

**5.05 DECITABINE + CEDAZURIDINE,  
Tablet containing decitabine 35 mg + cedazuridine  
100 mg,  
Inqovi<sup>®</sup>,  
Otsuka Australia Pharmaceutical Pty Ltd.**

**1 Purpose of submission**

- 1.1 The submission requested Authority Required listing for decitabine+cedazuridine for the treatment of myelodysplastic syndrome (MDS) and chronic myelomonocytic leukaemia (CMML) in high-risk patients.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus azacitidine.

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

| Component      | Description   |
|----------------|---|
| Population     | High risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukaemia (CMML)                              |
| Intervention   | Decitabine 35mg + cedazuridine 100mg, fixed dose combination tablet taken on Day 1-5 in 28-day cycles             |
| Comparator     | Azacitidine   |
| Outcomes       | OS, time to AML transformation, overall response, complete response, partial response, haematological improvement |
| Clinical claim | Non-inferiority in terms of efficacy and safety   |

Source: Table 1.1, p28 of the submission.

AML=acute myeloid leukaemia; OS=overall survival

**2 Background**

**Registration status**

- 2.1 Decitabine+cedazuridine was approved by the TGA on 29 October 2020 for the treatment of adult patients with MDS/CMML. The TGA application was evaluated under the Project Orbis international collaboration with the FDA in the US and Health Canada.
- 2.2 The requested PBS listing is narrower than the TGA indication, as it is limited to patients with an intermediate-2 or high risk IPSS score for MDS, and for CMML patients. For CMML, the requested PBS listing specifies an additional eligibility criterion of 10% to 29% marrow blasts without myeloproliferative disorder. These criteria align with the current azacitidine PBS listing, but does not include low blast count (20-30%) acute myeloid leukaemia.

### 3 Requested listing

| Name, restriction, manner of administration, form | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats            | Dispensed price for maximum quantity                        | Proprietary name and manufacturer |
|---|--------------------------|--------------------------|---------------------------|---|-----------------------------------|
| DECITABINE 35MG and CEDAZURIDINE 100MG Tablet     | 5                        | 5                        | 2 initial<br>5 continuing | \$4,876.96 published price<br>\$ [REDACTED] effective price | INQOVI®<br>Otsuka Australia       |

|                            |   |
|----------------------------|---|
| <b>Category / Program:</b> | GENERAL – General Schedule (S85)  |
| <b>Prescriber type:</b>    | <input checked="" type="checkbox"/> Medical Practitioners   |
| <b>Condition:</b>          | Myelodysplastic syndrome and chronic myelomonocytic leukaemia   |
| <b>PBS Indication:</b>     | Myelodysplastic syndrome and chronic myelomonocytic leukaemia   |
| <b>Treatment phase:</b>    | Initial   |
| <b>Restriction:</b>        | <input checked="" type="checkbox"/> Authority Required - non-immediate/delayed (In Writing/Electronic)  |
| <b>Clinical criteria:</b>  | Myelodysplastic syndrome<br>The condition must be classified as Intermediate-2 OR high-risk according to the International Prognostic Scoring System (IPSS)<br>AND<br>The condition must have ≤30% marrow blasts<br>Chronic myelomonocytic leukaemia<br>The condition must have 10% to 29% marrow blasts without myeloproliferative disorder. |
| <b>Treatment phase:</b>    | Continuing  |
| <b>Restriction:</b>        | <input checked="" type="checkbox"/> Authority Required – immediate/real time (Telephone/Electronic)   |
| <b>Clinical criteria:</b>  | Myelodysplastic syndrome<br>The condition must be classified as Intermediate-2 OR high-risk according to the International Prognostic Scoring System (IPSS)<br>AND<br>The condition must have ≤30% marrow blasts<br>Chronic myelomonocytic leukaemia<br>The condition must have 10% to 29% marrow blasts without myeloproliferative disorder. |
| <b>Treatment criteria:</b> | Patient must have previously received PBS-subsidised treatment with this drug for this condition<br>AND<br>Patient must not have progressive disease  |

3.1 The current PBS listings for azacitidine include MDS, CMML and acute myeloid leukaemia (AML) as indications for each PBS item. The submission indicated (p29) there are overlapping population groups between the requested PBS listing and the azacitidine listing, which is illustrated in the table below.

**Table 2: Populations in the proposed PBS listing and the azacitidine listings for MDS, CMML and AML**

| Requested PBS listing  |   | Azacitidine PBS listings   |
|--|---|--|
| MDS<br>Condition must be classified as intermediate-2 or high risk according to the IPSS<br>Condition must have ≤30% marrow blasts | = | MDS<br>Condition must be classified as intermediate-2 or high risk according to the IPSS<br>AML<br>Condition must have 20% to 30% marrow blasts and multi-lineage dysplasia, according to WHO classification |
| CMML<br>Condition must have 10% to 29% marrow blasts without myeloproliferative disorder   | = | CMML<br>Condition must have 10% to 29% marrow blasts without myeloproliferative disorder   |

Source: Table 1.2, p29 of the submission.

AML=acute myeloid leukaemia; CMML=chronic myelomonocytic leukaemia; IPSS=International Prognostic Scoring System; MDS=myelodysplastic syndrome

- 3.2 While the requested restriction was largely consistent with the azacitidine PBS listing, it did not include detailed International Prognostic Scoring System (IPSS) criteria that are part of the azacitidine PBS listing. The Pre-Sub-Committee Response (PSCR) indicated that the sponsor is willing to include the IPSS risk clarification used in the azacitidine PBS listing if it is considered necessary.
- 3.3 The ESC noted that the requested listing for MDS is based on the French-American-British (FAB) classification system where patients with <30% myeloblasts were classified as MDS and those with ≥30% myeloblasts within the bone marrow or peripheral blood were classified as AML. The ESC noted that the FAB classification was now outdated with the World Health Organisation (WHO) classification system being developed in 2001. Under the WHO classification system, the upper threshold of blast count for MDS diagnosis is 20% which means that a subtype of MDS under the FAB classification system would fall into AML under the WHO classification system (20% to 30% marrow blasts). The PBAC advised that the restrictions for decitabine+cedazuridine should align with the existing azacitidine restrictions (i.e. restrictions for MDS, AML and CMML) and that the restriction for MDS should specify an upper threshold of 20% for bone marrow blasts consistent with the WHO classification system.
- 3.4 The azacitidine listing also specifies that a bone marrow biopsy report must be provided, along with a full blood examination report and the pathology report detailing the cytogenetics demonstrating intermediate-2 or high risk according to IPSS. These requirements have not been included in the requested restriction. The PSCR indicated the sponsor was willing to accept changes to the restrictions to align the proposed restrictions with the existing azacitidine restrictions.
- 3.5 The submission requested broadening the restriction to include intermediate-1 low risk patients and provided associated clinical evidence and financial estimates (see 'Financial estimates' below for further detail). The clinical evidence presented by the submission was limited, and estimated patient numbers could not be verified. The ESC noted the request to include intermediate-1 low risk patients was based on IPSS

subgroup analyses of OS in Lubbert et al., 2011 and Fenaux et al., 2009. The ESC considered the available clinical evidence of the efficacy of decitabine+cedazuridine in intermediate-1 low risk patients was limited noting there were only 16 patients in Lubbert et al., 2011 and 13 patients in Fenaux et al., 2009 with an IPSS risk category of intermediate-1.

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

## **4 Population and disease**

- 4.1 Myelodysplastic syndrome is a heterogeneous group of haematopoietic stem cell disorders characterised by dysplastic changes in myeloid, erythroid and megakaryocytic progenitors and is associated with cytopenias affecting one or more of the three lineages. Chronic myelomonocytic leukaemia is also a heterogeneous group of haematopoietic stem cell disorders and is differentiated from other forms of MDS by persistent peripheral blood monocytosis ( $\geq 1 \times 10^9/L$ ; monocytes  $\geq 10\%$  of white blood cell count).
- 4.2 Most patients with MDS or CMML are elderly, with a median age at diagnosis of approximately 70 years, with around 10% of patients being younger than 50 years. Along with anaemia, neutropenia and thrombocytopenia, variable blast proliferation and leukocytosis may be observed.
- 4.3 Disease classification is based on the French-American-British (FAB) classification and the IPSS, both of which are part of the azacitidine PBS listing and the requested listing for decitabine+cedazuridine.
- 4.4 Both MDS and CMML may evolve into acute myeloid leukaemia (AML), and such patients have a less favourable prognosis than those presenting with de novo AML. Prognosis is also poor in patients with high risk MDS sub-types, such as MDS with 20%-30% bone marrow blast, which is associated with a median survival of 5 months and an AML evolution rate of 60%.
- 4.5 Decitabine+cedazuridine is a fixed dose combination tablet of decitabine 35mg and cedazuridine 100mg. Decitabine is a nucleoside metabolic inhibitor (referred to as a hypomethylating agent or HMA) and cedazuridine is a cytidine deaminase (CDA) inhibitor. The oral administration of cedazuridine with decitabine enhances the oral bioavailability of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA.
- 4.6 The submission considered that use of azacitidine comprised current treatment of MDS/CMML, and decitabine+cedazuridine would be used as an alternative to azacitidine in the proposed clinical management algorithm.

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

## 5 Comparator

- 5.1 The submission nominated azacitidine as the main comparator, with the primary justification being azacitidine is the only HMA currently available on the PBS for the MDS and CMML populations. The ESC considered azacitidine is the appropriate comparator.
- 5.2 While lenalidomide is PBS-listed for treatment of MDS, it is listed specifically for low-risk or intermediate-1 patients, who have a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities and who are red blood cell transfusion dependent, and hence is not a relevant comparator.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician noted that distribution of azacitidine across Australia was challenging given its limited stability. The clinician emphasised that travel and its associated financial costs are current barriers for rural and remote patients in accessing treatment with azacitidine. The clinician considered that as an oral therapy, decitabine+cedazuridine would ease the financial burden associated with travelling and provide a more flexible treatment regimen for patients which can be incorporated into a telehealth model of care. The clinician highlighted that the indirect comparison between IV decitabine and azacitidine showed no statistically significant differences in terms of response based outcomes. The clinician noted that Komrokji 2020 et al., 2020<sup>1</sup> found that complete response was significantly associated with a better OS than other response groups and can be used as a surrogate endpoint for OS in higher-risk MDS patients. The clinician considered that although there was evidence azacitidine was superior in terms of OS to decitabine in patients with MDS duration >1 year, and was superior in patients with ECOG score of 2-3, patients would likely be treated soon after diagnosis in clinical practice. The clinician considered that the interpretation of OS from the indirect comparison may be limited due to heterogeneity between patient populations, censoring and differences in subsequent therapies used in the trials. The clinician noted that the reporting of serious adverse events in the trials were problematic as most patients have grade 3 or 4 neutropenia and thrombocytopenia at baseline. The clinician considered that febrile neutropenia and requirement of intravenous antibiotics would be a better indicator

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<sup>1</sup> Komrokji RS, Al Ali NH, Sallman D, Padron E et al. Validation of International Working Group response criteria in higher-risk myelodysplastic syndromes: A report on behalf of the MDS Clinical Research Consortium. *Cancer Medicine* 2020; DOI: 10.002/cam4.3608.

of safety concerns and noted that a meta-analysis (Xie et al., 2015) found no significant differences between in febrile neutropenia between decitabine and azacitidine.

### **Consumer comments**

- 6.2 PBAC noted and welcomed the input from health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health care professionals noted that current treatment with azacitidine requires patients to attend outpatient clinics over several days each month. The comments emphasised that the availability of an oral hypomethylating agent such as decitabine+cedazuridine would provide more flexibility for patients who live remotely and reduce the burden on outpatient clinics.
- 6.3 The Leukaemia foundation and Rare Cancers Australia strongly supported listing decitabine+cedazuridine on the PBS, noting that blood cancers are associated with debilitating effects on quality of life and the availability of an oral agent which reduces the need to travel for treatment, would be valuable for these patients.

### **Clinical trials**

- 6.4 The submission provided a two-step approach to support its claim of non-inferior effectiveness and safety of decitabine+cedazuridine versus azacitidine:
- Indirect comparison of IV decitabine vs. azacitidine using best supportive care (BSC) as the common reference.
  - Direct comparison (pharmacokinetic evidence) of decitabine+cedazuridine vs. IV decitabine.
- 6.5 The submission was based on six trials, two comparing decitabine IV and BSC and two comparing azacitidine and BSC that were used in the indirect comparison, and two pharmacokinetic trials comparing decitabine+cedazuridine and decitabine IV. Details of the trials are provided in the table below.

**Table 3: Trials and associated reports presented in the submission**

| <b>Trial ID</b>   | <b>Protocol title/ Publication title</b>   | <b>Publication citation</b>   |
|---|--|---|
| <b>Indirect comparison decitabine vs. azacitidine with BSC as common comparator</b> |  |   |
| Kantarjian 2006<br>(decitabine vs. BSC)   | Kantarjian H, Issa J PJ, Rosenfeld CS, Bennett JM et al. Decitabine improves patient outcomes in myelodysplastic syndromes: Results of a phase III randomised study.   | <i>Cancer</i> 2006;106(8): 1794-803   |
| Lubbert 2011<br>(decitabine vs. BSC)  | Lubbert M, Suci S, Baila L, Rüter BH et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: Final results of the randomised phase III study of the European organisation for research and treatment of cancer leukaemia group and the German MDS study group.  | <i>J Clin Oncol</i> 2011; 29(15): 1987-96.  |
| Fenaux 2009<br>(azacitidine vs. BSC)  | Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open label, phase III study.  | <i>Lancet Oncol</i> 2009; 10(3): 223-32.  |
| Silverman 2002<br>(azacitidine vs. BSC)   | Silverman LR, Demakos EP, Peterson BL, Kornblith AB et al. Randomised controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukaemia group B.  | <i>J Clin Oncol</i> 2002; 20(10): 2429-40.  |
| <b>Decitabine+cedazuridine vs. IV decitabine</b>                                    |  |   |
| ASCERTAIN   | A Phase 3, Randomised, Open Label, Cross-over Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukaemia (CMML), Garcia-Manero G, McCloskey J, Griffiths EA, Yee KWL, Zeidan AM, Al-Kali A, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomised cross-over phase 3 study (ASCERTAIN study) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine.   | September 2019<br><br><i>Blood</i> 2019; 134.                                       |
| ASTX727-01-B  | A Phase 1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAI) E7727 with Oral Decitabine in Subjects with Myelodysplastic Syndromes (MDS), Garcia-Manero G, Griffiths EA, Steensma DP, Roboz GJ, Wells R, McCloskey J, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomised cross-over study. Garcia-Manero G, Griffiths EA, Roboz GJ, Busque L, Wells RA, Odenike O, et al. A phase 2 dose-confirmation study of oral ASTX727, a combination of oral decitabine with a cytidine deaminase inhibitor (CDAI) cedazuridine (E7727), in subjects with myelodysplastic syndromes (MDS). | March 2019<br><br><i>Blood</i> 2020; 136(6): 674-83.<br><br><i>Blood</i> 2017; 130. |

Source: Table 2.4, p59-61 of the submission.

BSC=best supportive care; IV=intravenous

6.6 The key features of the randomised trials are summarised in the table below.

**Table 4: Key features of the included evidence**

| Trial  | N                                  | Design        | Risk of bias | Patient population   | Outcomes                                 |
|--|------------------------------------|---------------|--------------|--|--|
| <b>Decitabine IV vs. BSC</b>                     |                                    |               |              |  |  |
| Kantarjian 2006                                  | Dec: 89<br>BSC: 81<br>Total: 170   | R, OL, MC     | High         | FAB-based MDS; IPSS ≥intermediate-1  | ORR, time to AML transformation or death |
| Lubbert 2011                                     | Dec: 99<br>BSC: 114<br>Total: 233  | R, OL, MC     | High         | FAB or WHO-based MDS; IPSS ≥intermediate-1; bone marrow blasts 11% to 30% or ≤10% and poor cytogenetics                        | OS                                       |
| <b>Azacitidine vs. BSC</b>                       |                                    |               |              |  |  |
| Fenaux 2009                                      | Aza: 117<br>BSC: 105<br>Total: 222 | R, OL, MC     | High         | MDS with IPSS intermediate-2 or high risk and FAB-based RAEB or RAEB-t, or CMML with at least 10% bone marrow blasts; ECOG 0-2 | OS                                       |
| Silverman 2002                                   | Aza: 99<br>BSC: 92<br>Total: 191   | R, OL, MC, CO | High         | FAB-based MDS; patients with RA or RARS must also have significant marrow dysfunction.   | Response                                 |
| <b>Decitabine+cedazuridine vs. decitabine IV</b> |                                    |               |              |  |  |
| ASCERTAIN  | 133                                | R, OL, MC, CO | High         | FAB-based RA, RARS, RAEB, CMML, or RAEB-t; IPSS ≥intermediate-1; ECOG 0-1  | Pharmacokinetic (AUC)                    |
| ASTX727-01-B                                     | Dose confirm:52<br>FDC: 34         | R, OL, MC, CO | High         | Peripheral blasts <20%; IPSS ≥intermediate-1; ECOG 0-2   | Pharmacokinetic (AUC)                    |

Source: Table 2.5, p64 of the submission.

AML=acute myeloid leukaemia; AUC=area under the curve; Aza=azacitidine; BSC=best supportive care; CO=cross-over; Dec=decitabine; ECOG=Eastern Cooperative Oncology Group; FAB=French-American-British; FDC=fixed dose combination; IPSS=International Prognostic Scoring System; MC=multicentre; MDS=myelodysplastic syndrome; OL=open label; ORR=overall response rate; OS=overall survival; R=randomised; RA=refractory anaemia; RAEB=refractory anaemia with excess blasts; RAEB-t=refractory anaemia with excess blasts in transformation; RARS=refractory anaemia with ringed sideroblasts.

- 6.7 The submission stated (p66) that the risk of bias ranged from unclear to high across the trials. All trials were open label and while some outcomes were objective, there remained potential for bias given unblinded outcome assessment or lack of information regarding outcome assessment. It would be reasonable to conclude that the risk of bias was high across all of the trials.
- 6.8 The ESC noted that the only trial which included a patient population entirely consistent with the proposed PBS population, was the Fenaux et al., 2009 trial which compared azacitidine and BSC. The ESC noted that the other trials also included lower risk MDS patients with an IPSS of intermediate-1. The ESC considered that the inclusion of lower risk patients would likely have impacted the efficacy results as patients with a risk category of intermediate-2 generally have a distinctively worse prognosis compared to intermediate-1 patients, characterised by shorter survival and shorter time to AML evolution. The ESC noted that subgroup analyses by IPSS risk category were not available for all trials.
- 6.9 In regard to dosing, the decitabine+cedazuridine pharmacokinetic trials used 5-day dosing in each 28-day cycle, while in the indirect comparison, the IV decitabine trials used 3-day dosing and the azacitidine trials used 7-day dosing. The decitabine trials

used in the indirect comparison (Kantarjian 2006; Lubbert 2011) had a 42 day treatment cycle, i.e. patients received 3 days of treatment every 6 weeks or 42 days, instead of the 28-day cycles used in all other trials. The submission provided one randomised controlled trial (We et al., 2015)<sup>2</sup> and naïve comparisons of trials using 5-day dosing to claim similar results with 3-day dosing. The ESC noted that the results from Wu et al., 2015, a randomised controlled trial which compared 3-day and 5-day dosing regimens for decitabine IV concluded that the two dosing regimens for decitabine were equally efficacious and safe. The ESC considered there was some support that 5-day and 3-day dosing for decitabine would produce similar results.

- 6.10 The number of treatment cycles (28 days) varied across the trials presented by the submission. In the decitabine+cedazuridine trials, a median of 4 treatment cycles were received in ASCERTAIN, and a median of 7 treatment cycles were received in ASTX727-01-B. In the IV decitabine trials, a median of 3 cycles were received in the Kantarjian (2006) trial and 4 cycles in the Lubbert (2011) trial. In the azacitidine trials, the Fenaux (2009) trial reported that azacitidine was given for a median of 9 cycles, while Silverman (2002) reported median time to exit from azacitidine treatment was 9.1 months. In addition to the trial evidence, the azacitidine Product Information (PI) recommends a minimum of 6 cycles of treatment, while the decitabine+cedazuridine PI recommends a minimum of 4 cycles of treatment. The PSCR noted that the recommended number of cycles in the azacitidine (6) and decitabine+cedazuridine (4) PIs are based on the reporting in the pivotal trials upon which the TGA registrations are based. The PSCR noted that while patients in Fenaux et al., 2009 were evaluated for response every 6 months, patients in Lubbert et al., 2011 were evaluated at the end of 4 cycles. However, the PSCR claimed that both studies show that the median best response for azacitidine and decitabine is usually by 3-4 months. The PSCR claimed that the treatments should have similar duration of treatment and that the within-trial difference in median treatment cycle is attributable to differences in study protocols. Overall, the ESC considered that the average number of cycles that would be used in clinical practice was uncertain. The ESC noted that the number of cycles used would also depend on the OS benefit in the real world setting and it was uncertain how applicable the trial data was to the Australian setting.
- 6.11 While there were no randomised trials comparing decitabine and azacitidine identified in the submission's literature search, there were four retrospective reviews available, of which two provide direct comparisons of decitabine and azacitidine (Lee et al., 2013; Lee et al., 2013a<sup>3</sup>). The Lee et al., 2013 publication was cited by the submission (p111) in its discussion of the decitabine treatment regimen, but no

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<sup>2</sup> Wu D, Du X, Jin J, Xiao Z et al. Decitabine for Treatment of Myelodysplastic Syndromes in Chinese Patients: An Open-Label, Phase-3b Study. *Adv Ther* 2015; 32:1140–1159.

<sup>3</sup> Lee YG, Kim I, Yoon SS, Park S et al. Comparative analysis between azacitidine and decitabine for the treatment of myelodysplastic syndromes. *Br J Haematol* 2013; 161: 339-347.

further information on the comparison provided in this paper was provided. The second publication (Lee et al., 2013a) reported a retrospective review of registry data, and provided statistical comparisons of 300 patients treated with azacitidine and 97 treated with decitabine. While only approximately half of the patient population in the two comparisons corresponded to the proposed PBS population (IPSS intermediate-2 or high risk; remainder were intermediate-1 or low-risk) it would have been informative had the results of these comparisons been provided. A summary of the characteristics and results of these studies is provided in the table below.

**Table 5: Summary of comparative studies: decitabine vs. azacitidine**

| Publication | Study characteristics   | Key results   |
|-------------|---|---|
| Lee 2013    | <p><u>Design</u>: retrospective analysis<br/> <u>Patient population</u>: MDS or CMML patients at three Korean institutes treated with azacitidine (N=75) or decitabine (N=74)<br/> <u>Treatment</u>: azacitidine vs. decitabine<br/> <u>Outcomes</u>: ORR, CR, PR, OS</p>   | <p>There was no significant difference between azacitidine and decitabine for ORR. In higher risk MDS, median OS was 16.8 months with azacitidine and 14.6 months with decitabine (no significant difference). Subgroup analyses showed that azacitidine tended to be superior to decitabine in patients with MDS duration &gt;1 year, and was superior in patients with ECOG score of 2-3 (HR=3.520; 95% CI: 1.322, 9.367). Decitabine was associated with more frequent Grade <math>\geq</math>3 neutropenia than azacitidine (p=0.040).</p>  |
| Lee 2013a   | <p><u>Design</u>: retrospective analysis<br/> <u>Patient population</u>: MDS patients sourced from the Korean MDS registry treated with azacitidine (N=203) or decitabine (N=97). Propensity-matched cohort of 97 patients in each group.<br/> <u>Treatment</u>: azacitidine vs. decitabine<br/> <u>Outcomes</u>: OS, ORR, CR, PR, time to AML transformation</p> | <p>No significant difference in ORR between azacitidine and decitabine in the overall cohort and the propensity-matched cohort. The proportion of patients with marrow complete response was greater for decitabine than azacitidine (p=0.006). There was no significant difference in OS between azacitidine and decitabine (HR=1.0; 95% CI: 0.71, 1.43), and also no difference in OS for the propensity-matched cohort. Grade 3 or 4 neutropenia was more common in the decitabine group (87%) than the azacitidine group (67%) and higher incidence was unchanged in the propensity-matched cohort. The number of infectious episodes treated with intravenous antimicrobials was significantly lower in the azacitidine group (RR=0.75; 95% CI: 0.58, 0.96).</p> |

Source: Lee 2013; Lee 2013a

AML=acute myeloid leukaemia; CMML=chronic myelomonocytic leukaemia; CR=complete response; HMA=hypomethylating agent; HSCT=haematopoietic stem cell transplantation; MDS=myelodysplastic syndrome; ORR=overall response rate; OS=overall survival; PR=partial response

6.12 The Lee et al., 2013 comparison was based on patients at three Korean institutes treated between 2006 and 2010, while the Lee et al., 2013a comparison was based on patients in the Korean MDS registry who were treated between 2004 and 2011. While there could be some overlap between the patient populations, the degree of this overlap could not be determined. The results of both studies showed there was no significant difference between decitabine and azacitidine for overall response rate (ORR). In Lee et al., 2013 the subgroup analyses for overall survival (OS) showed that azacitidine tended to be superior to decitabine in patients with MDS duration >1 year, and was superior in patients with ECOG score of 2-3 (HR=3.520; 95% CI: 1.322, 9.367).

Both studies showed significantly greater occurrence of Grade  $\geq 3$  neutropenia and other adverse events (AEs) with decitabine. The results are consistent with the submission's indirect comparisons, where significant advantages were observed for azacitidine (see 'Comparative effectiveness' below). The pre-PBAC Response considered that patients with ECOG 2-3 would likely represent a small proportion of patients who would be eligible for decitabine+cedazuridine. The pre-PBAC further noted that there was no difference in terms of OS between therapies for the IPSS intermediate-2 and high risk subgroup in Lee et al., 2013.

### ***Comparative effectiveness***

#### Indirect comparison – IV decitabine vs. azacitidine

6.13 The table below provides results for the indirect comparison of IV decitabine and azacitidine for survival outcomes, including subgroup analyses of OS.

**Table 6: Results of the indirect comparison of decitabine IV and azacitidine for OS and time to AML**

|   | Overall survival - median months (95% CI) |                         |                          | HR (95% CI)                    |
|---|---|-------------------------|--------------------------|--------------------------------|
|   | Decitabine IV                             | Common reference BSC    | Azacitidine              |                                |
| <b>Base case - OS</b>   |   |                         |                          |                                |
| Kantarjian 2006   | N=89<br>14                                | N=81<br>14.9            | -                        | 1.19 (0.83, 1.69)              |
| Lubbert 2011  | N=119<br>10.1                             | N=114<br>8.5            | -                        | 0.88 (0.66, 1.17)              |
| pooled decitabine IV fixed effects ( $I^2=41%$ ; $p=0.95$ )   |   |                         |                          | 0.99 (0.80, 1.24)              |
| Fenaux 2009   | -   | N=105<br>11.5 (5.7, NR) | N=117<br>21.1 (10.5, NR) | <b>0.58 (0.40, 0.84)</b>       |
| Silverman 2002  | -   | N=92<br>14 (12, 14)     | N=99<br>20 (16, 26)      | 0.79 (0.57, 1.08)              |
| pooled azacitidine fixed effects ( $I^2=32%$ ; $p=0.006$ )    |   |                         |                          | <b>0.69 (0.54, 0.88)</b>       |
| Indirect pooled decitabine IV vs. pooled azacitidine (95% CI) |   |                         |                          | <b>1.43 (1.03, 1.99)</b>       |
| <b>IPSS intermediate-2 and high risk subgroup</b>             |   |                         |                          |                                |
| Lubbert 2011  | NR  | NR                      | -                        | 0.91 (0.62, 1.32)              |
| Fenaux 2009   | -   | NR                      | NR                       | <b>0.49 (0.35, 0.68)</b>       |
| Indirect decitabine IV vs. azacitidine (95% CI)               |   |                         |                          | <b>1.86 (1.12, 3.07)</b>       |
| <b>ECOG 0-1 subgroup</b>                                      |   |                         |                          |                                |
| Lubbert 2011  | NR  | NR                      | -                        | 0.81 (0.55, 1.21)              |
| Fenaux 2009   | -   | NR                      | NR                       | <b>0.51 (0.29, 0.88)</b>       |
| Indirect decitabine IV vs. azacitidine (95% CI)               |   |                         |                          | 1.59 (0.8, 3.14)               |
| <b>Disease duration &gt;3 months subgroup</b>                 |   |                         |                          |                                |
| Lubbert 2011  | NR  | NR                      | -                        | 0.68 (0.4, 1.16)               |
| Fenaux 2009   | -   | NR                      | NR                       | <b>0.58 (0.4, 0.84)</b>        |
| Indirect decitabine IV vs. azacitidine (95% CI)               |   |                         |                          | 1.17 (0.61, 2.24)              |
| <b>Time to AML – median months</b>                            |   |                         |                          |                                |
|   | Decitabine IV                             | Common reference BSC    | Azacitidine              | HR (95% CI)                    |
| Kantarjian 2006   | N=89<br>12.1                              | N=81<br>7.8             | -                        | 0.99 (0.62, 1.59)              |
| Lubbert 2011  | N=119<br>8.8                              | N=114<br>6.1            | -                        | 0.85 (0.64, 1.13)              |
| pooled decitabine IV random effects ( $I^2=0%$ ; $p=0.33$ )   |   |                         |                          | 0.89 (0.70, 1.13) <sup>a</sup> |
| Fenaux 2009   | -   | N=105<br>10.1           | N=117<br>15.0            | <b>0.41 (0.27, 0.62)</b>       |
| Silverman 2002  | -   | N=92<br>12 (8, 15)      | N=99<br>21 (16, 27)      | <b>0.60 (0.44, 0.82)</b>       |
| pooled azacitidine random effects ( $I^2=51%$ ; $p=0.0003$ )  |   |                         |                          | <b>0.51 (0.35, 0.74)</b>       |
| Indirect pooled decitabine IV vs. pooled azacitidine (95% CI) |   |                         |                          | <b>1.75 (1.12, 2.72)</b>       |

Source: Table 2.16, p88; Table 2.17, p92; Table 2.24, p104-105 of the submission.

BSC=best supportive care; CI=confidence interval; HR=hazard ratio; IV=intravenous; NR=not reported; OS=overall survival; **bold**=statistically significant

6.14 The pre-PBAC Response acknowledged the limitations associated with the indirect comparison of survival data between azacitidine and decitabine+cedazuridine. The pre-PBAC Response indicated that in the absence of more reliable survival data, comparative efficacy could be informed by additional data sources such as indirect analyses of other outcomes, retrospective studies, and real-world evidence.

- 6.15 There was a statistically significant advantage for azacitidine compared to decitabine IV for OS (HR=1.43; 95% CI: 1.03, 1.99), and this advantage was also observed for the IPSS intermediate-2 and high-risk subgroup. However, the comparison in the subgroup was difficult to interpret, with no estimates of median survival available and number of patients not provided. The overall comparison had a moderately high level of heterogeneity, between 30% and 40%, which was acknowledged by the submission. A similar level of heterogeneity was observed in the analysis of time to AML (51%), which also showed an advantage for azacitidine. The submission also noted the varying levels of OS in the BSC arms, ranging from 8.5 to 14 months. While the ESC acknowledged the uncertainty associated with the indirect comparison of OS, the ESC noted that the OS advantage for azacitidine compared with decitabine is consistent with the results from Lee et al., 2013 (see paragraph 6.8). The pre-PBAC Response noted that an analysis of the Surveillance, Epidemiology, and End Results (SEER) database found no difference in survival (median OS of 15 months) in 2025 MDS patients based on the HMA received (Zeidan et al., 2016).
- 6.16 The submission stated that the OS comparisons were potentially influenced by the results of Fenaux (2009), where there are disparities between the survival rates and those expected in clinical practice and it is likely this trial overestimated the survival benefit for azacitidine. While median survival for azacitidine in the overall population for the Fenaux (2009) trial was relatively long (21.1 months), an estimate of median OS was not provided for the subgroup analysis, and it could not be determined how survival in the subgroup compared with that expected in clinical practice. The pre-PBAC Response stated that based on a 10% sample of PBS data, the median survival in patients treated with azacitidine is 13-14 months. The pre-PBAC Response noted this is similar to median OS reported in Lee et al., 2013 for the IPSS intermediate-2 and high risk subgroup (16 months) and the analysis of the SEER database (Zeidan et al., 2016) of HMA-treated patients. The PBAC noted that a later study using the same database (Zeidan et al., 2020) showed that MDS patients had a median OS of 10 months.
- 6.17 Given the above, the ESC considered the results of the indirect comparison for survival outcomes should be interpreted with caution.
- 6.18 Results for response outcomes are provided in the table below.

Table 7: Results of the indirect comparison of decitabine IV and azacitidine for response outcomes

| Overall response rate  | Decitabine IV<br>n/N (%) | Common reference: BSC<br>n/N (%) | Azacitidine<br>n/N (%) | RR (95% CI)                 |
|--|--------------------------|----------------------------------|------------------------|-----------------------------|
| Kantarjian 2006  | 15/89 (16.9%)            | 0/81 (0.0%)                      | -                      | <b>28.24 (1.72, 464.57)</b> |
| Lubbert 2011   | 23/119 (19.3%)           | 0/114 (0.0%)                     | -                      | <b>45.04 (2.77, 732.91)</b> |
| pooled decitabine IV random effects (I <sup>2</sup> =0%; p=0.0004) |                          |                                  |                        | <b>35.70 (4.95, 257.59)</b> |
| Fenaux 2009  | -                        | 5/105 (4.8%)                     | 32/117 (27.4%)         | <b>5.74 [2.32, 14.20]</b>   |
| Silverman 2002   | -                        | 0/92 (0.00%)                     | 23/99 (23.23%)         | <b>2.43 (1.53, 3.86)</b>    |
| pooled azacitidine random effects (I <sup>2</sup> =55%; p=0.02)    |                          |                                  |                        | <b>10.95 (1.43, 83.84)</b>  |
| Indirect pooled decitabine IV vs. pooled azacitidine (95% CI)      |                          |                                  |                        | 3.26 (0.19, 55.63)          |
| <b>Complete response</b>   |                          |                                  |                        |                             |
| Kantarjian 2006  | 8/89 (9.0%)              | 0/81 (0.0%)                      | -                      | 15.49 (0.91, 264.16)        |
| Lubbert 2011   | 16/119 (13.5%)           | 0/114 (0.0%)                     | -                      | 14.38 (0.83, 248.83)        |
| pooled decitabine IV random effects (I <sup>2</sup> =0%; p=0.008)  |                          |                                  |                        | <b>14.92 (2.00, 111.48)</b> |
| Fenaux 2009  | -                        | 1/105 (1.0%)                     | 14/117 (25.5%)         | <b>12.56 (1.68, 93.92)</b>  |
| Silverman 2002   | -                        | 0/92 (0.0%)                      | 7/99 (7.1%)            | 13.95 (0.81, 240.86)        |
| pooled azacitidine random effects (I <sup>2</sup> =0%; p=0.002)    |                          |                                  |                        | <b>13.01 (2.52, 67.28)</b>  |
| Indirect pooled decitabine IV vs. pooled azacitidine (95% CI)      |                          |                                  |                        | 1.15 (0.09, 15.38)          |
| <b>Partial response</b>  |                          |                                  |                        |                             |
| Kantarjian 2006  | 7/89 (7.9%)              | 0/81 (0.0%)                      | -                      | 13.67 (0.79, 235.57)        |
| Lubbert 2011   | 7/119 (5.9%)             | 0/114 (0.0%)                     | -                      | 14.38 (0.83, 248.83)        |
| pooled decitabine IV random effects (I <sup>2</sup> =0%; p=0.01)   |                          |                                  |                        | <b>14.02 (1.87, 105.09)</b> |
| Fenaux 2009  | -                        | 4/105 (3.8%)                     | 18/117 (15.4%)         | <b>4.04 (1.41, 11.55)</b>   |
| Silverman 2002   | -                        | 0/92 (0.0%)                      | 16/99 (16.2%)          | <b>30.69 (1.87, 504.33)</b> |
| pooled azacitidine random effects (I <sup>2</sup> =53%; p=0.05)    |                          |                                  |                        | <b>7.75 (1.02, 58.87)</b>   |
| Indirect pooled decitabine IV vs. pooled azacitidine (95% CI)      |                          |                                  |                        | 1.81 (0.1, 31.53)           |
| <b>Haematological improvement</b>                                  |                          |                                  |                        |                             |
| Kantarjian 2006  | 12/89 (13.5%)            | 6/81 (7.4%)                      | -                      | 1.82 (0.72, 4.63)           |
| Lubbert 2011   | 18/119 (15.1%)           | 2/114 (1.8%)                     | -                      | <b>8.62 (2.05, 36.32)</b>   |
| pooled decitabine IV random effects (I <sup>2</sup> =71%; p=0.11)  |                          |                                  |                        | 3.61 (0.75, 17.28)          |
| Fenaux 2009  | -                        | 32/105 (30.5%)                   | 57/117 (48.7%)         | <b>1.60 (1.13, 2.25)</b>    |
| Silverman 2002   | -                        | 5/92 (5.4%)                      | 37/99 (37.4%)          | <b>6.88 (2.82, 16.74)</b>   |
| pooled azacitidine random effects (I <sup>2</sup> =90%; p=0.14)    |                          |                                  |                        | 3.14 (0.69, 14.29)          |
| Indirect pooled decitabine IV vs. pooled azacitidine (95% CI)      |                          |                                  |                        | 1.15 (0.13, 10.18)          |

Source: Table 2.17, p92; Table 2.24, p104-105 of the submission.

BSC=best supportive care; CI=confidence interval; HR=hazard ratio; NR=not reported; **bold**=statistically significant

<sup>a</sup> Table 2.17 reported this result as 0.84 (0.66, 1.08) however that appeared to be a typographical error and the value reported in Table 2.25 and Table 2.33 and Figure 2.10 of the submission is reported here

6.19 The above comparisons showed no statistically significant differences between IV decitabine and azacitidine for response-based outcomes. The submission stated (p106) that it was unclear why the results of the indirect comparisons for survival outcomes differ from those for response-based outcomes. The submission suggested the survival benefit of azacitidine in Fenaux (2009) overestimated the true effect size, and while there was not an advantage for decitabine in terms of response, the ability of IV decitabine to induce a high response rate is clinically significant. There was also high heterogeneity across all comparisons, ranging from an I<sup>2</sup> of approximately 50% to 90%, except for complete response, where the I<sup>2</sup> value was 0%. The confidence intervals were also wide across many of the comparisons. The ESC considered that

inferiority of decitabine vs azacitidine in terms of ORR cannot be fully excluded given the wide confidence intervals.

Pharmacokinetic comparison of decitabine+cedazuridine and IV decitabine

6.20 For both the ASCERTAIN and ASTX727-01-B trials, patients received decitabine+cedazuridine or IV decitabine in the first treatment cycle, then crossed over to the alternate treatment in the second treatment cycle. In the third and ongoing treatment cycles, decitabine+cedazuridine was administered.

6.21 The following table provides the key results of the ASCERTAIN trial.

**Table 8: Key results of the ASCERTAIN trial**

|   | Decitabine+cedazuridine<br>(N=123)      | IV decitabine<br>(N=123)      | Ratio Geometric LSM<br>(90% CI) |              |
|---|---|-------------------------------|---------------------------------|--------------|
| <b>Pharmacokinetic and pharmacodynamic outcomes</b> |   |                               |                                 |              |
| 5-day AUC <sub>0-24</sub>                           | 855.69                                  | 864.94                        | 98.93 (92.66, 105.6)            |              |
| Maximum %line-1 demethylation                       | Decitabine+cedazuridine<br>LSM (95% CI) | IV decitabine<br>LSM (95% CI) | Difference (95% CI)             |              |
| Cycle 1   | 13.289 (11.798, 14.780)                 | 14.019 (12.528, 15.510)       | -0.730 (-2.838, 1.378)          |              |
| Cycle 2   | 11.151 (9.685, 12.616)                  | 11.968 (10.503, 13.434)       | -0.818 (-2.890, 1.255)          |              |
| <b>Clinical response</b>                            |   |                               |                                 |              |
|   | All patients (N=133)                    |                               |                                 |              |
|   | March 2019 data cut                     |                               | November 2019 data cut          |              |
|   | n (%)                                   | 95% CI                        | n (%)                           | 95% CI       |
| Complete response (CR)                              | 12 (9.0%)                               | (4.7, 15.2)                   | 28 (21.1%)                      | (14.5, 29.0) |
| Partial response (PR)                               | 0                                       | -                             | 0                               | -            |
| Marrow CR (mCR)                                     | 46 (34.6%)                              | (26.6, 43.3)                  | 43 (32.3%)                      | (24.5, 41.0) |
| mCR with HI   | 14 (10.5%)                              | (5.9, 17.0)                   | 20 (15.0%)                      | (9.4, 22.3)  |
| Haematological improvement (HI)                     | 7 (5.3%)                                | (2.1, 10.5)                   | 10 (7.5%)                       | (3.7, 13.4)  |
| Overall response (CR+PR+mCR+HI)                     | 65 (48.9%)                              | (40.1, 57.7)                  | 81 (60.9%)                      | (52.1, 69.2) |
| Stable disease                                      | 28 (21.1%)                              | (14.5, 29.0)                  | 0                               | -            |
| Progressive disease                                 | 8 (6.0%)                                | (2.6, 11.5)                   | 6 (4.5%)                        | (1.7, 9.6)   |
| Not evaluable                                       | 32 (24.1%)                              | (17.1, 32.2)                  | 17 (12.8%)                      | (7.6, 19.7)  |
|   | Median days (95% CI)                    |                               |                                 |              |
| OS  | NE (500, NE)                            |                               | NR                              |              |
| Leukaemia-free survival                             | NE (NE, NE)                             |                               |                                 |              |

Source: Table 2.27, p113; Table 2.28, p114; Table 2.29, p114-115 of the submission; Table 6, p9; Table 7, p11 of the efficacy update CSR. CI=confidence interval; IV=intravenous; LSM=least square means; NE=not evaluable; NR=not reported; OS=overall survival

6.22 In the ASCERTAIN trial decitabine+cedazuridine showed bioavailability equivalent to IV decitabine. The 5-day AUC<sub>0-24</sub> ratio (oral/IV) of geometric least square means (LSM) was 98.93% (90% CI: 92.66, 105.6), and the 90% CI was within the pre-specified range of 80% to 125%. Pharmacodynamic results (%line-1 demethylation) showed similar effects for decitabine+cedazuridine and IV decitabine, with non-significant differences in both Cycle 1 and Cycle 2. The TGA Delegate’s Overview (p14) states that the pharmacodynamic data suggests that the demethylation effect (on LINE-1) is equivalent between the two dosage forms, and exposure to decitabine is bioequivalent.

- 6.23 Complete response was higher at the November 2019 data cut (21.1%) than the March 2019 data cut (9.0%). Overall response was 60.9% at the November 2019 data cut and 48.9% at the earlier March 2019 data cut. The CSR noted (p96) that the results suggest a clinical profile for decitabine+cedazuridine consistent with the established clinical profile of IV decitabine from published data. Neither median OS nor median leukaemia-free survival was reached.
- 6.24 The ASTX727-01-B trial was a similar design to ASCERTAIN, with two initial cross-over cycles, although in this trial there was a dose confirmation stage when patients were administered decitabine and cedazuridine in separate capsules, and a fixed dose combination (FDC) stage, where the two drugs were administered in a combined tablet.
- 6.25 The pharmacokinetic results from ASTX727-01-B showed equivalent bioavailability for decitabine+cedazuridine and IV decitabine in the dose confirmation and FDC stages of the trial. The difference in maximum %line-1 demethylation was small in the dose confirmation and FDC stages. The TGA Delegate's Overview (p9) noted these results indicated a similar target effect of the oral and IV products. The TGA Delegate's Overview also indicated that this trial was the same design as ASCERTAIN but had a longer duration of follow-up. Median OS was 549 days (18 months), and median time to AML or death was 364 days (12 months).

### ***Comparative harms***

- 6.26 The submission provided tabulated safety data for the occurrence of Grade 3-4 adverse events (AEs) in the four decitabine IV or azacitidine vs. BSC trials. The following table includes the most common Grade 3-4 AEs identified by the submission.

**Table 9: Summary of key adverse events in the randomised trials used in the indirect comparison of decitabine IV and azacitidine**

| AE                  | Kantarjian 2006 |                  | Lubbert 2011   |                | Total decitabine IV | Total BSC              | RR (95% CI)              | RD (95% CI)               |
|---------------------|-----------------|------------------|----------------|----------------|---------------------|------------------------|--------------------------|---------------------------|
|                     | Decitabine IV   | BSC              | Decitabine IV  | BSC            |                     |                        |                          |                           |
| Febrile neutropenia | 23%             | 4%               | NR             | NR             | 19/83 (22.9%)       | 3/81 (3.7%)            | <b>6.18 (1.90,20.09)</b> | <b>0.19 (0.09, 0.30)</b>  |
| Neutropenia         | 87%             | 50%              | 54/114 (47.4%) | 40/114 (35.1%) | 126/202 (62.4%)     | 81/195 (41.5%)         | <b>1.50 (1.23, 1.83)</b> | <b>0.21 (0.11, 0.31)</b>  |
| Thrombocytopenia    | 85%             | 43%              | NR             | NR             | 71/83 (85.5%)       | 35/81 (43.2%)          | <b>1.98 (1.52, 2.58)</b> | <b>0.42 (0.28, 0.57)</b>  |
|                     | Fenaux 2009     |                  | Silverman 2002 |                | Total azacitidine   | Total BSC <sup>a</sup> | RR (95% CI) <sup>a</sup> | RD (95% CI) <sup>a</sup>  |
|                     | Azacitidine     | BSC <sup>a</sup> | Azacitidine    | BSC            |                     |                        |                          |                           |
| Febrile neutropenia | NR              | NR               | NR             | NR             | NR                  | NR                     | NR                       | NR                        |
| Neutropenia         | 104/114 (91.2%) | 70/102 (68.6%)   | NR             | NR             | 104/114 (91.2%)     | 70/102 (68.6%)         | <b>1.33 [1.15, 1.53]</b> | <b>0.23 [0.12, 0.33]</b>  |
| Thrombocytopenia    | 93/114 (81.6%)  | 72/102 (70.6%)   | 70.0%          | NR             | 162/213 (76.1%)     | 72/102 (70.6%)         | <b>1.08 [0.93, 1.25]</b> | <b>0.05 [-0.05, 0.16]</b> |

Source: Table 2.22, p97; Table 2.23, p98 of the submission.

BSC=best supportive care; CI=confidence interval; IV=intravenous; RD=risk difference; RR=relative risk; bold=statistically significant

<sup>a</sup> Values have been corrected to account for the correct number of patients in the BSC group of 102.

- 6.27 The submission stated that the most common serious AEs caused by treatment with decitabine were thrombocytopenia, neutropenia and febrile neutropenia, and for azacitidine, thrombocytopenia and neutropenia. The significant differences in the table above indicated greater occurrence of AEs for both decitabine IV and azacitidine compared to BSC. The available retrospective reviews (Lee et al., 2013; Lee et al., 2013a) suggested that decitabine was associated with significantly more neutropenia and infectious episodes than azacitidine (see Table 5).
- 6.28 The submission claimed non-inferior safety of decitabine IV compared to azacitidine. The ESC noted it would be difficult to draw conclusions on the safety of decitabine and azacitidine from the available trial data as the rates of key adverse events in the BSC arms across the trials varied greatly.
- 6.29 The pre-PBAC Response stated that an indirect trial comparison of safety data was not originally provided in the submission in part due to some outcomes (i.e. febrile neutropenia) not being reported in the azacitidine studies. However, the pre-PBAC noted that rates of Grade 3/4 febrile neutropenia are provided in the TGA-approved PI for Vidaza. The pre-PBAC Response provided an indirect comparison based on the AEs reported in the Product Information for Vidaza (see table below). The pre-PBAC Response noted there appeared to be a discrepancy between the rates of other AEs reported in the PI and the rates reported in the publication by Fenaux (2009) from which the safety data were originally sourced.

**Table 10: Indirect trial comparison of safety data from decitabine trials (Kantarjian 2006 and Lubbert 2011) and Fenaux 2009 or Vidizia PI**

| AE                              | Azacitidine     | BSC            | RR (95% CI)<br>DEC vs BSC | RR (95% CI)<br>AZA vs BSC | RR (95% CI)<br>DEC vs AZA              |
|---------------------------------|-----------------|----------------|---------------------------|---------------------------|--|
| <b>Based on Vidizia PI</b>      |                 |                |                           |                           |  |
| Neutropenia (Grade 3/4)         | 22/175 (12.6%)  | 7/102 (6.0%)   | 1.5 (1.23, 1.83)          | 2.83 (1.92, 4.18)         | <b>0.53 (0.34, 0.82);<br/>P=0.0044</b> |
| Thrombocytopenia (Grade 3/4)    | 107/175 (61.1%) | 22/102 (21.6%) | 1.98 (1.52, 2.58)         | 2.05 (1.47, 2.86)         | 0.97 (0.63, 1.48);<br>P=0.8727         |
| Febrile neutropenia (Grade 3/4) | 102/175 (58.3%) | 29/102 (28.4%) | 6.18 (1.9, 20.09)         | 1.83 (0.81, 4.14)         | 3.38 (0.81, 14.17);<br>P=0.0962        |
| <b>Based on Fenaux (2009)</b>   |                 |                |                           |                           |  |
| Neutropenia (Grade 3/4)         | 104/114 (91.2%) | 70/102 (68.6%) | 1.5 (1.23, 1.83)          | 1.33 (1.15, 1.53)         | 1.13 (0.88, 1.44);<br>P=0.3352         |
| Thrombocytopenia (Grade 3/4)    | 93/114 (81.6%)  | 72/102 (70.6%) | 1.98 (1.52, 2.58)         | 1.08 (0.93, 1.25)         | 1.83 (1.35, 2.48);<br>P=0.0001         |
| Febrile neutropenia (Grade 3/4) | NR              | NR             | 6.18 (1.9, 20.09)         | -                         | -                                      |

Source: Table 2 of the pre-PBAC Response

BSC=best supportive care; CI=confidence interval; IV=intravenous; PI=product information; RD=risk difference; RR=relative risk; bold=statistically significant

- 6.30 The pre-PBAC Response noted that the results of show a statistically significant benefit in favour of decitabine relative to AZA in terms of neutropenia. The PBAC considered that the interpretation of these results are uncertain given the heterogeneity between trials included in the submission and the uncertain applicability of the trials to the eligible PBS population.
- 6.31 The ASCERTAIN CSR stated (p103) that the treatment-related AEs of Grade ≥3 with the highest incidence were neutropenia, thrombocytopenia, anaemia, leukopenia and febrile neutropenia. A summary of these treatment-related AEs are provided in the table below, for both ASCERTAIN and ASX727-01-B.

Table 11: Summary of key treatment-related adverse events in the decitabine+cedazuridine pharmacokinetic trials

| AE   | IV decitabine<br>cycle 1 or 2 (N=132) | Decit+ced<br>cycle 1 or 2 (N=130) | Decit+ced<br>cycle ≥3 (N=119) | Decit+ced<br>Total (N=130) |
|--|---------------------------------------|-----------------------------------|-------------------------------|----------------------------|
| <b>ASCERTAIN</b>                                       |                                       |                                   |                               |                            |
| Number with at least one treatment-related AE Grade ≥3 | 51 (38.6%)                            | 55 (42.3%)                        | 33 (27.7%)                    | 62 (47.7%)                 |
| Neutropenia  | 24 (18.2%)                            | 31 (23.8%)                        | 15 (12.6%)                    | 36 (27.7%)                 |
| Thrombocytopenia                                       | 26 (19.7%)                            | 27 (20.8%)                        | 13 (10.9%)                    | 36 (27.7%)                 |
| Anaemia  | 19 (14.4%)                            | 19 (14.6%)                        | 6 (5.0%)                      | 21 (16.2%)                 |
| Leukopenia   | 12 (9.1%)                             | 17 (13.1%)                        | 10 (8.4%)                     | 21 (16.2%)                 |
| Febrile neutropenia                                    | 3 (2.3%)                              | 8 (6.2%)                          | 3 (2.5%)                      | 10 (7.7%)                  |
| <b>ASTX727-01-B</b>                                    |                                       |                                   |                               |                            |
|  | IV decitabine<br>course 1 or 2 (N=75) | Decit+ced<br>course 1 or 2 (N=78) |                               | Decit+ced<br>Total (N=78)  |
| Number with at least one treatment-related AE Grade ≥3 | 24 (32.0%)                            | 21 (26.9%)                        |                               | 37 (47.4%)                 |
| Neutropenia  | 16 (21.3%)                            | 11 (14.1%)                        |                               | 26 (33.3%)                 |
| Thrombocytopenia                                       | 11 (14.7%)                            | 9 (11.5%)                         |                               | 19 (24.4%)                 |
| Leukopenia   | 6 (8.0%)                              | 6 (7.7%)                          |                               | 16 (20.5%)                 |
| Anaemia  | 4 (5.3%)                              | 5 (6.4%)                          |                               | 11 (14.1%)                 |
| Febrile neutropenia                                    | 4 (5.3%)                              | 3 (3.8%)                          |                               | 7 (9.0%)                   |

Source: Table 36, p104 of the ASCERTAIN CSR; Table 48, p116 of the ASTX727-01-B CSR.

Decit+ced=decitabine+cedazuridine; IV=intravenous

6.32 For the ASCERTAIN trial, the CSR noted that the incidence of Grade ≥3 AEs was generally similar or higher with decitabine+cedazuridine in the first two cycles compared to IV decitabine, but then generally similar or lower in cycle 3 and beyond. The TGA Delegate's Overview stated (p15) that the safety analysis was consistent with the known cytotoxic effects of decitabine, as well as the underlying manifestations of MDS and CMML. The Overview indicated that the safety analysis did not suggest any additional toxicities as a result of the combination of decitabine and cedazuridine, although the Delegate noted that cedazuridine is not a cytotoxic agent itself.

### **Benefits/harms**

6.33 Based on the non-inferiority results presented in the submission, and the indirect treatment comparison, no benefits and harms table has been compiled.

### **Clinical claim**

6.34 The submission described decitabine+cedazuridine as non-inferior in terms of effectiveness compared with azacitidine and non-inferior in terms of safety compared to azacitidine.

6.35 The ESC considered while the pharmacokinetic evidence has adequately demonstrated that decitabine+cedazuridine is bioequivalent to IV decitabine, the claim of non-inferiority of IV decitabine and azacitidine was not strongly supported by the evidence, for the following reasons:

- There was considerable heterogeneity between the trials included in the indirect comparison, with differences in IPSS risk category, FAB classification, disease duration and ECOG performance score. There was also variation in estimates of OS across the BSC trial arms, ranging from 8.5 months to 14 months. Further, the interpretation of the IPSS intermediate-2 and high-risk subgroup OS analysis was limited by the lack of information on patient numbers and no estimates of median survival being available.
  - The indirect comparison of survival outcomes favoured azacitidine, but for response outcomes there were no statistically significant differences between the two drugs. The PSCR noted that while there are a number of uncertainties associated with the indirect comparison of OS data, results for response-based outcomes consistently demonstrate non-inferiority between decitabine and azacitidine. The PSCR noted that the validity of response-based outcomes as surrogate outcomes for OS was recently confirmed by the MDS Clinical Research Consortium. The ESC considered that response-based outcomes were appropriate surrogate outcomes for OS only in the absence of mature OS data.
  - There was high heterogeneity across all comparisons for response-based outcomes, except for complete response. There were also wide confidence intervals across many of the comparisons which make the interpretation of these results uncertain.
- 6.36 Given the limited support for the submission's claim, and the uncertainty around the average number of cycles of decitabine+cedazuridine that would be used in clinical practice compared to azacitidine, the equi-effective doses used by the submission in its cost-minimisation analysis is highly uncertain. The pre-PBAC Response noted that the median number of treatment cycles in the ASCERTAIN trial (8 cycles) is roughly consistent with that from a 10% PBS sample where 50% of patients have discontinued therapy after 6 months and 7 scripts. The pre-PBAC Response further noted that similar results were observed in analyses of the SEER database (Zeidan, 2016), which found that 74% and 52% of patients received  $\geq 4$  and  $\geq 6$  cycles of HMAs, respectively.
- 6.37 The PBAC considered that the claim of non-inferior comparative effectiveness was uncertain given the issues raised in paragraph 6.35.
- 6.38 The PBAC considered that the claim of non-inferior comparative safety was uncertain noting it was difficult to compare adverse events between the trials due to heterogeneity.

### ***Economic analysis***

- 6.39 The submission presented a cost-minimisation analysis based on the indirect comparison versus azacitidine and the pharmacokinetic evidence comparing

decitabine+cedazuridine and IV decitabine. The ESC advised that this approach is appropriate only if non-inferior comparative effectiveness between decitabine+cedazuridine and azacitidine is accepted.

- 6.40 The submission estimated equi-effective doses based on the dosing regimen proposed for decitabine+cedazuridine and the dosing recommended for azacitidine in its PI (see Table 12).

**Table 12: Equi-effective doses**

|                      | <b>Decitabine+cedazuridine</b>  | <b>Azacitidine</b>   |
|----------------------|---|--|
| Dosing regimen       | One tablet daily on Day 1 to 5 in 28-day cycles   | IV or SC daily on Day 1 to 7 at 75mg/m <sup>2</sup> in 28-day cycles |
| Equi-effective doses | decitabine 35mg+cedazuridine 100mg tablet daily × 5 days every 28 days =<br>azacitidine 75mg/m <sup>2</sup> IV or SC daily × 7 days every 28 days |  |

Source: Table 3.7, p130; Section 3.2, p130-131 of the submission.  
IV=intravenous; SC=subcutaneous

- 6.41 The submission stated that both treatments continue until disease progression or intolerance, and the cost-minimisation assumed no difference in the number of treatment cycles between the two treatments. The cost-minimisation calculated the cost for treatment over one cycle (see Table 13 below).
- 6.42 Cost offsets were based on administration costs for azacitidine as well as anti-nausea medication (granisetron) costs. For the administration cost for azacitidine, the submission used MBS item 13915, which was an item number for intravenous administration of chemotherapy. On 1 November 2020 the structure of chemotherapeutic procedures listed on the MBS changed. Eleven administration items (MBS items 13915 to 13942 and item 13948) were replaced by a single parenteral administration item (item 13950). Thus, item 13915 used by the submission no longer exists, and has been replaced by item 13950. The fee for item 13915 was \$67.10, compared with \$111.40 for item 13950. The following table provides the cost inputs used in the submission’s cost-minimisation analysis, as well as the updated cost for the MBS administration item and updated cost for granisetron. The ESC noted that the supply chain costs (mark-ups and fees) for decitabine+cedazuridine (\$161.16 per script) are higher than for azacitidine (\$47.78 per script for S100 Highly Specialised Drugs – Private Hospital and \$0 per script for S100 Highly Specialised Drugs – Public Hospital) and as a consequence, the listing of decitabine+cedazuridine would result in additional government cost. The pre-PBAC response revised the requested price to \$ [REDACTED] (AEMP) on the basis of an analysis that included the higher cost offset with the updated MBS administration fee and also accounted for the difference in supply chain costs.

**Table 13: Cost inputs for the cost-minimisation analysis**

| Component                                   | Submission | Change and reason                               |
|---|------------|---|
| Azacidine: AEMP per vial                    | \$156.61   | -   |
| Granisetron: DPMQ per day of administration | \$10.63    | \$8.29 AEMP instead of DPMQ                     |
| MBS item for administration 13915           | \$67.10    | \$111.40 MBS item removed and replaced by 13950 |

Source: Worksheet 'Current PBS prices' of the Excel workbook 'Section 3 INQOVI November 2020 PBAC SUBMITTED'.

AEMP=approved ex-manufacturer price; DPMQ=dispensed price for maximum quantity

6.43 The results of the cost-minimisation analysis presented by the submission are provided in the table below. Also provided are results using the updated cost for the MBS item for azacidine administration, as well as use of ex-manufacturer price for granisetron instead of DPMQ. The ESC noted the clinical claim of non-inferior effectiveness is highly uncertain and considered that it may be appropriate for this uncertainty to be reflected in the price for decitabine+cedazuridine.

**Table 14: Results of the cost-minimisation analysis**

|   | Cost per day | Cost per treatment cycle |
|---|--------------|--------------------------|
| <b>Azacidine cost (7 treatment days in each cycle)</b>  |              |                          |
| Azacidine: 2 vials at \$156.61 per vial   | \$313.22     | \$2,266.95               |
| Granisetron: 1 tablet per day (DPMQ)  | \$10.63      |                          |
| Azacidine administration: MBS item 13915  | \$67.10      | \$469.70                 |
| Total cost  | \$390.95     | \$2,736.65               |
| <b>Cost-minimisation</b>  |              |                          |
| <b>Per cycle cost of decitabine+cedazuridine to match azacidine</b>                                 |              | <b>\$2,736.65</b>        |
| Administration days   | 5            |                          |
| Daily cost at cost neutrality   | \$547.33     |                          |
| <b>Alternate cost-minimisation using updated MBS cost and AEMP cost for granisetron<sup>a</sup></b> |              |                          |
| Azacidine: 2 vials at \$156.61 per vial   | \$313.22     | \$2,250.57               |
| Granisetron: 1 tablet per day (AEMP)  | \$8.29       |                          |
| Azacidine administration: MBS item 13950  | \$111.40     | \$779.80                 |
| Total cost  | \$432.91     | \$3,030.37               |
| <b>Per cycle cost of decitabine+cedazuridine to match azacidine</b>                                 |              | <b>\$3,030.37</b>        |
| Administration days   | 5            |                          |
| Daily cost at cost neutrality   | \$606.07     |                          |

Source: Table 3.9, p131 of the submission; Worksheet 'Current PBS prices' of the Excel workbook 'Section 3 INQOVI November 2020 PBAC SUBMITTED'.

AEMP=approved ex-manufacturer price; DPMQ=dispensed price maximum quantity

<sup>a</sup> Calculated during the evaluation

### **Drug cost/patient/course**

6.44 Based on the requested effective price of decitabine+cedazuridine, the drug cost per cycle of treatment would be \$ [REDACTED]. When the updated administration cost for MBS item 13950 (used as a cost offset in the cost-minimisation analysis) and the 1 January 2021 wholesale mark-up (\$54.14) is applied, the drug cost per cycle becomes \$ [REDACTED]. Based on the revised price for decitabine+cedazuridine in the pre-PBAC response the drug cost per cycle would be \$ [REDACTED].

### Estimated PBS usage & financial implications

6.45 This submission was not considered by DUSC.

6.46 The submission applied a market share approach to develop the financial estimates. A summary of the sources used and values applied is provided in Table 15.

**Table 15: Data sources and parameter values applied in the utilisation and financial estimates**

| Component                        | Data source  |               |               |               |               |               |               |
|----------------------------------|--|---------------|---------------|---------------|---------------|---------------|---------------|
| <b>Script numbers</b>            |  |               |               |               |               |               |               |
| Market growth rate               | Based on azacitidine usage over the past 5 years, with linear growth applied. The annual growth rate applied was 4.24% in Year 1, 4.07% in Year 2, 3.91% in Year 3, 3.76% in Year 4, and 3.63% in Year 5.  |               |               |               |               |               |               |
| Initial and continuation         | Based on azacitidine data, with proportion initiating and continuing in Year 1 close to equivalent, and with the initiation proportion decreasing and continuation proportion increasing.                  |               |               |               |               |               |               |
|                                  |  | <b>Year 1</b> | <b>Year 2</b> | <b>Year 3</b> | <b>Year 4</b> | <b>Year 5</b> | <b>Year 6</b> |
|                                  | Initiation   | 49%           | 33%           | 27%           | 27%           | 26%           | 26%           |
|                                  | Continuation   | 51%           | 67%           | 73%           | 73%           | 74%           | 74%           |
| <b>Utilisation</b>               |  |               |               |               |               |               |               |
| Uptake rate                      | Sponsor assumption: 30% in Year 1 with a 6% increase each year, up to 60% in Year 6.   |               |               |               |               |               |               |
|                                  |  | <b>Year 1</b> | <b>Year 2</b> | <b>Year 3</b> | <b>Year 4</b> | <b>Year 5</b> | <b>Year 6</b> |
|                                  | Uptake   | 30%           | 36%           | 42%           | 48%           | 54%           | 60%           |
| <b>Cost of medicines</b>         |  |               |               |               |               |               |               |
| Decitabine+cedazuridine          | \$ [REDACTED] (requested price)  |               |               |               |               |               |               |
| Azacitidine                      | \$2,240.32 (PBS item 6100C; PBS item 6138C); \$2,192.54 (PBS item 9597D; PBS item 9598E)   |               |               |               |               |               |               |
| Granisetron                      | \$74.41 (PBS item 8728J)   |               |               |               |               |               |               |
| Patient co-payment               | Based on current usage of azacitidine (average of \$15.69 for PBS and \$5.96 for RPBS).  |               |               |               |               |               |               |
| <b>Impact on other medicines</b> |  |               |               |               |               |               |               |
| Substitution of azacitidine      | Azacitidine is the only PBS-listed agent for treatment of MDS/CMML. Thus it was assumed decitabine+cedazuridine will substitute for azacitidine.   |               |               |               |               |               |               |
| Granisetron                      | The submission assumed that each substituted script of azacitidine would be associated with a granisetron script (for nausea and vomiting).  |               |               |               |               |               |               |
| <b>MBS usage and costs</b>       |  |               |               |               |               |               |               |
| MBS items                        | \$67.10 for MBS item 13915 (80%) for administration. On 1 November 2020 eleven MBS administration items, including item 13915, were replaced by a single parenteral administration item (13950; \$111.40). |               |               |               |               |               |               |

Source: Section 4.1 to Section 4.5, p136-144 of the submission.

MDS=myelodysplastic syndrome; CMML=chronic myelomonocytic leukaemia.

6.47 The estimated script numbers and costs for the PBS listing of decitabine+cedazuridine are provided in Table 16.

Table 16: Estimated use and financial implications

|   | Year 1                 | Year 2                 | Year 3                 | Year 4                 | Year 5                 | Year 6                 |
|---|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| <b>Estimated extent of use</b>  |                        |                        |                        |                        |                        |                        |
| Number of scripts dispensed   | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>2</sup>         | █ <sup>2</sup>         |
| Initiation scripts  | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         |
| Continuation scripts  | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         | █ <sup>1</sup>         |
| <b>Estimated financial implications of decitabine+cedazuridine</b>    |                        |                        |                        |                        |                        |                        |
| Cost to PBS/RPBS less copayments                                      | \$█ <sup>3</sup>       | \$█ <sup>3</sup>       | \$█ <sup>4</sup>       | \$█ <sup>4</sup>       | \$█ <sup>4</sup>       | \$█ <sup>4</sup>       |
| Cost offsets for substituted azacitidine and granisetron <sup>a</sup> | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      | -\$█ <sup>4</sup>      | -\$█ <sup>4</sup>      |
| <b>Net financial implications</b>                                     |                        |                        |                        |                        |                        |                        |
| Net cost to PBS/RPBS  | \$█ <sup>3</sup>       | \$█ <sup>3</sup>       | \$█ <sup>3</sup>       | \$█ <sup>3</sup>       | \$█ <sup>3</sup>       | \$█ <sup>3</sup>       |
| Net cost to MBS <sup>b</sup>  | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      | -\$█ <sup>3</sup>      |
| <b>Net cost to PBS/RPBS/MBS<sup>c</sup></b>                           | <b>\$█<sup>3</sup></b> | <b>\$█<sup>3</sup></b> | <b>\$█<sup>3</sup></b> | <b>\$█<sup>3</sup></b> | <b>\$█<sup>3</sup></b> | <b>\$█<sup>3</sup></b> |

Source: Table 4.5, p140; Table 4.6, p141; Table 4.10, p143; Table 4.11, p144 of the submission; worksheet '3c. Impact – proposed (eff)'; worksheet '4c. Impact – affected (eff)'; worksheet '5. Impact – net' of the Excel workbook 'Section 4 INQOVI November 2020 PBAC Submitted'.

<sup>a</sup> The submission assumed that one script of granisetron (to manage nausea and vomiting) will accompany each script of azacitidine.

<sup>b</sup> Based on MBS item 13915 (\$67.10)

<sup>c</sup> The estimated financial implications are based on mark-ups as of 1 December 2020.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> \$0 to < \$10 million

<sup>4</sup> \$10 million to < \$20 million

- 6.48 The estimated net cost to Government is \$0 to < \$10M in Year 1, increasing to \$0 to < \$10M in Year 6, for a total of \$0 to < \$10M over the first 6 years of listing. The submission acknowledged that due to patient contribution to MBS costs and mark-ups for the decitabine+cedazuridine dispensed price, there was a net cost to Government. The PSCR stated that had other possible but very likely savings in terms of travel / accommodation costs and lost incomes associated with azacitidine been included, decitabine+cedazuridine would most likely provide overall cost savings to the Australian society as a whole.
- 6.49 The ESC noted that the additional cost to Government is due to the higher mark-ups for decitabine+cedazuridine (requested listing in the General Schedule) versus azacitidine (listed under the Section 100 (Highly Specialised Drugs) program) (approximately 43% of the total costs), and the lower cost offsets for azacitidine associated with the patient copayment for the administration MBS item (approximately 52% of the total cost) and the patient co-payment for granisetron (approximately 5%) being included in the cost-minimisation analysis but not the financial estimates.
- 6.50 The PBAC has previously advised that, where a recommendation is made to move a drug from Section 100 to General Schedule, the cost of the increased pharmacy remuneration should be borne by the manufacturer (paragraph 5.6, apomorphine

Public Summary Document (PSD), March 2020). The request in this instance is for the listing of a new drug.

- 6.51 The estimates rely on assumed uptake of 30% in Year 1 increasing to 60% in Year 6. The uptake of decitabine+cedazuridine could be greater, on the basis that it is a tablet administered orally as opposed to the IV or subcutaneous administration of azacitidine. In addition, the azacitidine market is uncertain given that the submission applied linear growth to historical azacitidine usage estimates, but the market growth was variable, in particular there was a decline in market growth over the last 3 years. The ESC considered that the assumed uptake rate was likely a substantial underestimate. The ESC noted that patients on azacitidine treatment currently require significant resources from oncology day centres given the 7 day dosing regimen. The ESC also acknowledged that azacitidine treatment is associated with access issues for rural and remote patients. Based on these factors, the ESC considered that patients would likely be transitioned to decitabine+cedazuridine rapidly if it were PBS-listed. The pre-PBAC Response considered that switching from azacitidine to decitabine+cedazuridine would be slow and gradual as azacitidine has been the only treatment option for some time. The pre-PBAC Response indicated that patients who are responding to treatment with azacitidine may not readily switch to a new treatment.
- 6.52 The ESC considered there may also be an increase in patient numbers if decitabine+cedazuridine were listed as there would likely be patients who are currently not on therapy due to the administration requirements for azacitidine.
- 6.53 The submission requested that the PBAC consider an expanded listing which includes intermediate-1 or lower risk patients, using the revised IPSS to stratify patients. The submission provided an estimate of script numbers, assuming 100% substitution from azacitidine and generated estimated costs from \$0 to < \$10M to \$40M to < \$50M over the first 6 years of listing. The submission noted that the sponsor was willing to implement a risk-sharing arrangement to manage financial uncertainties. The submission also emphasised that the sponsor did not wish these estimates to negatively affect consideration of the requested listing, but the sponsor is open to further discussion with the PBAC to achieve wider eligibility for decitabine+cedazuridine.

### **Financial Management – Risk Sharing Arrangements**

- 6.54 The pre-PBAC Response indicated the sponsor was willing to discuss a possible risk sharing arrangement if required.

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

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of decitabine+cedazuridine for the treatment of patients with myelodysplastic syndrome (MDS) classified as intermediate-2 or high-risk according to the International Prognostic Scoring System (IPSS) and patients with chronic myelomonocytic leukaemia (CMML) due to the claims of non-inferior effectiveness and safety compared with azacitidine being uncertain. The PBAC considered that this uncertainty also impacted on the reliability of the cost minimisation analysis presented in the submission.
- 7.2 The PBAC noted the comments received from consumers and organisations, and the sponsor's hearing, which highlighted the advantages, in particular for patients living in rural and remote areas, of an oral treatment over the current standard of care, azacitidine, which is administered subcutaneously or intravenously and requires attendance at an outpatient clinic for seven days each month. The PBAC noted that some clinics offer home chemotherapy, however acknowledged the substantially reduced treatment burden with the oral therapy and that this may also make treatment available to more patients.
- 7.3 The PBAC considered that the nominated comparator, azacitidine, was appropriate given it is the only hypomethylating agent currently PBS-listed for MDS and CMML.
- 7.4 The PBAC noted the submission presented a two-step comparison in which (i) decitabine+cedazuridine was compared with IV decitabine on the basis of pharmacokinetic/pharmacodynamic studies, and (ii) IV decitabine was compared with azacitidine on the basis of an indirect comparison using best supportive care (BSC) as the common reference.
- 7.5 The PBAC noted that the TGA Delegate concluded that the pharmacodynamic data suggested that the demethylation effect is equivalent between decitabine+cedazuridine and IV decitabine, and the exposure to decitabine is bioequivalent.
- 7.6 The PBAC noted the four trials included in the indirect comparison (Kantarjian 2006 and Lubbert 2011 comparing IV decitabine and BSC; Fenaux 2009 and Silverman 2002 comparing azacitidine and BSC) had a high risk of bias. The PBAC further noted there were substantial applicability and transitivity issues relating to the trial eligibility criteria, patient populations enrolled and the treatment regimens administered. The IV decitabine studies used a 3-day dosing regimen whereas in the pharmacokinetic studies used a 5-day dosing regimen (both with a 42 day treatment cycle). Although the study by Wu et al., 2015 found no statistically significant differences in outcomes for the 3-day and 5-day regimens, the PBAC noted the results across the 5 studies included in the naïve comparison presented in the submission were heterogeneous making any claim based on these data uncertain. Overall, the PBAC agreed with ESC that the results of the indirect comparison of IV decitabine and azacitidine should be

interpreted with caution. In this context the PBAC considered the results from the Lee et al., 2013 and Lee et al., 2013a retrospective reviews informative.

- 7.7 The PBAC noted the indirect comparisons suggested reduced overall survival and time to AML with IV decitabine compared with azacitidine, and that the differences were statistically significant. The PBAC noted the arguments in the submission and pre-PBAC response that the comparisons may have been influenced by the results of Fenaux 2009 in which the survival with azacitidine was longer than reported in observational studies. The PBAC considered the difference in survival may reflect reduced treatment adherence in clinical practice and that this had implications for the applicability of the trial results to the PBS population. Lee et al., 2013 also suggested reduced survival with IV decitabine, in particular in patients with a MDS duration of less than 1 year or an ECOG score of 2 or 3, whereas a difference in survival was not observed in Lee et al., 2013a in the overall cohort or the propensity matched cohort.
- 7.8 In contrast to the overall survival results, the indirect comparisons suggested no statistically significant differences in response based outcomes. The PBAC noted the arguments in the PSCR and sponsor hearing that response can be used as a surrogate for overall survival in higher-risk MDS patients, however considered the interpretation of the response data was hindered by the heterogeneous results across the trials and the wide confidence intervals for the indirect estimates.
- 7.9 The PBAC noted the TGA Delegate considered that the adverse events reported for decitabine+cedazuridine were consistent with the known cytotoxic effects of decitabine, as well as the underlying manifestations of MDS and CMML, and there were no additional toxicities as a result of the combination of decitabine and cedazuridine. The PBAC noted in the trials included in the indirect comparison, the most common serious adverse events reported for IV decitabine were thrombocytopenia, neutropenia and febrile neutropenia and for azacitidine were thrombocytopenia and neutropenia. The PBAC noted in Lee et al., 2013 decitabine was associated with more frequent Grade  $\geq 3$  neutropenia than azacitidine ( $p=0.040$ ), and in Lee et al., 2013a the number of infectious episodes treated with antimicrobials was significantly lower for patients treated with azacitidine (RR=0.75; 95% CI: 0.58, 0.96). The PBAC noted the sponsor hearing and pre-PBAC response cited a meta-analysis of trials (Xie, 2015) that reported no statistically significant differences between IV decitabine and azacitidine in terms of safety, including no differences in the rates of febrile neutropenia.
- 7.10 Overall the PBAC considered the claim of non-inferior effectiveness and safety for decitabine+cedazuridine and azacitidine to be uncertain as it relied on the acceptance of non-inferior effectiveness and safety for IV decitabine and azacitidine. The PBAC acknowledged the substantially reduced treatment burden with decitabine+cedazuridine, and that further data may not be available to increase the certainty for the non-inferiority claim. In this context, the PBAC considered any

economic evaluation versus azacitidine would need to be informed by conservative assumptions.

- 7.11 The PBAC noted the cost minimisation analysis presented in the submission was over one treatment cycle, based on the recommended dosage regimens in the product information documents for decitabine+cedazuridine and azacitidine, and included cost-offsets for granisetron and the administration of azacitidine. The PBAC noted the analysis assumed all patients receive 2 vials of azacitidine, and did not consider dose reductions, which may be substantial given the average age of the patient population. Overall, the PBAC considered that the assumptions used to inform the cost-minimisation analysis were not appropriately conservative in the context of the limited clinical data. The PBAC further noted the listing of decitabine+cedazuridine resulted in additional cost to the Government due to (i) the additional supply chain costs for decitabine+cedazuridine, (ii) the patient copayments for the administration of azacitidine and (iii) the patient co-payments for granisetron being incorporated into the price of decitabine+cedazuridine. The PBAC noted the cost minimisation analysis presented in the pre-PBAC response accounted for the difference in supply chain costs.
- 7.12 The PBAC noted a market share approach was used to estimate the financial impact of listing decitabine+cedazuridine. The PBAC considered the assumed market growth (4.24% declining to 3.63% over 5 years) to be overestimated given lower growth rates in 2019 (2%) and 2020 (-2%). The PBAC noted that ESC considered that the assumed uptake rates (30% in Year 1 increasing to 60% in Year 6) were likely a substantial underestimate whereas the pre-PBAC Response considered that switching from azacitidine to decitabine+cedazuridine would be slow and gradual as azacitidine has been the only treatment option for some time, and that patients who are responding to treatment with azacitidine may not readily switch to a new treatment. The PBAC considered the uptake rates assumed in the submission were unlikely to be exceeded noting the uncertainty regarding if decitabine+cedazuridine is non-inferior to azacitidine in terms of effectiveness and the potential for increased adverse effects.
- 7.13 The PBAC agreed with ESC that there may be an increase in the number of patients treated if decitabine+cedazuridine was listed due to the treatment of patients who are currently not on therapy because of the administration requirements for azacitidine. The PBAC noted that the sponsor was willing to consider a Risk Sharing Arrangement (RSA), and considered that such an agreement could address the risk of use in a broader patient population compared with azacitidine.
- 7.14 The PBAC advised that the restrictions for decitabine+cedazuridine should align with the existing azacitidine restrictions (i.e. restrictions for MDS, AML and CMML) and that the restriction for MDS should specify an upper threshold of 20% for bone marrow blasts consistent with the WHO classification system.

- 7.15 The PBAC noted the sponsor's request for an expanded listing for decitabine+cedazuridine which includes intermediate-1 or lower risk patients, using the revised IPSS to stratify patients. The PBAC did not consider this to be appropriate noting the available data to support this request was very limited.
- 7.16 The PBAC considered the outstanding issues may be addressed in a simple resubmission for decitabine+cedazuridine if the following changes were made, without any additional amendments to the economic evaluation or financial implications:
- A revised cost-minimisation analysis informed by conservative assumptions.
  - Revised financial estimates which account for the revised lower cost-minimised price and reduced growth rates.
  - A proposed RSA which include expenditure caps and rebate for use in excess of these caps.
- 7.17 The PBAC considered an early re-entry pathway would be acceptable if the resubmission addressed each of the points in the above paragraph with no further adjustment. The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If any of these terms are not acceptable to the sponsor, a standard re-entry pathway is available.
- 7.18 The PBAC noted that this submission is eligible for an independent review.

**Outcome:**

Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised 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.

## **9 Sponsor's Comment**

Otsuka Australia Pharmaceutical is disappointed that decitabine+cedazuridine has not received a positive recommendation and is committed to working with the PBAC

and the Department of Health to find a way to make this important treatment accessible to patients in Australia