PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR AZACITIDINE

This is a summary of the Risk Management Plan (RMP) for azacitidine (Azacitidine Celgene; Vidaza). The RMP details important risks of azacitidine, how these risks can be minimised, and how more information will be obtained about azacitidine's risks and uncertainties (missing information).

Azacitidine's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how azacitidine should be used.

This summary of the RMP for azacitidine should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of azacitidine's RMP.

1.1. The Medicine and what it is Used for

Azacitidine (Azacitidine Celgene; Vidaza) is authorised for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System,
- chronic myelomonocytic leukaemia (CMML) with 10% to 29% marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20% to 30% blasts and multi-lineage dysplasia according to the World Health Organisation (WHO) classification.
- AML with > 30% marrow blasts according to the WHO classification.

See SmPC for the full indication. It contains azacitidine as the active substance and it is given by subcutaneous route of administration.

Further information about the evaluation of azacitidine's benefits can be found in azacitidine's EPAR for Azacitidine Celgene and Vidaza, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/azacitidine-celgene (Azacitidine Celgene); https://www.ema.europa.eu/en/medicines/human/EPAR/vidaza (Vidaza).

1.2. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of azacitidine (Azacitidine Celgene; Vidaza), together with measures to minimise such risks and the proposed studies for learning more about azacitidine's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of azacitidine is not yet available, it is listed under 'missing information' below.

1.3. List of Important Risks and Missing Information

Important risks of azacitidine (Azacitidine Celgene; Vidaza) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of azacitidine. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Important identified and potential risks, together with missing information, are summarised in Table 1.

Table 1: List of Important Risks and Missing Information

Important Identified Risks:	• Haemorrhagic events • Infections
Important Potential Risks:	• None
Missing Information:	• None

1.4. Summary of Important Risks

Table 2: Haemorrhagic Events

Important Identified Risk	
Evidence for linking the risk to the medicine	Bleeding events have been reported in patients receiving azacitidine. In the clinical studies in MDS (AZA PH GL 2003 CL 001, CALGB 9221, CALGB 8921 and CALGB 8421) and in AML (AZA-AML-001), serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage have been reported in patients receiving azacitidine.

Table 2: Haemorrhagic Events (Continued)

Important Identified Risk	
Risk factors and risk groups	In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to haemorrhage (Fukumoto, 2005). In one study in which 58% of newly diagnosed AML patients experienced bleeding during induction chemotherapy, risk factors for mild (WHO Grades 1 and 2) bleeding events included elevated body temperature and decreased platelet count. Risk factors for severe (WHO Grades 3 and 4) bleeding events included mild bleeding (Grade 1) on the previous day and decreased platelet count (Webert, 2006).
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose recommendations are provided. Section 4.4 of the SmPC — Warnings regarding thrombocytopenia and how to monitor this risk. Section 4.8 of the SmPC — Details on haemorrhagic ADRs and advice regarding monitoring. **Additional risk minimisation measures:** None.

Table 3: Infections

Important Identified Risk	
Evidence for linking the risk to the medicine	In the clinical studies in MDS (AZA PH GL 2003 CL 001, CALGB 9221, CALGB 8921 and CALGB 8421) and in AML (AZA-AML-001), serious adverse reactions such as sepsis (including neutropenic sepsis) and pneumonia have been reported in patients receiving azacitidine.
Risk factors and risk groups	Risk factors include chemotherapy-induced immunosuppression, myelosuppression, stem cell transplant, and graft-versus-host disease. There is the potential risk of re-activation of latent viruses, including the Epstein-Barr virus (EBV), in patients who become immunocompromised secondary to disease or treatment with anticancer agents that can affect the host immune system. A study by Chan and colleagues found that expression of previously silent viral antigens observed in one viral antigen (Zta) was detected in only one of the study's 10 patients, and this re-expression did not result in clinical infection or the development of secondary EBV malignancy (Chan, 2004). In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to infection (Fukumoto, 2005). However, in an international, multicentre, controlled, open-label, parallel-group, Phase 3 comparative study, azacitidine treatment was associated with a reduction in cytopenias, and their related symptoms (SmPC, Section 5.1). An examination of the azacitidine safety database did not reveal any case reports linking treatment, reactivation and clinical disease, including the development of non-Hodgkin's lymphoma.
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose recommendations are provided. Section 4.4 of the SmPC — Warnings regarding neutropenia and how to monitor this risk. Warnings regarding necrotising fasciitis. Section 4.8 of the SmPC — ADRs of infections, including necrotising fasciitis, are listed, and advice regarding management. **Additional risk minimisation measures:** None.

1.5. Postauthorisation Development Plan

1.5.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of azacitidine.

1.5.2. Other Studies in Postauthorisation Development Plan

There are no studies required for azacitidine.