## A.3 AZACITIDINE – Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Does the application adequately address the issue of the public health need for the medicine?</strong></td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td>The application does summarize the core issue - Whether use of azacitidine during initial treatment (induction and/or consolidation) improves overall survival when compared to alternatives including supportive care, low intensity chemotherapy and higher intensity chemotherapy. The setting most applicable for the EML relates to patients who are unfit or unsuitable for the standard induction/consolidation therapy with intensive chemotherapy as used in fit younger patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.</strong></td>
<td>Only the current standard chemotherapy drugs (cytosine arabinoside and daunorubicin) are included in the EML for Acute Myeloid Leukemia (excluding acute promyelocytic leukemia). Azacitidine is an alternative treatment to either supportive care alone or low dose cytosine arabinoside for patients unsuitable for standard induction therapy. This specific group of patients is substantial in number and represents a demographic with high unmet need. Azacitidine is proposed to improve survival and quality of life through induction of remissions in a minority of patients and through improvement in blood counts and reductions in transfusion requirements in a proportion of patients. Azacitidine use requires a major commitment to supportive care with blood products (red cell and platelet transfusions, antibiotic treatments) and is non-curative.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Have all important studies and all relevant evidence been included in the application?</strong></td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If no, please provide brief comments on any relevant studies or evidence that have not been included:</td>
<td>It is possible that the approach taken to analyses of the data precludes identification of indications for injectable azacitidine in subpopulations of AML where substantial benefit can be observed. The application takes a holistic approach and includes data from trials with quite disparate designs, disparate comparators, and heterogeneous populations. It identifies one randomized trial where heterogeneity in outcome was apparent, but states that the cause of this heterogeneity was not apparent after considering several plausible possibilities. However, those data are not shown separately. The stand out results come from Fenaux et al JCO 2010, and in fact are a secondary analysis of a subgroup of patients (AML with 20-30% blast count) entered into the pivotal trial. These data do indicate a significantly improved survival with azacitidine (HR 0.47; 95% CI, 0.28 to 0.79; P = .005 and 2-year overall survival rates of 50% compared with 16% for standard care; P = .001). These particular data have led to the widespread use of azacitidine for such patients in many high resource countries.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Application review

#### Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?

- ☐ Yes
- ☒ No
- ☐ Not applicable

Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).

The meta-analysis suggests that there is minimal advantage in survival when injectable azacitidine is compared variously to supportive care alone, low dose chemotherapy and more intense chemotherapy in first-line treatment of AML - 0.2 months (HR 0.96, 95% CI 0.69-1.35).

Across all first-line use in AML studied, the totality of the evidence does not indicate a major advantage for patients with AML over standard alternative treatments, including those listed on the EML already. As indicated above, there may be specific subgroups of AML where patients may receive clinically important benefits, but this represents a minority of patients with AML and is dependent on ongoing active supportive care.

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

There is minimal evidence of use in low-resource settings. As azacitidine use may exacerbate symptomatic cytopenias in early cycles, its use requires availability and commitment to substantial supportive care which may exceed routine availability in low-resource settings. Even in the single setting where superiority over conventional treatment is evident (Fenaux et al), early mortality was increased in the azacitidine arm, and benefits were manifest predominantly in the minority of survivors beyond the second year.

#### Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?

- ☐ Yes
- ☒ No
- ☐ Not applicable

Comments: There is an adequate overall summary that toxicity is similar to comparators, but no granular detail is provided. This is reasonable in the circumstances. AML is a highly morbid condition that destroys quality of life and requires quite intensive supportive care (both ambulatory and within hospitals). As with other treatments for AML, quality of life can be improved in the small minority of patients who achieve complete remissions with azacitidine.

#### Are there any adverse effects of concern, or that may require special monitoring?

- ☐ Yes
- ☒ No
- ☐ Not applicable

Comments:

As with other active therapies (ie low dose chemotherapy and especially high dose chemotherapy), azacitidine increases infections and transfusion requirements in the early phases of treatment when compared with supportive care alone. Azacitidine treatment requires the availability of similar levels of supportive care as needed for patients receiving intensive induction therapy, and this is an important consideration in low-resource countries.
| **2021 Expert Committee on Selection and Use of Essential Medicines**  
**Application review** | **There is considerable uncertainty from the data as to which patients with AML achieve a major benefit from azacitidine over what could be achieved with existing EML-recommended medications. Overall, azacitidine is considered to have a favourable benefit to risk ratio by registering authorities in highly resourced countries.** |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</strong></td>
<td><strong>While the evidence for clinical efficacy and safety come from randomised trials, the use of a basket of comparators in the pivotal trials reduces the strength of the evidence. The meta-analysis of data does not improve the strength of the evidence, in part because of some heterogeneity in outcomes and most likely because of significant design differences in the included trials.</strong></td>
</tr>
</tbody>
</table>
| **Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)** | ☒ Yes  
☐ No  
☐ Not applicable  
Comments: The use of azacitidine as treatment for patients with AML requires access to high level supportive care, including red cell and platelet transfusion availability. |
| **Are there any special requirements for the safe, effective and appropriate use of the medicine(s)? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)** | ☐ Yes  
☒ No  
☐ Not applicable  
Comments: Azacitidine has regulatory approval for AML in both the USA and in Europe, but not in all high resource countries. In some, registration and/or public subsidy is restricted to AML with blast counts of 30% or less where the randomised trial data demonstrated a survival benefit. |
| **Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)** | ☐ Yes  
☒ No  
☐ Not applicable  
Comments: Azacitidine by injection is recommended in multiple guidelines for treatment of AML in high resource countries. |
| **Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to:**  
[https://www.who.int/publications/who-guidelines](https://www.who.int/publications/who-guidelines)**)** | ☐ Yes  
☒ No  
☐ Not applicable  
Comments: Azacitidine by injection is recommended in multiple guidelines for treatment of AML in high resource countries. |
| **Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.** | Injectable azacitidine is off patent, and drug pricing is not as important a barrier to uptake as it would have been when on patent. Nevertheless, this injectable remains an expensive treatment, as costs are also incurred through pharmacy and supportive care expenses. |
Any additional comments

An oral formulation of azacitidine (CC-486), with different pharmacokinetic and pharmacodynamic properties to injectable azacitidine, is now approved and marketed in the USA as maintenance therapy for patients with AML achieving a complete remission after standard induction chemotherapy. This approval was based on the results of a single high quality randomized trial (Wei et al, N Engl J Med 2020; 383:2526-2537 DOI: 10.1056/NEJMoa2004444) which demonstrated a clinically and statistically significant difference to placebo in overall survival (difference in median 9.9 months) and relapse-free survival (difference in median 5.4 months), at the cost of increased gastro-intestinal and hematological toxicity. As a patented cancer medicine, the price of CC-486 is extremely high (approximately US$20,000 per cycle, median number of cycles = 12 in the pivotal trial).

However, injectable azacitidine has not been demonstrated to improve overall survival after induction therapy, but does improve relapse-free survival (Blood 2019; 133(13):1457-1464. doi: 10.1182/blood-2018-10-879866). As injectable and oral azacitidine are not interchangeable, the data for CC-486 do not materially change the assessment of injectable azacitidine considered for inclusion on the EML.

Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.

Despite the major unmet need for effective therapy for AML in patients unsuitable for intensive induction therapy, the recommendation is against the inclusion of injectable azacitidine on the EML. The meta-analysis indicates that the impact of injectable azacitidine on the survival of populations of patients with AML is small. Treatment with azacitidine generates toxicities and in the short term increases the need for intensive supportive care. Clearer definition of subgroups of patients who experience major improvement in survival and/or more compelling evidence of efficacy in the maintenance setting are required before injectable azacitidine could warrant reconsideration.

References (if required)