PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR ONUREG (ORAL AZACITIDINE)

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

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

This summary of the RMP for Onureg 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 Onureg's RMP.

1.1. The Medicine and What it is Used for

Onureg is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT).

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

Further information about the evaluation of Onureg's benefits can be found in the EPAR for Onureg, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

[link to EPAR to be added once available].

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

Important risks of Onureg, together with measures to minimise such risks and the proposed studies for learning more about Onureg'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 (eg, 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 Onureg is not yet available, it is listed under 'missing information' below.

1.3. List of Important Risks and Missing Information

Important risks of Onureg 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 Onureg. 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 (eg, 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:	• Infections
Important Potential Risks:	• None
Missing Information:	• None

1.4. Summary of Important Risks

Table 2: Infections

Important Identified Risk	
Evidence for linking the risk to the medicine	In the clinical study in AML maintenance (CC-486-AML-001), serious adverse reactions were reported in patients receiving oral 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 Epstein-Barr virus, 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 1viral antigen (Zta) was detected in only 1 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, randomised, parallel-group, Phase 3 comparative study, azacitidine treatment was associated with a reduction in cytopenias, and their related symptoms (Section 5.1 of the SmPC for azacitidine for injection). An examination of the

Table 2: Infections (Continued)

Important Identified Risk	
	azacitidine safety database did not reveal any case reports linking treatment, viral reactivation (for example EBV) and the development of clinical disease, including 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 — Advice regarding management of infections is provided. Section 4.8 of the SmPC — Adverse drug reactions (ADRs) of infections are listed. **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 a specific obligation of Onureg.

1.5.2. Other Studies in Postauthorisation Development Plan

There are no required additional pharmacovigilance activities for Onureg.