: Figure 3.2, p98 of the submission

KM = Kaplan Meier; OS = overall survival; Tx = treatment

- 6.48 The submission applied the OS HR from CEREMAST (see paragraph 6.21) to the OS curve for midostaurin to derive the modelled SOC survival. The evaluation considered CEREMAST was a less reliable study compared to Reiter 2017 and did not produce externally valid OS estimates (i.e., the median OS for SOC in the base case was ~11 months compared to the 19.5 months in the historical control group in Reiter 2017 and ~36 months in CEREMAST). The evaluation considered the propensity score matched analysis from Reiter 2017 provided the most reliable estimate for OS benefit in patients treated with midostaurin compared to those not treated with midostaurin. Since Reiter 2017 included patients directly from D2201 and A2213, the modelled SOC survival also would be internally consistent. Applying the propensity score matched results in Reiter 2017 (OS HR = 0.636) led to a modelled median OS in the SOC arm of ~18 months and increased the ICER by +1% (see Table 12). The ESC noted the arguments from the evaluation and PSCR regarding the reliability of the CEREMAST versus the Reiter 2017 studies (see paragraph 6.22). The ESC agreed with the evaluation that the use of the more conservative Reiter 2017 propensity score matched analysis OS HR was appropriate given the uncertainty due to the limitations of the clinical evidence. However, the ESC noted that there is considerable uncertainty associated with this parameter. The pre-PBAC response argued that using a Reiter 2017 multivariate analyses which reported a HR of 0.517 (95% CI 0.319, 0.839) was more appropriate than the Reiter 2017 propensity score matched analysis OS HR (see paragraph 6.22).
- 6.49 Time on treatment (ToT) in the midostaurin arm was based on mature ToT KM data from D2201 and hence no extrapolation of ToT was conducted (see Figure 7). ToT in the SOC arm was modelled using the PH approach and the HR of 1.23 was applied to the ToT curve in midostaurin arm. This ratio was based on the pooled ORR in the midostaurin arm (64.3%) and in the SOC arm (52.2%). No PFS data was used or provided in the model. There were applicability issues when informing the PF health states using ToT data from D2201 as the PD health state would have included patients who stopped treatment due to reasons not related to disease progression (e.g., 30% [35/116] of patients discontinued treatment due to unacceptable toxicity in D2201 [FAS]).

Figure 7: ToT KM curve midostaurin



Source: Figure 3.4, p102 of the submission
 KM = Kaplan Meier; ToT = time on treatment

6.50 Under the base case assumption that midostaurin patients were treated to response, the treatment durations in the model were as follows:

- Midostaurin arm 12.04 months for responders and 0.71 months in the first two cycles for non-responders (12.76 months total) with no half cycle correction (HCC) or 11.72 months for responders and 0.69 months in the first two cycles for non-responders (12.42 months) with HCC. The HCC duration of 12.42 months was used in the model.
- SOC arm 15.65 months no HCC (patients received SOC regardless of response) or 15.15 months with HCC. The HCC duration of 15.15 months was used in the model.

The ESC noted that the treat to response approach used in the model resulted in a modelled treatment duration for midostaurin that was considerably lower than in D2201 (12.76 vs 18.7 months, respectively) and was therefore not internally valid with the data in which informed it. In addition, 12.1% (14/116) of patients in D2201 discontinued due to “administrative problems” which were patients who accessed midostaurin on a compassionate access scheme at the end of the study (D2201 CSR final analysis). As such 12.1% of the ToT data in D2201 did not truly reflect treatment discontinuation. The PBAC noted the median duration of midostaurin treatment in D2201 was 11.4 months (range: 0.3, 68.3 months). The PBAC noted the mean duration of midostaurin treatment in A2213 was 21.4 months and the median duration of treatment was 9.8 months.

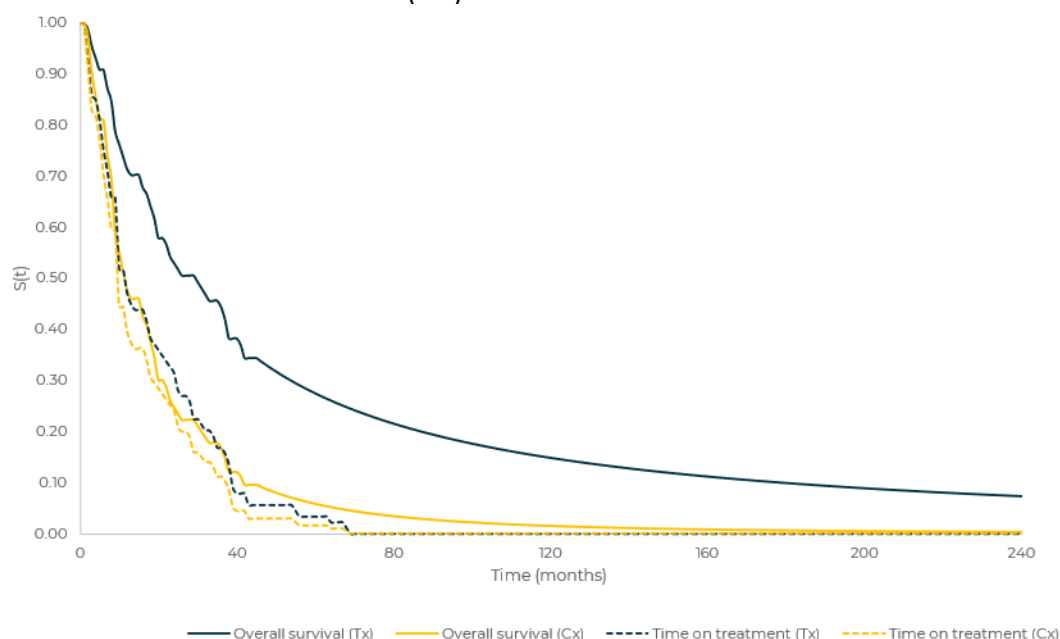
6.51 The modelled PFS (ToT) in the SOC arm was uncertain as there were:

- Translational issues with the PFS (ToT) HR ($ORR^{midostaurin}/ORR^{SOC}$) and D2201. The modelled PFS (ToT) in the SOC arm assumed that ORR was proportionally related to PFS (ToT) which may not be a reasonable assumption since the PH approach was dependent on the ToT curve from D2201 where treatment discontinuation was irrespective of response. Further, uncertain ORR estimates in both arms added uncertainty to the SOC treatment duration; and
- The SOC PFS (ToT) was not internally consistent. Since PFS (ToT) in the SOC arm was dependent on the ratio $ORR^{midostaurin}/ORR^{SOC}$, the PFS (ToT) of the SOC arm could change independent of changes to SOC response. For example, if the response of midostaurin increased to 100% while remaining unchanged in the SOC arm, the PFS and therefore treatment duration of the SOC decreased from 15.65 to 10.59 months. This suggested that if the response of midostaurin improved, then patients on SOC will be PF and treated for less time despite the response to SOC being unchanged, which was not plausible. Moreover, it was not clear whether treatment duration in the SOC was externally valid against the literature which was limited in AdvSM.

Assuming a fixed HR that was not dependent on ORR would reduce the uncertainties discussed. For example, assuming the PFS (ToT) HR that informed SOC was equal to the OS HR that informed SOC (e.g., CEREMAST or Reiter 2017) was an internally consistent approach. Applying the OS HR from CEREMAST and Reiter 2017 led to a +1% and +1% increase in the ICER, respectively (see Table 12).

6.52 The base case OS and PFS (ToT) curves are presented in Figure 8.

Figure 8: Base case modelled OS and PFS (ToT) for midostaurin and SOC arms



Source: Figure 3.7, p113 of the submission.

Cx = comparator arm; OS = overall survival; SOC = standard of care; S(t) = survival; ToT = time on treatment; Tx = treatment arm

6.53 The submission informed the utility values for the PF with response, PF without response, and PD health states based on the SF-12v2 data from D2201 and mapped to the EuroQol 5-Dimension questionnaire (EQ-5D) using the algorithm by Sullivan and Ghushchyan 2006. The utility values based on D2201 were uncertain, particularly the PF without response (0.80) and PD health states (0.75). Noting that AdvSM is associated with debilitating symptoms and poor QoL, a PD utility value of less than 0.75 may be plausible. The ESC noted the EQ-5D-3L population norm utility values for Australians aged 55-64 and 65-74 years old were 0.85 and 0.82 respectively.¹³ Given the impact of AdvSM on QoL the ESC considered a PD utility value of 0.75 was unlikely to have face validity.

6.54 PD utility was a driver of the model, whereas PF with response and PF without response health states were not. This appeared to be attributed to the OS modelling assumptions favouring midostaurin in which the majority of benefits accumulated in the PD health state over the 20-year time horizon (89% of incremental LYGs occurred in the PD health state). Though, given the model did not include post-progression therapies for patients entering the PD state, it may not have been clinically plausible

¹³ Clemens, S., Begum, N., Harper, C. et al. A comparison of EQ-5D-3L population norms in Queensland, Australia, estimated using utility value sets from Australia, the UK and USA. *Qual Life Res* 23, 2375–2381 (2014). <https://doi.org/10.1007/s11136-014-0676-x>

that most of the benefits from midostaurin occurred while off-treatment and with progressed disease. The ESC noted that reducing the PD utility from 0.75 to 0.70 and to 0.60 increased the ICER by +1% and +1%, respectively (see Table 12). The ESC considered the PD utility value of 0.75 to be too high and that a value in the range of 0.6 to 0.7 was more plausible. In this context the ESC considered it may be appropriate for a value of 0.65 to inform the base case model. The pre-PBAC response argued that trial-based utilities were the most appropriate for use in the economic model.

- 6.55 The model applied an AE utility decrement of -0.00836 in the midostaurin arm and -0.01865 in the SOC arm. Application of AE management costs were also lower in the midostaurin arm compared to the SOC arm (\$9,039.94 vs \$18,428.83, respectively). This implied a superior safety profile compared to SOC. This was not appropriate and biased the model towards midostaurin given there was no comparative safety evidence presented to even support the submission's clinical claim of non-inferiority. Assuming equal AE utility decrement and management costs increase the ICER +1% (see Table 12). The PSCR stated that midostaurin has a non-inferior but different safety profile compared to cladribine and peginterferon. The PSCR argued that the differences resulted in varying costs associated with managing specific AEs, reflected in the model.
- 6.56 The model also applied a utility decrement of -0.02 to account for administrations requiring injection (e.g., intravenous [IV] cladribine) and was applied only to the SOC arm. This was informed by Matza 2015.¹⁴ Application of this decrement was inappropriate since in Matza 2015 the utility decrement represented weekly injections whereas the model applied the decrement 28-days; and the decrement was only applied the SOC arm despite midostaurin-treated patients in the model receiving SOC as a post-discontinuation therapy. The ESC noted the impact of excluding this utility decrement was minimal (excluding this utility decrement led to a <1% change in the ICER).
- 6.57 Treatment costs were only incurred in the PF health states. Midostaurin costs were only incurred in the PF with response state and in the first two cycles of the PF without response state. Patients who discontinued midostaurin due to lack of response would go on to receive SOC therapies in the PF without response state. Patients in the SOC arm continued treatment in the PF states regardless of response status. No treatment costs were incurred in the PD health state (i.e., post-progression therapies were not considered). Treatment discontinuation due to lack of response was not aligned with D2201 and likely underestimated treatment costs compared to that expected in clinical practice. In addition, the absence of treatment costs after disease progression did not reflect the clinical pathway of patients after progression as it is expected that

¹⁴ Matza, LS et al. (2015) Health State Utilities Associated With Attributes Of Treatments For Hepatitis C, Value in Health, Volume 17, Issue 3, A9

- progressed patients will seek alternative treatments in practice (as observed in D2201, A2213, and NCCN 2019 guidelines) and underestimated the total costs in the model.
- 6.58 The model assumed lower disease management costs for midostaurin compared to SOC in the pre-progression health states (\$230.53 vs \$429.82, respectively) and was attributed to lower frequency of visits for bone density monitoring, platelet transfusions, and RBC transfusions in the midostaurin arm. This was not justified and favoured midostaurin. Setting pre-progression costs for SOC equal to the midostaurin arm led to \downarrow% change in the ICER (see Table 12).
- 6.59 The post-progression health state cost was less than pre-progression health state costs (\$226.27 in both arms vs \$230.53 midostaurin and \$429.82 SOC, respectively) and this was attributed to less frequent GP, specialist, and bone density monitoring visits. This was also not justified in the submission and its plausibility was questioned. Assuming post-progression costs to be at least equal to the pre-progression costs of the SOC arm (\$429.82) increased the ICER by $+\uparrow$%.
- 6.60 The terminal care costs were informed by Goldsbury 2018 (\$52,291 once off upon death) were based on the category of "Other" cancers. This did not appear representative of AdvSM patients since this category excluded haematological cancers (e.g., leukaemia and non-Hodgkin's lymphoma [NHL]). Noting that SM-AHN is a distinct subtype within AdvSM, the terminal care costs associated with haematological cancers such as leukaemia or NHL would be more representative (\$66,240). Nonetheless, this had a minor impact on the ICER (\downarrow% change). Excluding terminal care costs from the model increased the ICER by $+\uparrow$% (see Table 12).

6.61 The key drivers of the model are presented in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact Base: \$ ¹ /QALY gained
Condense PF health states	The evidence did not reliably inform separating the PF health state according to response. Assuming responders and non-responders were treated with midostaurin until disease progression reduced the impact from uncertain ORR and utility values from the model.	High favours midostaurin Assuming non-responders received midostaurin irrespective of response increased ICER to \$ ² /QALY gained (+ ¹ %)
OS modelling	The base case adopted OS modelling assumptions that favoured the midostaurin arm, namely, extrapolating OS in the midostaurin arm using the most optimistic function i.e., generalised gamma; and applying the OS HR from CEREMAST. Both were not appropriately justified. No convergence was considered despite highly uncertain comparative OS benefit from midostaurin compared to SOC. Adopting a more conservative OS modelling approach involved applying the log normal, Weibull, or exponential (most conservative) to extrapolate midostaurin OS; and informing SOC OS using Rieter 2017 propensity score match OS HR of 0.636 instead of CEREMAST.	High favours midostaurin Log normal increased ICER to \$ ² /QALY gained (+ ¹ %) Weibull increased ICER to \$ ² /QALY gained (+ ¹ %) Exponential increased ICER to \$ ² /QALY gained (+ ¹ %) Reiter 2017 HR increased ICER to \$ ² /QALY gained (+ ¹ %)
Time horizon	The base case used a time horizon of 20 years which was considered optimistic when compared to the median OS of 26.8 months in D2201 in midostaurin-treated patients. Assuming a shorter time horizon would be consistent with the conservative OS modelling approach where most downstream costs and benefits are captured at 15 and 10 years under the log normal and exponential functions.	High favours midostaurin 15-years increased the ICER to \$ ² /QALY gained (+ ¹ %) 10-years increased the ICER to \$ ² /QALY gained (+ ¹ %)
PD utility	PD utility value was 0.75 and in absence of other data, decreasing the PD utility value to an arbitrary 0.70 or 0.60 may reflect the uncertainties from D2201 QoL data and the debilitating symptoms associated with AdvSM.	High favours midostaurin PD = 0.70 increased the ICER to \$ ¹ /QALY gained (+ ¹ %) PD = 0.60 increased the ICER to \$ ² /QALY gained (+ ¹ %)

Source: Table 3.2.1, p117 of the submission and additional sensitivity analyses conducted in the economic model workbook
HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ORR = overall response rate; OS = overall survival; PD = progressed disease; PF = progression free; QALY = quality adjusted life year; QoL = quality of life; SOC = standard of care

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$155,000 to < \$255,000

6.62 The base case results from the stepped economic evaluation and disaggregated results are presented in Table 10 and Table 11.

Table 10: Results of the stepped economic evaluation (discounted and HCC)

Step and component	Midostaurin	SOC	Increment
Step 1: Cost per LY over 5-year trial horizon: trial-based costs and outcomes			
Costs	\$	\$84,160	\$
LYG	2.45	1.43	1.019
Incremental cost/extra LYG gained			\$ ¹
Step 2: Cost per LY over a 20-year time horizon			
Costs	\$	\$86,541	\$
LYG	3.66	1.57	2.084
Incremental cost/extra LYG gained			\$ ²
Step 3: Cost per QALY over a 20-year time horizon (base case)			
Costs	\$	\$86,541	\$
QALY	2.85	1.23	1.62
Incremental cost/extra QALY gained			\$ ³

Source: Table 3.18-3.20, pp115-6 of the submission; 'Setting and Results' worksheet from the economic model

AE = adverse event; HCC = half cycle corrected; ICER = incremental cost effectiveness ratio; LYG = life year gains; PD = progressed disease; PDT = post discontinuation treatment; PF = progression-free; QALY = quality adjusted life year; SOC = standard of care.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$95,000 to < \$115,000

³ \$135,000 to < \$155,000

Table 11: Disaggregated summary of cost and benefits over 20-year time horizon (discounted and HCC)

	Midostaurin	SOC	Increment	% of increment
Costs				
Treatment costs	\$	\$12,330	\$	%
Pre-medication	\$0	\$0	\$0	0%
Administration	\$0	\$362	-\$362	%
PDT with admin	\$0 ^a	\$0	\$0	0%
Disease management	\$10,004	\$7,196	\$2,807	%
AEs	\$9,040	\$18,429	-\$9,389	-%
Terminal care costs	\$41,544	\$48,223	-\$6,679	-%
Total cost	\$	\$86,540	\$	100%
LYG				
LYG (PF response)	0.92	0.62	0.29	14%
LYG (PF no response)	0.51	0.57	-0.06	-3%
LYG (PD)	2.23	0.38	1.85	89%
LYG (total)	3.66	1.57	2.08	100%
QALY gains				
QALYs (PF response)	0.78	0.53	0.25	15%
QALYs (PF no response)	0.41	0.46	-0.05	-3%
QALYs (PD)	1.67	0.28	1.39	86%
QALYs (AEs)	-0.01	-0.02	0.01	1%
QALYs (treatment admin)	0.00	-0.02	0.02	1%
QALYs (total)	2.85	1.23	1.62	100%

Source: Table 3.18-3.20, pp115-6 of the submission; 'Setting and Results' worksheet from the economic model

AE = adverse event; HCC = half cycle corrected; ICER = incremental cost effectiveness ratio; LYG = life year gains; PD = progressed disease; PDT = post discontinuation treatment; PF = progression-free; QALY = quality adjusted life year; SOC = standard of care.

^a the submission did not include post-discontinuation treatment after a patient experienced disease progression. For patients who discontinued midostaurin due to lack of response, post discontinuation treatment with SOC was included as part of the total treatment costs

6.63 The results of key sensitivity analyses conducted by the submission and additional sensitivity analyses conducted during the evaluation are summarised in Table 12.

Table 12: Sensitivity analyses

Variable	Inc cost	Inc QALYs	ICER (\$/QALY)	%Δ
Base case	\$█	1.62	\$█ ¹	-
Time horizon = 15 years (base case = 20 years)	\$█	1.49	\$█ ²	+█%
Time horizon = 10 years (base case = 20 years)	\$█	1.27	\$█ ²	+█%
Discount rate = 0% (base case = 5%)	\$█	2.28	\$█ ³	-█%
Discount rate = 3.5% (base case = 5%)	\$█	1.78	\$█ ⁴	-█%
PF health states				
Include treatment for non-responders (base case = excluded after two months)	\$█	1.62	\$█ ²	+█%
Condense the PF health states (base case = separate PF health states by response)	\$█	1.61	\$█ ²	+█%
Response rates (base case: ORR midostaurin = 64.3%; ORR SOC = 46.2%)				
ORR midostaurin = 59.6% direct from D2201	\$█	1.62	\$█ ⁴	-█%
ORR midostaurin = 100% (testing extremes)	\$█	1.67	\$█ ²	+█%
ORR midostaurin = 1% (testing extremes)	\$█	1.56	\$█ ⁵	-█%
OS modelling for midostaurin (base case: generalised gamma function; truncation point = 46 months)				
Log normal	\$█	1.49	\$█ ²	+█%
Exponential	\$█	1.24	\$█ ²	+█%
Weibull	\$█	1.27	\$█ ²	+█%
Log logistic	\$█	1.51	\$█ ¹	+█%
OS modelling for SOC (base case: OS HR = 2.2 from CEREMAST applied in the PH approach)				
OS HR = 0.636 from Reiter 2017 propensity score matched results (i.e., OS HR of 1.57 was used in the PH model)	\$█	1.10	\$█ ²	+█%
ToT modelling for SOC (base case: ratio of ORR_{midostaurin}/ORR_{SOC} = 1.23)				
ToT HR for SOC = 2.2 i.e., same OS HR as CEREMAST	\$█	1.65	\$█ ¹	+█%
ToT HR for SOC = 1.57 i.e., same OS HR as Reiter 2017	\$█	1.64	\$█ ¹	+█%
Utilities (base case: PF response = 0.85; PF no response = 0.80; PD = 0.75)				
PD utility = 0.60	\$█	1.35	\$█ ²	+█%
PD utility = 0.70	\$█	1.53	\$█ ¹	+█%
PF with response = 0.80 (same as PF without response)	\$█	1.61	\$█ ¹	+█%
AE disutility and costs (base case: AE disutility = -0.0084 midostaurin and -0.0187 SOC; AE costs = \$9,039.94 midostaurin and \$18,429.83 SOC)				
AE disutility from SOC = -0.0084 i.e., equal midostaurin	\$█	1.61	\$█ ¹	+█%
AE management costs SOC = \$9,039.94 i.e. equal midostaurin	\$█	1.62	\$█ ¹	+█%
Healthcare resource use and costs				
Pre-progression costs in SOC = \$230.53 i.e., equal midostaurin (base case = \$429.82)	\$█	1.62	\$█ ¹	+█%
Post-progression costs = \$429.82 i.e., equal to pre-progression cost of SOC arm (base case = \$226.27)	\$█	1.62	\$█ ¹	+█%
Multivariate sensitivity/scenario analyses conducted during the preparation of the ESC advice				
(A1) Midostaurin OS extrapolation – log normal function	\$█	1.49	\$█ ²	+█%
(A2) A1 + SOC OS based on Reiter 2017 propensity score match HR (0.636)	\$█	1.01	\$█ ²	+█%
(A3) A2 + Time horizon = 10 years	\$█	0.80	\$█ ⁶	+█%
(A4) A3 + Condense PF health states ^a	\$█	0.81	\$█ ⁷	+█%
(A5) A4 + PD utility = 0.65	\$█	0.76	\$█ ⁸	+█%
(A6) A4 + PD utility = 0.60	\$█	0.74	\$█ ⁸	+█%
(A7) A4 + PD utility = 0.70	\$█	0.79	\$█ ⁷	+█%

Variable	Inc cost	Inc QALYs	ICER (\$/QALY)	%Δ
Base case	\$█	1.62	\$█ ¹	-
Multivariate sensitivity/scenario analyses conducted during the preparation of the PSD				
(A5) with condense PF health states removed + EMP \$█ ^b	\$█	0.72	\$█ ⁶	+█%

Source: Table 3.2.1, p117 of the submission; additional sensitivity analyses were conducted in the economic model workbook.

AE = adverse event; Inc = incremental; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ORR = overall response rate; OS = overall survival; PD = progressed disease; PF = progression free; PH = proportional hazards; PSD = Public Summary Document; QALY = quality adjusted life year; SOC = standard of care; ToT = time on treatment; Δ = change from baseline ICER

^a Condense PF health states was conducted as: Include treatment costs for non-responders + Set ORR in the midostaurin and SOC arms to 100% + Assumed the ToT HR was the same as the OS HR (maintain clinical plausibility in the model and was the same approach as NICE TA728)

^b The pre-PBAC response offered a price reduction resulting in an EMP for a 56 pack of 25 mg capsules of \$█.

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$155,000 to < \$255,000

³ \$95,000 to < \$115,000

⁴ \$115,000 to < \$135,000

⁵ \$15,000 to < \$25,000

⁶ \$255,000 to < \$355,000

⁷ \$355,000 to < \$455,000

⁸ \$455,000 to < \$555,000

6.64 The ICER was most sensitive to midostaurin treatment costs (which were indirectly driven by the ORR inputs and the occupation of the PF response health states), the OS modelling approach, the time horizon and the PD utility value.

6.65 The ESC advised that a respecified base case incorporating the following inputs would be appropriate:

- Log normal function used to model OS in the midostaurin arm;
- Reiter 2017 propensity score matched OS HR (0.636) to model OS in the SOC arm;
- A time horizon of 10 years;
- Condense the PF health states;
- Assume a PD utility value of 0.65.

The ESC noted that incorporating these inputs increased the base case ICER from \$135,000 to < \$155,000 per QALY gained to \$455,000 to < \$555,000 per QALY gained.

6.66 The pre-PBAC response proposed a respecified base case that incorporated the following inputs:

- Log normal function used to model OS in the midostaurin arm;
- Reiter 2017 multivariate analyses OS HR (0.517) to model OS in the SOC arm;
- A time horizon of 10 years.

The pre-PBAC response noted that incorporating the price reduction offered in the response (EMP for a 56 pack of 25 mg capsules of \$█) resulted in an ICER of \$155,000 to < \$255,000 per QALY gained.

Drug cost/patient/course

- 6.67 The drug cost per patient per course of treatment is presented in Table 13. Comparator costs are not presented given the comparator is supportive care (i.e., SOC) and the cost inputs from the model are uncertain.
- 6.68 The midostaurin drug costs in the economic model and financial estimates assumed patients stopped treatment after lack of response in the first two cycles. The midostaurin drug costs in the economic model also included SOC costs in patients who discontinued midostaurin after lack of response. As such, Table 13 also included economic model-based costs that exclude SOC from the midostaurin arm and economic model-based costs under conditions of the requested restriction.

Table 13: Drug cost per patient for proposed and comparator drugs (undiscounted and HCC)

	Midostaurin Trial dose and duration	Midostaurin Model	Midostaurin Financial estimates	Model base case but midostaurin treatment costs only	Scenario: assumed all patients in PF state are treated
Mean duration	18.7 months ^a	12.42 months ^b	12.42 months ^b	12.42 months ^b	18.22 months ^c
Mean daily dose and RDI	186.6 mg 87%	186.6 mg 87%	186.6 mg 87%	186.6 mg 87%	186.6 mg 87%
Cost/patient/month	NA	\$	\$	\$	\$
Cost/patient/course ^d	NA	\$ ^e	\$	\$ ^g	\$ ^h

Source: Table 3.16, p114 of the submission; Table 12-1, p145 and Table 12-3, pp146-47 of D2201 CSR primary analysis; 'Settings and Results' worksheet from the economic model

HCC = half cycle corrected; NA = not applicable

^a in D2201 there were 12.1% (14/116) who discontinued due to "administrative problems" which was noted to be patients who accessed midostaurin on a compassionate access scheme at the end of the study.

^b 12.42 months with HCC (12.76 months without HCC). Includes non-responders in the first two cycles.

^c treatment duration was 18.72 without HCC

^d course of treatment was based on treatment until discontinuation

^e cost per patient reported in the submission included subsequent SOC costs from patients after not responding to midostaurin. Calculated from the model as the sum of midostaurin treatment costs incurred in the PF with response and PF without response health states. The proportion split between public and private in the economic model was 33.17% and 66.83% respectively.

^f cost per patient per course in the financial estimates calculated as the weighted DPMQ (\$) which was based on the proportion split between public and private of 90.87% and 9.13% multiplied by RDI of 87.17% and converted to 30.4 days (cost per patient per month) then multiplied by the treatment duration of 12.42 months

^g cost per patient excluding SOC costs. Calculated from the economic model as the sum of midostaurin treatment costs incurred in the PF with response and PF without response health states excluding SOC.

^h cost per patient that assumed all patients who are PF received midostaurin irrespective of response (this scenario excluded SOC as a subsequent therapy cost). Calculated from the economic model as the sum of midostaurin treatment costs incurred in the condensed PF health state.

- 6.69 The cost per patient per course was slightly higher in the economic model (excluding SOC costs) compared to the financial estimates (\$ vs \$, respectively). This difference appeared to be attributed to the difference in the proportion split between public and private scripts in the economic model (33.17% public and 66.83% private) compared to the financial estimates (90.87% public and 9.13% private).
- 6.70 The pre-PBAC response offered a price reduction resulting in an EMP for a 56 pack of 25 mg capsules of \$. For the maximum dispensed quantity of 224 capsules the pre-PBAC response effective EMP was \$.

Estimated PBS usage & financial implications

6.71 This submission was not considered by DUSC.

6.72 The submission adopted an epidemiological approach to the financial estimates.

6.73 The data sources and inputs are summarised in Table 14.

Table 14: Data sources and parameter values applied in the utilisation and financial estimates

Data	Source	Comment															
Eligible population																	
Incident and prevalent patients	The incident and prevalent patients were based a retrospective cohort study of three Danish national health registries (Cohen 2014).	Reasonable in absence of other evidence. Low AdvSM patient numbers in Cohen 2014 added uncertainty to prevalence and incidence estimates.															
	<table border="1"> <thead> <tr> <th>Subtype</th> <th>Incident per 100,000 (95% CI)</th> <th>Prevalence per 100,000 (95% CI)</th> </tr> </thead> <tbody> <tr> <td>ASM</td> <td>0.01 (0.006, 0.03)</td> <td>0.09 (0.03, 0.21)</td> </tr> <tr> <td>SM-AHN</td> <td>0.04 (0.03, 0.06)</td> <td>0.31 (0.18,0.50)</td> </tr> <tr> <td>MCL</td> <td>0.01 (0.003, 0.02)</td> <td>0 (0,0)</td> </tr> <tr> <td>AdvSM^a</td> <td>0.06</td> <td>0.4</td> </tr> </tbody> </table>		Subtype	Incident per 100,000 (95% CI)	Prevalence per 100,000 (95% CI)	ASM	0.01 (0.006, 0.03)	0.09 (0.03, 0.21)	SM-AHN	0.04 (0.03, 0.06)	0.31 (0.18,0.50)	MCL	0.01 (0.003, 0.02)	0 (0,0)	AdvSM ^a	0.06	0.4
	Subtype		Incident per 100,000 (95% CI)	Prevalence per 100,000 (95% CI)													
	ASM		0.01 (0.006, 0.03)	0.09 (0.03, 0.21)													
	SM-AHN		0.04 (0.03, 0.06)	0.31 (0.18,0.50)													
MCL	0.01 (0.003, 0.02)	0 (0,0)															
AdvSM ^a	0.06	0.4															
Source: Table 4.1, p121 of the submission																	
^a calculated as the sum of subtypes																	
Grandfathered	There were ██████ ¹ grandfathered patients from the Sponsor's compassionate access program. The submission accounted for grandfathered patients in Year 1 by applying 88% to the prevalent population.	█████ ¹ grandfathered patients out of ██████ ¹ prevalent patients in Year 1 corresponded to 92% patients who are not grandfathered (i.e., ██████ ¹ -█████ ¹)/█████ ¹ = 92%). The 88% used in the submission could not be verified. The PSCR (p4) acknowledged that percentage of grandfathered patients was incorrectly calculated.															
Treatment utilisation																	
% Eligible for cytoreduction therapy	The submission assumed there would be 90% of patients eligible for cytoreductive therapy. This was an assumption based on clinical opinion from four Australian haematologists that midostaurin will be 1L therapy for AdvSM in Australia. The submission also assumed that a small proportion of patients will not opt for treatment due to frailty or at high risk of cytopenia.	Reasonable in absence of other evidence. Clinician input indicated a high clinical need for treatments in AdvSM and given equitable access, midostaurin would be the preferred 1L therapy.															
Uptake rate	The uptake rate in prevalent and incident patients were based on assumptions by the Sponsor and are presented in the table below.	A higher initial uptake rate may be appropriate given midostaurin would be the first PBS-listed targeted therapy for AdvSM. Though, this just shifted costs to incur earlier in the forecast. The application of assuming all prevalent patients were treated in Yr 1-3 led to potential double counting (discussed in paragraph 6.70). The PSCR (p4) acknowledged that the approach taken led to double counting.															
	<table border="1"> <thead> <tr> <th>Uptake</th> <th>Year 1</th> <th>Year 2</th> <th>Year 3</th> <th>Year 4-6</th> </tr> </thead> <tbody> <tr> <td>Prevalent</td> <td>30%^a</td> <td>50%^a</td> <td>100%^a</td> <td>0%</td> </tr> <tr> <td>Incident</td> <td>100%</td> <td>100%</td> <td>100%</td> <td>100%</td> </tr> </tbody> </table>		Uptake	Year 1	Year 2	Year 3	Year 4-6	Prevalent	30% ^a	50% ^a	100% ^a	0%	Incident	100%	100%	100%	100%
	Uptake		Year 1	Year 2	Year 3	Year 4-6											
Prevalent	30% ^a	50% ^a	100% ^a	0%													
Incident	100%	100%	100%	100%													
Source: Table 4.1, p121 of the submission ^a Cumulative uptake																	
The submission assumed that all prevalent patients will have taken up midostaurin by Year 3 and that there will be no prevalent patients electing treatment after Year 3.																	
Treatment duration	The submission assumed a treatment duration of 12.42 months stating this was from the economic model which included the 2 months of treatment in non-responders (12.42 months = 2 months initial + 10.42 months continuing).	Patients in D2201 and patients under the requested restriction were treated to disease progression, irrespective of response. Under these conditions, the mean treatment															

Public Summary Document - March 2025 PBAC Meeting

Data	Source	Comment																					
	<p>For grandfathered patients the treatment duration was 6.21 months which the submission calculated as the average duration of two months initial and 10.42 months continuing.</p> <p>The submission also stated that for some patients, treatment will extend beyond the six-year financial estimates and therefore were not captured in the financial model.</p>	<p>duration was 18.72 months in the model (i.e., 16.72 months continuing treatment) or 18.22 months with a HCC. The PSCR (p1) proposed amending the restriction to treat to response. The ESC considered the appropriateness of this proposed change, given that the data upon which effectiveness and cost effectiveness depends on (mainly D2201), remained an issue.</p>																					
Scripts dispensed	<p>The submission estimated the mean number of packs for a full year of treatment was 11.35 packs (RDI of 87% from D2201).</p>	Reasonable.																					
Beneficiary type	<p>The submission informed the public/private (90.87%/9.13%) and PBS/RPBS splits (98.86%/1.14%) for the proposed listing using PBS data of midostaurin for AML</p>	Reasonable.																					
Costs																							
Midostaurin	<p>The DPMQ for midostaurin is \$ [redacted] public and \$ [redacted] private based on the maximum dispensed units of 224 (2 x 112 pack) which allows for 28-day supply. The proportion split between public and private was 90.87% and 9.13%, respectively.</p>																						
SOC therapies	<p>The submission included cladribine and peginterferon alpha-2a as cost offsets and details are presented in the table below.</p> <table border="1" data-bbox="336 1122 1034 1361"> <thead> <tr> <th>Form/strength</th> <th>Dosing</th> <th>Pack qty</th> <th>Max qty</th> <th>No. scripts</th> <th>AEMP</th> <th>DPMQ/DPMA</th> </tr> </thead> <tbody> <tr> <td>Cladribine Injection, 10mg/10 mL injection, 10 mL vial</td> <td>0.14 mg/kg/day</td> <td>1</td> <td>17 mg</td> <td>30.53</td> <td>\$548.36</td> <td>\$627.54</td> </tr> <tr> <td>Peginterferon alpha-2a Injection 180 µg, 4x0.5 mL syringes</td> <td>180 mcg per week</td> <td>4</td> <td>4 pens</td> <td>22.68</td> <td>\$404.62</td> <td>\$545.09</td> </tr> </tbody> </table> <p>Source: constructed from Table 4.14 to 4.16, pp131-2 of the submission</p> <p>The submission assumed the doses for peginterferon alpha-2a to be 180 mcg (1 pen) per week (assumed in the model); and for cladribine 0.14 mg/kg/day for five days with 52 days (or 7.43 weeks) between courses (based on Barete 2015). The submission adjusted the cladribine dose per period to account for 7.43 weeks between courses. The submission assumed a patient weight of 71.3 kg and no vial sharing.</p> <p>The submission assumed a 10-month treatment duration for cost offsets based on the model. This was calculated as the sum of time on SOC for responders, and the first two cycles for non-responders.</p> <p>The proportion split between cladribine and peginterferon alpha-2a was 22.22% and 41.28%, respectively and was calculated as the market share of 65% peginterferon alpha-2a and 35% cladribine multiplied by the response rate of midostaurin (63.5%) from the model.</p> <p>The compliance was assumed to be 87% as per D2201.</p>	Form/strength	Dosing	Pack qty	Max qty	No. scripts	AEMP	DPMQ/DPMA	Cladribine Injection, 10mg/10 mL injection, 10 mL vial	0.14 mg/kg/day	1	17 mg	30.53	\$548.36	\$627.54	Peginterferon alpha-2a Injection 180 µg, 4x0.5 mL syringes	180 mcg per week	4	4 pens	22.68	\$404.62	\$545.09	<p>Cost offsets would only be appropriate for peginterferon alpha-2a as it is a general schedule therapy on the PBS and cladribine is not. The PSCR (p4) argued that including cost offsets for cladribine was appropriate and noted that they have minimal effect on the overall budget impact.</p> <p>The SOC treatment duration of 10 months was not appropriate since in the model patients in the SOC arm received SOC irrespective of response. Treatment duration of 10 months was underestimated compared to 15.65 months in the model.</p> <p>The adjusted market share by midostaurin response was not reasonable, since under the requested restriction patients are not treated to response, therefore the offset would apply to all treated patients irrespective of response. The PSCR (p1) proposed amending the restriction to treat to response. As outlined above, the ESC considered the appropriateness of this change remained an issue. Regardless, the evidence indicated that midostaurin would displace, rather than replace SOC therapies and including these cost offsets</p>
Form/strength	Dosing	Pack qty	Max qty	No. scripts	AEMP	DPMQ/DPMA																	
Cladribine Injection, 10mg/10 mL injection, 10 mL vial	0.14 mg/kg/day	1	17 mg	30.53	\$548.36	\$627.54																	
Peginterferon alpha-2a Injection 180 µg, 4x0.5 mL syringes	180 mcg per week	4	4 pens	22.68	\$404.62	\$545.09																	

Public Summary Document - March 2025 PBAC Meeting

Data	Source	Comment
		underestimated total midostaurin costs.
MBS costs	Net changes to MBS item 13950 were included as part of the cost offsets to IV cladribine. The model applied a decrease in one service per script of cladribine claimed.	As outlined above, the evaluation considered that inclusion of cost offsets for cladribine was not appropriate as it was not a general schedule listing. The PSCR (p4) argued that including cost offsets for cladribine was appropriate.

Source: Section 4.1 to Section 4.4 of the submission

AdvSM = advance systemic mastocytosis; AEMP = approved ex-manufactures price; AML = acute myeloid leukaemia; ASM = aggressive systemic mastocytosis; CI = confidence interval; DPMA = dispensed price maximum amount; DPMQ = dispensed price maximum quantity; HCC = half cycle corrected; IV = intravenous; M = million; MBS = Medicare Benefits Schedule ; MCL = mast cell leukemia; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RDI = relative dose intensity; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with an associated haematological neoplasm; SOC = standard of care; WHO = World Health Organisation; 1L = first line.

The redacted values correspond to the following ranges:

1 < 500

6.74 The submission's estimated use of midostaurin is presented in Table 15.

Table 15: Estimation of number of treated patients for midostaurin

	Value	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Australian population	-	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Prevalent patients							
B	Prevalent	A x 0.4/100,000	█ ²	█ ²	█ ²	█ ²	█ ²
C	Eligible for treatment	B x 90%	█ ²	█ ²	█ ²	█ ²	█ ²
D	Proportion not GF	C x 88% in Yr 1	█ ²	█ ²	█ ²	█ ²	█ ²
E	No. pts not on midostaurin from prev. yr	D x 100%, 70%, 35% in Yr 1-3 ^{a, b}	█ ²	█ ²	█ ²	█ ²	█ ²
F	Uptake rate	E x 30%, 50%, 100% in Yr1-3	█ ²	█ ²	█ ²	█ ²	█ ²
Assuming only the remaining prevalent patients from Year 1 are treated from Year 1 to 3							
E1	No. pts not on midostaurin from prev. yr	D of Yr 1 only x 100%, 70%, 35% in Yr 1-3 ^{b, c}	█ ²	█ ²	█ ²	█ ²	█ ²
F1	Uptake rate based on only Year 1	E1 x 30%, 50%, 100% in Yr1-3	█ ²	█ ²	█ ²	█ ²	█ ²
Incident patients							
G	Incident	A x 0.06/100,000	█ ²	█ ²	█ ²	█ ²	█ ²
H	Eligible for treatment	G x 90%	█ ²	█ ²	█ ²	█ ²	█ ²
I	Uptake rate	H x 100%	█ ²	█ ²	█ ²	█ ²	█ ²
Grandfathered patients							
J	Grandfathered pt	-	█ ²	█ ²	█ ²	█ ²	█ ²
K	Eligible for treatment	J x 100%	█ ²	█ ²	█ ²	█ ²	█ ²
Total treated patients							
L	Total treated	F+I+K	█ ²	█ ²	█ ²	█ ²	█ ²
M	Total treated (using F1)	F1+I+K	█ ²	█ ²	█ ²	█ ²	█ ²

Source: Table 4.9 to Table 4.18, pp127-133; Table 4.21, p135; Table 4.23 and Table 4.24, pp137-8 of the submission; '2a. Patients – incident', '2b. Patients – prevalent', '2c. Patients – GF' worksheets from the financial workbook.

GF = grandfathered; prev. = previous; Yr = year

^a the number of patients who did not receive midostaurin in the previous year was calculated as the product of (100% - uptake rate) from each previous year e.g., Year 1 = 100% x 0% uptake in Year 0 = 100%; Year 2 = 100% x (100% - 30% uptake in Year 1) = 70%; Year 3 = 70% x (100% - 50% uptake in Year 2) = 35%; Year 4+ = 35% x (100% - 100%) = 0%.

^b in the base case, the number of remaining prevalent patients who would uptake midostaurin each year was calculated as: Year 1 = 100% x < 500 = < 500 patients; Year 2 = 70% x < 500 = < 500 patients; and Year 3 = 35% x < 500 = < 500 patients. The sum of Year 1 to 3 was < 500 patients. This approach potentially double counted incident patients in Year 2 and 3, since the remaining prevalent patients who would uptake midostaurin were based on the prevalent patient numbers in Year 2 (< 500) and 3 (< 500) which appeared to include incident patients.

^c To avoid double counting of incident patients in Year 2 and Year 3 the evaluation recalculated the number of remaining prevalent patients who would uptake midostaurin based on patients in Year 1 only: Year 1 = 100% x < 500 = < 500 patients; Year 2 = 70% x < 500 = < 500 patients; Year 3 = < 500 x 35% = < 500 patients. The sum of Year 1 to 3 was < 500 patients.

The redacted values correspond to the following ranges:

¹ > 10,000,000

² < 500

6.75 The submission accounted for grandfathered patients in the prevalent population by applying the proportion of 88%. However, <500 grandfathered patients out of < 500 prevalent patients in Year 1 equated to 8% grandfathered patients (i.e., 92% should have been applied to account for grandfathered patients in Year 1). This increased prevalent patients in Year 1 from < 500 to < 500 patients and midostaurin costs in Year 1 by +3%. The PSCR acknowledged that percentage of grandfathered patients was incorrectly calculated and accepted the approach proposed by the evaluation.

6.76 The submission assumed that all prevalent patients would be treated within the first three years by assuming cumulative uptake rates of 30%, 50%, and 100% in Year 1 to 3 for patients who had not yet received midostaurin. By assuming that all prevalent patients would be treated by Year 3 in the financial model, it would be expected that the total treated patients would equal that in Year 1 (i.e., a total of < 500 prevalent patients would uptake treatment). However, the submission estimated there would be a total of < 500 prevalent patients treated. This double count was attributed to financial model calculating the remaining eligible prevalent patients each year based on the population from Year 2 (n=< 500) and Year 3 (n=< 500) rather than from Year 1. In a scenario analysis, when the number of remaining prevalent patients who would uptake midostaurin were based on patients in Year 1 only,¹⁵ the sum of Year 1 to 3 was < 500 patients. This approach was internally consistent and avoided double counting of incident patients in Year 2 and 3 (decreased total costs by 5%; see Table 17). The PSCR acknowledged that the approach taken led to double counting and accepted the method proposed by the evaluation.

6.77 The estimated net financial impact of midostaurin is presented in Table 16.

Table 16: Estimated financial impact of midostaurin in the submission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed	2	2	2	1	1	1
Estimated financial implications of midostaurin						
Cost to PBS/RPBS less copayments	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4	\$ 4
Estimated financial implications for SOC						
Cost to PBS/RPBS less copayments	-\$ 5	-\$ 5	-\$ 5	-\$ 5	-\$ 5	-\$ 5
Net financial implications						
Net cost to PBS/RPBS	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4	\$ 4
Net cost to MBS	-\$ 5	-\$ 5	-\$ 5	-\$ 5	-\$ 5	-\$ 5
Net cost to the health budget	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4	\$ 4

Source: Table 4.9, Table 4.11 and Table 4.13, pp127-9 of the submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SOC = standard of care

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$10 million to < \$20 million

⁴ \$0 to < \$10 million

⁵ net cost saving

6.78 The total cost to the health budget of listing midostaurin was estimated to be \$10 million to < \$20 million in Year 1, increasing to \$10 million to < \$20 million in

¹⁵ Calculated as: Year 1 = 100% x <500 = <500 patients; Year 2 = 70% x <500 = <500 patients; Year 3 = <500 x 35% = <500 patients (note: <500 patients already accounted for the 90% eligible for cytoreductive therapy and the 12% grandfathered).

Year 3, then decreasing to \$0 to < \$10 million in Year 6, and a total of \$50 million to < \$60 million in the first 6 years of listing.

6.79 The sensitivity analysis of the financial estimates conducted by the submission and additional sensitivity analyses conducted during the evaluation is presented in Table 17.

Table 17: Sensitivity analyses conducted by the submission and during the evaluation

	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Total cost	%Δ ^a
Base case								
Health budget	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ³	-
Incidence rate +20%								
Health budget	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ³	+9.4%
Incidence rate -20%								
Health budget	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ⁴	-9.4%
Prevalence rate +20%								
Health budget	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ³	+10.1%
Prevalence rate -20%								
Health budget	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ⁴	-10.1%
% Eligible for treatment = 100%^b								
Health budget	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ³	+10.9%
% Eligible for treatment -20% as conducted during the evaluation ^c								
Health budget	\$ ²	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ⁴	-19.6%
Assume midostaurin treatment duration = 18.72 months								
Health budget	\$ ¹	\$ ¹	\$ ⁵	\$ ¹	\$ ²	\$ ²	\$ ⁶	+48.3%
Assuming only the remaining prevalent patients from Year 1 are treated from Year 1 to 3^d								
Health budget	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²	\$ ⁴	-5.1%

Source: Table 4.25, p139 of the submission and additional analyses conducted during the evaluation using the financial workbook
 GF = grandfathered; MBS = Medicare Benefits Schedule; Mido = midostaurin; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation
 Pharmaceutical Benefits Scheme; SOC = standard of care; Yr = year; %Δ = percentage change from baseline total costs

^a % change based on total costs

^b the submission conducted a sensitivity analysis that increased the % patients eligible for cytoreductive therapy by 20%. However, increasing 90% by 20% led to a proportion of 108% which was not plausible. Instead, a sensitivity analysis assuming 100% eligible patients was performed.

^c the sensitivity analysis presented in the submission for this variable could not be replicated. The analyses conducted during the evaluation was 0.8 x 90% for incident and prevalent patients and are presented in italicised text

^d see Row F1 Table 15 for the patient numbers informing this scenario analysis

The redacted values correspond to the following ranges:

¹ \$10 million to < \$20 million

² \$0 to < \$10 million

³ \$50 million to < \$60 million

⁴ \$40 million to < \$50 million

⁵ \$20 million to < \$30 million

⁶ \$70 million to < \$80 million

6.80 The financial estimates were most sensitive to:

- Assuming a midostaurin treatment duration of 18.72 months where all patients are treated until disease progression, irrespective of response (+48% in total costs).
- Varying the incidence rates by +20% and -20% (+9.4% and -9.4% change in total costs, respectively) and prevalence rates by +20% and -20% (+10% and -10% change in total costs, respectively).

- Varying the proportion of patients eligible for cytoreductive therapy (72% eligible i.e., 20% reduction, decreased the total costs by 20%; and 100% eligible increased the total costs by 11%.
- 6.81 Overall, the financial estimates were likely underestimated primarily due to the submission assuming that patients were treated according to response which was not aligned with the requested restriction or D2201 study, and substantially reduced time on treatment with midostaurin. Further, removing cost offsets to align with midostaurin displacing SOC therapies increased total costs (+3%). The prevalence and incidence rates had a moderate impact on the total financial estimates but were highly uncertain and so the net effect from these estimates was unclear.
- 6.82 The PSCR proposed to update the restriction to include response criteria and genetic testing. As such, the PSCR argued that the time on treatment of 12.42 months derived from the economic model would be appropriate and that the eligible patient population be adjusted to take into account that KIT D816V mutations occur in approximately 80% of AdvSM patients. The PSCR provided revised financial estimates which corrected errors identified in the calculation of grandfathered patients (see paragraph 6.75) and the number of prevalent patients (see paragraph 6.76) and that assumed 80% of patients would have a KIT D816V mutation. The resulting revised total cost to the health budget of listing midostaurin was estimated to be \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 3, then decreasing to \$0 to < \$10 million in Year 6. The ESC considered the appropriateness of the proposed restriction change to include response criteria, given that the data upon which effectiveness and cost effectiveness depends on (mainly D2201), remained an issue. In addition, the ESC reiterated that the restriction should not include a requirement for KIT D816V mutation testing (see paragraph 3.4) and hence considered that restricting the eligible patient population to account for KIT D816V mutation status was not appropriate.
- 6.83 The pre-PBAC response acknowledged the ESC's assessment that the restriction should not include a requirement for *KIT D816V* mutation testing. The pre-PBAC response provided revised financials that removed this requirement and, with the price reduction proposed in the response, estimated the total cost of listing midostaurin to be \$10 million to < \$20 million in Year 1, increasing to \$10 million to < \$20 million in Year 3, then decreasing to \$0 to < \$10 million in Year 6, and a total of \$40 million to < \$50 million in the first 6 years of listing.

Quality Use of Medicines

- 6.84 Quality use of medicines was not discussed in the submission.
- 6.85 There was potential patient burden associated with consuming 8x25 mg capsules of midostaurin per day to achieve the recommended dose. This may impact adherence and potentially increase wastage.

Financial Management – Risk Sharing Arrangements

6.86 No risk-sharing arrangements were proposed in the submission.

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 [HSD]) listing of midostaurin for treatment of adult patients with advanced systemic mastocytosis (AdvSM). The PBAC is satisfied that midostaurin provides, for some patients, a significant improvement in efficacy over supportive care (i.e., standard of care [SOC]). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of midostaurin would be acceptable with a price reduction to achieve an incremental cost effectiveness ratio (ICER) in the order of \$75,000 to < \$95,000 per QALY gained using the ESC respecified economic model (modified to remove condensing progression free [PF] health states).

7.2 The PBAC noted the input from the sponsor hearing along with that from the Leukaemia Foundation which highlighted the need for new treatment options in this rare disease that was associated debilitating symptoms and a poor prognosis. The PBAC acknowledged that there was a clear unmet need for treatment options in this rare disease.

7.3 With regard to the requested listing and restriction, the PBAC advised that:

- A Section 100 (HSD) listing as a Complex Authority Required (CAR) Authority Required (Written/online PBS authorities system) listing was appropriate for the initial and Grandfather (GF) treatment restrictions. A Section 100 (HSD) listing as a CAR Authority Required (telephone/online) listing was appropriate for first continuing and subsequent continuing restrictions.
- The indication should be AdvSM with the subtypes of aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukemia (MCL) specified as a clinical criterion.
- An initial treatment restriction with 1 repeat, to allow for response to treatment to be assessed within 2 months of commencement of therapy was appropriate.
- The initial and GF treatment restriction should include treatment criteria that restricts prescribing to haematologists and population criteria that limits use to patients aged 18 years or older.
- The restriction should not include a requirement for KIT D816V mutation testing.
- The D2201 and A2213 trial parameters outlined in paragraph 3.5 were not required in the restriction.
- The initial treatment restriction should include a prescribing instruction that requests prescribers to document in the patient's medical record, the date and

details of the patient's diagnostic reports confirming measurable C-findings at baseline. The diagnostic reports should not be more than 12 months old at the time of authority application. The reports will be used to assess response to treatment or whether a patient has developed progressive disease.

- Details of the full blood count (FBC) and bone marrow (BM) reports to confirm the absence of progressive disease were not required in the restriction as not all patients would have such abnormalities.
- A new first continuing treatment restriction with 2 repeats which allows continuation of therapy if a patient has experienced a major response (MR) or partial response (PR) with midostaurin within 8 weeks of treatment initiation was appropriate. The continuing treatment restriction be renamed as a subsequent continuing treatment restriction where patients should continue treatment only if they don't have progressive disease.
- The new first continuing and subsequent continuing restrictions should include a treatment criterion that allows medical practitioners to prescribe midostaurin in consultation with a haematologist to facilitate access to patients in rural or remote areas.
- The restrictions should include prescribing instructions defining what a MR, PR with midostaurin and progressive disease mean.
- A grandfathering restriction that would expire 12 months from the listing date would be appropriate.

7.4 The PBAC considered the nomination of SOC as the main comparator was appropriate.

7.5 The submission was based on two single-arm, open-label, phase II studies of midostaurin (D2201, N=116; A2213, N=26) which the PBAC considered were associated with a high risk of bias. The PBAC noted the differences in discontinuation rules, with D2201 primarily treating until disease progression and A2213 discontinuing treatment if a MR or PR was not achieved in the first 2 two cycles. In D2201, the overall response rate (ORR) after 6 cycles of treatment was 59.6% (95% CI 48.6, 69.8) and the PBAC noted that this was statistically significantly greater than the prespecified 30% threshold. In A2213, the ORR was 73.1% (95% CI 52.2, 88.4) after the first two cycles of treatment with midostaurin. The PBAC considered that the D2201 and A2213 studies indicate midostaurin has activity in AdvSM. The median time to response (TTR) in D2201 was 0.3 months (range: 0.1, 3.7) and 0.95 months (range: 0.85, 1.87) in A2213. The PBAC considered that the median TTR reported for both studies supported the assessment of response within 2 months of therapy in the restriction (see paragraph 7.3). The PBAC also noted that D2201 reported improvements in quality of life (QoL) with midostaurin (see paragraph 6.26) but considered these were indicative only due to the single arm nature of the study.

7.6 In the absence of a direct comparison, two historical control studies (Reiter 2017, N=131; CEREMAST, N=72) were used to provide supportive evidence for overall

survival (OS). The PBAC noted the limitations of the historical control studies (see paragraph 6.34) and acknowledged the difficulty of obtaining data in this rare disease. The PBAC noted that both the Reiter 2017 primary unadjusted and the CEREMAST comparisons reported a significantly superior OS rate in the midostaurin treated arm (HR = 0.5, 95% CI 0.33, 0.76 and HR = 2.2, 95% CI 1.08, 4.47¹⁶ [inverse HR = 0.45] respectively). The PBAC noted that while the increase in OS was no longer statistically significant for the Reiter 2017 analysis when propensity score matching was used, the point estimate for the increase in OS remained numerically in favour of midostaurin (HR=0.64, 95% CI 0.33, 1.24). Overall, the PBAC considered that, while there was significant uncertainty due to the limitations in the evidence, the claim of superior comparative effectiveness was reasonable in this rare disease.

- 7.7 The PBAC noted that gastrointestinal toxicities were the most common adverse events (AE) suspected to be study drug-related in the D2201 and A2213 studies. The PBAC noted that although 25 deaths occurred while on-treatment, no deaths were related to midostaurin. The PBAC considered that there was a lack of comparative data to support a claim of non-inferiority. However, the PBAC advised that the toxicities were as expected and agreed with the ESC that in this rare disease it was uncertain but likely that midostaurin was non-inferior in safety compared with SOC.
- 7.8 The submission presented a cost-utility analysis of midostaurin versus SOC. The PBAC noted that ESC raised concerns regarding the separation of the PF health state into PF with response and PF without response, the OS modelling assumptions used (generalised gamma to model OS in the midostaurin arm and the use of the OS HR from CEREMAST), the 20-year time horizon and the face validity of the progressed disease (PD) utility value (0.75). As such, the ESC proposed a respecified base case that: used the log normal function to model OS in the midostaurin arm; used the Reiter 2017 propensity score matched OS HR (0.64); applied a time horizon of 10 years; condensed PF health states; and assumed a PD utility value of 0.65. The PBAC noted that incorporating these inputs increased the base case ICER from \$135,000 to < \$155,000 per QALY gained to \$455,000 to < \$555,000 per QALY gained.
- 7.9 The PBAC noted that the pre-PBAC response accepted the use of the log normal function to model OS in the midostaurin arm and the application of a 10 year time horizon and included the offered midostaurin price reduction in the model (see paragraph 3.1). However, the pre-PBAC response argued against condensing the PF health states stating it would allow non-responders to continue therapy. In addition, the pre-PBAC response argued for the use of the Reiter 2017 multivariate analyses OS HR (0.517) in the model and for the PD utility value of 0.75 to be retained. With the incorporation of response criteria in the restriction (see paragraph 7.3), the PBAC accepted the pre-PBAC response argument that the PF health states should not be condensed. However, the PBAC acknowledged that some uncertainty remained

¹⁶ The historical control group was the reference in this analysis

regarding the duration of treatment with midostaurin using this proposed approach (Mean treatment duration: model 12.42 months; D2201 18.7 months; A2213 21.4 months. Median: D2201 11.4 months; A2213 9.8 months). The PBAC did not accept the argument for the use of the Reiter 2017 multivariate analyses OS HR (0.517) in the model. Instead, the PBAC agreed with the ESC that the use of the more conservative Reiter 2017 propensity score matched analysis OS HR was appropriate given the uncertainty in the model due to the limitations of the clinical evidence. The PBAC also agreed with the ESC that the PD utility value of 0.75 was unlikely to have face validity given the impact of this condition on QoL. The PBAC agreed with the ESC that the PD utility value was likely too high and did not capture the full impact of the illness during what was a long period of time spent in the model for the midostaurin cohort. The PBAC accepted the ESC advice that decreasing the PD utility value to an arbitrary 0.65 was appropriate in the context of this rare disease to reflect the uncertainties from D2201 QoL data and the debilitating symptoms associated with AdvSM.

- 7.10 Overall, the PBAC accepted the ESC respecified base case, with the approach taken to condense the PF health states removed, as an appropriate model to determine cost-effectiveness. The PBAC noted that incorporating the price reduction offered in the pre-PBAC response the revised ESC respecified base case returned an ICER of \$255,000 to < \$355,000 per QALY gained. The PBAC considered the ICER was high and remained uncertain. Considering relevant precedents and model uncertainties as outlined, the PBAC advised that the cost-effectiveness of midostaurin would be acceptable with a price reduction to achieve an ICER in the order of \$75,000 to < \$95,000 per QALY gained.
- 7.11 The PBAC noted the submission adopted an epidemiological approach to the financial estimates. The PBAC considered that the incidence and prevalence rates, while highly uncertain in this rare disease, were reasonable in the absence of other evidence. In addition, the PBAC considered the proportion eligible for cytoreduction therapy and the uptake rates used were reasonable. The PBAC noted the Pre-Sub-Committee Response (PSCR) accepted the approach taken by the evaluation to correct the errors identified in the calculation of grandfathered patients (see paragraph 6.75) and the number of prevalent patients (see paragraph 6.76) and considered this was appropriate. The PBAC agreed with the ESC that restricting the eligible patient population to account for *KIT D816V* mutation status as proposed in the PSCR was not appropriate and noted that this was accepted in the pre-PBAC response. The PBAC acknowledged that the financial estimates were sensitive to the duration of treatment with midostaurin. The PBAC noted that this was also an area of uncertainty identified in the economic model. The PBAC considered that with the incorporation of response criteria in the restriction (see paragraph 7.3) the mean treatment duration of 12.42 months used in the financial estimates was reasonable. The PBAC agreed with the evaluation that midostaurin is likely to displace rather than replace SOC but noted that the associated offsets had minimal impact on the overall budget impact.

- 7.12 The PBAC advised that there was the potential for use outside of the proposed population in patients with indolent or smouldering systemic mastocytosis. However, the PBAC considered that the risk was small due to the adverse event profile of midostaurin and the requirement for prescribers to provide evidence of AdvSM as part of the Authority Required (Written) process for initial and GF restrictions. As such, the PBAC advised that that a risk-sharing arrangement was not required.
- 7.13 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for midostaurin:
- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over SoC, as while clinically relevant the OS treatment benefit was associated with significant uncertainty due to the limitations in the evidence.
 - The treatment is expected to address a high and urgent unmet clinical need.
 - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.14 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive PBAC recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIDOSTAURIN					
midostaurin 25 mg capsule, 112	NEW (HSD Private) NEW (HSD Public)	2	224	1	Rydapt
	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Benefit type: <input checked="" type="checkbox"/> Authority Required (written/ online PBS authorities)				
	Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)				
	Prescribing rule level:				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				

Public Summary Document - March 2025 PBAC Meeting

	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Restriction Summary [new1] / Treatment of Concept: [new1A]</p>	
	<p>Indication: Advanced systemic mastocytosis (AdvSM)</p>
	<p>Treatment Phase: Initial treatment</p>
	<p>Clinical criteria:</p>
	<p>The condition must be advanced systemic mastocytosis including: (i) aggressive mastocytosis (ASM), (ii) systemic mastocytosis with an associated haematological neoplasm (SM-AHN), (iii) mast cell leukaemia (MCL).</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have documented measurable C-findings at baseline.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must not have received prior treatment with this drug for this condition.</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a haematologist</p>
	<p>Population criteria:</p>
	<p>Patient must be at least 18 years of age.</p>
	<p>Prescribing Instructions: The date and details of the patient's diagnostic reports confirming measurable C-findings at baseline (prior to initiation of treatment with this drug) must be documented in the patient's medical record. Measurable C-findings at baseline will be required to assess if the patient has responded to treatment or developed progressive disease.</p>
	<p>Prescribing Instructions: The diagnostic reports must not be more than 12 months old at the time of the authority application.</p>
	<p>Prescribing Instructions: The assessment of response must be conducted within 8 weeks of treatment initiation to determine patient's eligibility for continuing treatment.</p>
	<p>Prescribing Instructions: Measurable C-findings include any of the following:</p> <ul style="list-style-type: none"> (i) Bone marrow dysfunction manifested by 1 or more cytopenia(s) (i.e. Absolute Neutrophil Count (ANC) less than $1.0 \times 10^9/L$, haemoglobin (Hgb) level less than 100 g/L, or platelets count less than $100 \times 10^9/L$) but with no obvious non-mast cell haematopoietic malignancy; (ii) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; (iii) Skeletal involvement with large osteolytic lesions and/or pathological fractures; (iv) Palpable splenomegaly with hypersplenism; (v) Malabsorption with weight loss due to gastrointestinal mast cell infiltrate.

Public Summary Document - March 2025 PBAC Meeting

	<p>Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail, and must include: (a) details (dates, unique identifying number/code or provider number (if applicable)) of the diagnostic reports assessing the patient's measurable C-findings at baseline.</p>
	<p>Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</p>
	<p>Restriction Summary / Treatment of Concept:</p>
	<p>Indication: Advanced systemic mastocytosis (AdvSM)</p>
	<p>Treatment Phase: Transitioning from non-PBS to PBS-subsided treatment - Grandfather arrangements</p>
	<p>Clinical criteria:</p>
	<p>Patient must have previously received non-PBS-subsided treatment with this drug for this condition prior to [date of listing]</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must be receiving treatment with this drug for this condition at the time of application</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The condition must be advanced systemic mastocytosis including: (i) aggressive mastocytosis (ASM), (ii) systemic mastocytosis with an associated haematological neoplasm (SM-AHN), (iii) mast cell leukaemia (MCL).</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have documented measurable C-findings at baseline.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have demonstrated major or partial response within 8 weeks of treatment initiation with this drug for this condition if they have received at least 8 weeks of therapy.</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a haematologist</p>
	<p>Population criteria:</p>
	<p>Patient must be at least 18 years of age.</p>
	<p>Prescribing Instructions: The date and details of the patient's diagnostic reports confirming measurable C-findings at baseline (prior to initiation of treatment with this drug) must be documented in the patient's medical record. Measurable C-findings at baseline will be required to assess if the patient has responded to treatment or developed progressive disease.</p>
	<p>Prescribing Instructions: The diagnostic reports must not be more than 12 months old at the time of the authority application.</p>
	<p>Prescribing Instructions: The assessment of response must be conducted within 8 weeks of treatment initiation to determine patient's eligibility for continuing treatment.</p>
	<p>Prescribing Instructions: Major response is defined as complete resolution of at least one (=one or more) C-Finding(s) and no progression in other C-Findings.</p>

Public Summary Document - March 2025 PBAC Meeting

	<p>Prescribing Instructions: Partial response is defined as incomplete regression of one or more C-Finding(s) without complete regression and without progression in other C-Findings.</p>
	<p>Prescribing Instructions: Measurable C-findings include any of the following:</p> <ul style="list-style-type: none"> (i) Bone marrow dysfunction manifested by 1 or more cytopenia(s) (i.e. Absolute Neutrophil Count (ANC) less than $1.0 \times 10^9/L$, haemoglobin (Hgb) level less than 100 g/L, or platelets count less than $100 \times 10^9/L$) but with no obvious non-mast cell haematopoietic malignancy; (ii) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; (iii) Skeletal involvement with large osteolytic lesions and/or pathological fractures; (iv) Palpable splenomegaly with hypersplenism; (v) Malabsorption with weight loss due to gastrointestinal mast cell infiltrate.
	<p>Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail, and must include:</p> <ul style="list-style-type: none"> (a) details (dates, unique identifying number/code or provider number (if applicable)) of the diagnostic reports assessing the patient's measurable C-findings at baseline. (b) confirmation that the patient has achieved either major or partial response within 8 weeks of treatment initiation if they have received at least 8 weeks of therapy. <p>All reports must be documented in the patient's medical records.</p>
	<p>Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include:</p> <ul style="list-style-type: none"> (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	<p>Prescribing Instructions: 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 First continuing treatment criteria.</p>
	<p>Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIDOSTAURIN					
midostaurin 25 mg capsule, 112	NEW (HSD Private) NEW (HSD Public)	2	224	2	Rydapt
	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Benefit type: <input checked="" type="checkbox"/> Authority Required (telephone/ online PBS authorities)				
	Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)				
	Prescribing rule level:				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				

Public Summary Document - March 2025 PBAC Meeting

	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>
<p>Restriction Summary/ Treatment of Concept:</p>	
	<p>Indication: Advanced systemic mastocytosis (AdvSM)</p>
	<p>Treatment Phase: First continuing treatment</p>
	<p>Clinical criteria:</p>
	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition under the initial treatment restriction; OR</p>
	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition under the grandfather treatment restriction.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have demonstrated major or partial response to treatment with this drug for this condition within 8 weeks of treatment initiation.</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a haematologist; or</p>
	<p>Must be treated by a medical practitioner in consultation with a haematologist.</p>
	<p>Prescribing Instructions: The assessment of response must be conducted within 8 weeks of treatment initiation to determine patient's eligibility for continuing treatment.</p>
	<p>Prescribing Instructions: Major response is defined as complete resolution of at least one (=one or more) C-Finding(s) and no progression in other C-Findings.</p>
	<p>Prescribing Instructions: Partial response is defined as incomplete regression of one or more C-Finding(s) without complete regression and without progression in other C-Findings.</p>
	<p>Prescribing Instructions: For the subsequent continuing treatment, progressive disease must be monitored regularly and assessed before applying for each continuing authority application.</p>
	<p>Prescribing Instructions: Progressive disease is defined as a worsening of one or more C-findings from the best-recorded response.</p>
	<p>Prescribing Instructions: Measurable C-findings include any of the following:</p> <ul style="list-style-type: none"> (i) Bone marrow dysfunction manifested by 1 or more cytopenia(s) (i.e. Absolute Neutrophil Count (ANC) less than $1.0 \times 10^9/L$, haemoglobin (Hgb) level less than 100 g/L, or platelets count less than $100 \times 10^9/L$) but with no obvious non-mast cell haematopoietic malignancy; (ii) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; (iii) Skeletal involvement with large osteolytic lesions and/or pathological fractures; (iv) Palpable splenomegaly with hypersplenism; (v) Malabsorption with weight loss due to gastrointestinal mast cell infiltrate.
	<p>Prescribing Instructions: A patient who has developed progressive disease while being treated with this drug is no longer eligible for PBS-subsidised treatment with this drug for this condition.</p>

Public Summary Document - March 2025 PBAC Meeting

	<p>Prescribing Instructions: At the time of the authority application, medical practitioners must provide:</p> <ul style="list-style-type: none"> (a) details (dates, unique identifying number/code or provider number (if applicable)) of the diagnostic reports assessing the patient's current measurable C-findings compared to baseline; and (b) confirmation that the patient has achieved either major or partial response within 8 weeks of treatment initiation. <p>All reports must be documented in the patient's medical records.</p>
Restriction Summary / Treatment of Concept:	
	Indication: Advanced systemic mastocytosis (AdvSM)
	Treatment Phase: Subsequent continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this condition.
	Treatment criteria:
	Must be treated by a haematologist; or
	Must be treated by a medical practitioner in consultation with a haematologist
	Prescribing Instructions: For the subsequent continuing treatment, progressive disease must be monitored regularly and assessed before applying for each continuing authority application.
	Prescribing Instructions: Progressive disease is defined as a worsening of one or more C-findings from the best-recorded response.
	<p>Prescribing Instructions: Measurable C-findings include any of the following:</p> <ul style="list-style-type: none"> (i) Bone marrow dysfunction manifested by 1 or more cytopenia(s) (i.e. Absolute Neutrophil Count (ANC) less than $1.0 \times 10^9/L$, haemoglobin (Hgb) level less than 100 g/L, or platelets count less than $100 \times 10^9/L$) but with no obvious non-mast cell haematopoietic malignancy; (ii) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; (iii) Skeletal involvement with large osteolytic lesions and/or pathological fractures; (iv) Palpable splenomegaly with hypersplenism; (v) Malabsorption with weight loss due to gastrointestinal mast cell infiltrate.
	Prescribing Instructions: A patient who has developed progressive disease while being treated with this drug is no longer eligible for PBS-subsidised treatment with this drug for this condition.
	<p>Prescribing Instructions: At the time of the authority application, medical practitioners must provide:</p> <ul style="list-style-type: none"> (a) details (dates, unique identifying number/code or provider number (if applicable)) of the diagnostic reports assessing the patient's current measurable C-findings compared to the best recorded response; and (b) confirmation that the patient does not have progressive disease. <p>All reports must be documented in the patient's medical records.</p>

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

9 Context for Decision

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

10 Sponsor's Comment

Novartis acknowledges the positive recommendation of midostaurin, however the changes required by the PBAC to the model make listing impossible to achieve at this time. This is extremely disheartening for patients with AdvSM who do not have a reimbursed treatment option available to them. Unfortunately given the stage of the product lifecycle it is not feasible to resubmit midostaurin for PBS listing. Instead midostaurin will be made available to patients through private prescription.