EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Azacitidine Kabi 25 mg/mL powder for suspension for injection

RMP version to be assessed as part of this application:

RMP Version number	0.2
Data lock point for this RMP	01-May-2023
Date of final sign off	22-Jun-2023
Rationale for submitting an updated RMP	Not applicable (Initial RMP submission)
Summary of significant changes in this RMP	Not applicable (Initial RMP submission)
Other RMP versions under evaluation	RMP Version number: Not applicable
	Submitted on: Not applicable
	Procedure number: Not applicable
Details of the currently approved RMP	Version number: Not applicable
	Approved with procedure: Not applicable
	Date of approval (opinion date): Not applicable
QPPV name	Marcus Metternich
QPPV signature	[redacted]

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Table of content

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Azacitidine
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, pyrimidine analogues ATC code: L01BC07
Marketing Authorisation Holder or Applicant	Fresenius Kabi Deutschland GmbH, Else-Kroener-Strasse 1, 61352 Bad Homburg v.d.H., Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Azacitidine Kabi 25 mg/mL powder for suspension for injection
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Pyrimidine analogues
	Summary of mode of action: Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer suppressing functions to cancer cells.
	Important information about its composition: Each vial contains 100 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine.

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Hyperlink to the Product Information	For latest summary of product characteristics (SmPC) and package leaflet (PL) of Azacitidine Kabi 25 mg/mL powder for suspension for injection, please refer section 1.3.1 of eCTD.
Indication(s) in the EEA	Current: Azacitidine Kabi 25 mg/mL powder for suspension for injection is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with: • Intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS), • Chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder, • Acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification, • AML with > 30% marrow blasts according to the WHO classification. Proposed (if applicable): Not applicable
Dosage in the EEA	Current: Azacitidine Kabi treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting. <u>Posology</u> The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 of body surface area, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle). It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued for as long as the patient continues to benefit or until disease progression. Patients should be monitored for haematologic response/toxicity and renal toxicities; a delay in starting the next cycle or a dose reduction may be necessary. Azacitidine Kabi should not be used interchangeably with oral azacitidine. Due to differences in the exposure, the dose and schedule recommendations for oral azacitidine are different from those for injectable azacitidine. *Dose adjustment due to haematological toxicity* *Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) ≥ 3.0 x 10^9/l and ANC ≥ 1.5 x 10^9/l, and platelets ≥ 75.0 x 10^9/l) prior to the first treatment* If haematological toxicity is observed following Azacitidine Kabi treatment, the next cycle of the therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

<table>
<tr><td></td><td>
<table>
<tr><th colspan="2">Cycle Nadir count</th><th rowspan="2">Dose in the next cycle, if recovery* is not achieved within 14 days (%)</th></tr>
<tr><th>ANC (x 10^9/L)</th><th>Platelets (x 10^9/L)</th></tr>
<tr><td>≤ 1.0</td><td>≤ 50.0</td><td>50%</td></tr>
<tr><td>> 1.0</td><td>> 50.0</td><td>100%</td></tr>
</table>
*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/L or ANC < 1.5 x 10^9/L or platelets < 75.0 x 10^9/L) prior to the first treatment
Following Azacitidine Kabi treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is ≤ 50%, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC or ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of Azacitidine Kabi therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to the following table:

<table>
<tr><td>Bone marrow cellularity</td><td colspan="2">Dose in the next cycle if recovery is not achieved within 14 days (%)</td></tr>
<tr><td></td><td>Recovery* ≤ 21 days</td><td>Recovery* > 21 days</td></tr>
<tr><td>15-50%</td><td>100%</td><td>50%</td></tr>
<tr><td>< 15%</td><td>100%</td><td>33%</td></tr>
</table>
*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Following dose modifications, the next cycle duration should return to 28 days.

<u>Method of administration</u>
Reconstituted Azacitidine Kabi should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.
After reconstitution, the suspension should not be filtered.
</td></tr>
<tr><td></td><td>Proposed (if applicable): Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current:
– Powder for suspension for injection (strength: 25 mg/ml)</td></tr>
<tr><td></td><td>Proposed (if applicable): Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part II: Safety specification

Part II: Module SI – Epidemiology of the indication(s) and target populations

Not applicable

Part II: Module SII – Non-clinical part of the safety specification

Not applicable

Part II: Module SIII – Clinical trial exposure

Not applicable

Part II: Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part II: Module SVII - Identified and potential risks

Not applicable

Part II: Module SVIII - Summary of the safety concerns

The safety concerns for Azacitidine Kabi 25 mg/mL powder for suspension for injection are in line with those defined in the risk management plan for the reference product Vidaza (Celgene Europe B.V.).

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Haemorrhagic events • Infections
Important potential risks	None
Missing information	None

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Fresenius Kabi has established an effective pharmacovigilance system to collect, collate and evaluate individual case safety reports obtained through spontaneous reporting systems, identified from the worldwide scientific literature or received from competent authorities. Individual case safety reports are followed up to ensure that all relevant information is captured. Cumulative safety information is regularly reviewed during signal detection processes.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Specific adverse drug reaction follow-up forms (Targeted follow-up questionnaires) are proposed for:

- Haemorrhagic events
- Infections

For more information, please refer to Annex 4.

Other forms of routine pharmacovigilance activities:

Not applicable.

III.2 Additional pharmacovigilance activities

There are no planned, ongoing or completed additional pharmacovigilance activities.

III.3 Summary Table of additional Pharmacovigilance activities

There are no ongoing or planned safety studies.

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part IV: Plans for post-authorisation efficacy studies

There are no ongoing or proposed post-authorisation efficacy studies.

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the product information is aligned to the reference medicinal product Vidaza (Celgene Europe B.V.).

V.1. Routine Risk Minimisation Measures

Not Applicable

V.2. Additional Risk Minimisation Measures

Not Applicable

V.3. Summary of risk minimisation measures

Not Applicable

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part VI: Summary of the risk management plan

Summary of risk management plan for Azacitidine Kabi 25 mg/mL powder for suspension for injection (Azacitidine)

This is a summary of the risk management plan (RMP) for Azacitidine Kabi 25 mg/mL powder for suspension for injection. The RMP details important risks of Azacitidine Kabi 25 mg/mL powder for suspension for injection, how these risks can be minimised, and how more information will be obtained about Azacitidine Kabi 25 mg/mL powder for suspension for injection's risks and uncertainties (missing information).

Azacitidine Kabi 25 mg/mL powder for suspension for injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Azacitidine Kabi 25 mg/mL powder for suspension for injection should be used.

Important new concerns or changes to the current ones will be included in updates of Azacitidine Kabi 25 mg/mL powder for suspension for injection's RMP.

I. The medicine and what it is used for

Azacitidine Kabi 25 mg/mL powder for suspension for injection is authorised for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with:

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

It contains azacitidine as active substance and is injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Azacitidine Kabi 25 mg/mL powder for suspension for injection, together with measures to minimise such risks and the proposed studies for learning more Azacitidine Kabi 25 mg/mL powder for suspension for injection'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.
- Specific adverse drug reaction follow-up forms (Targeted follow-up questionnaires)

Together, these measures constitute *routine risk minimisation* measures.

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

II.A List of important risks and missing information

Important risks of Azacitidine Kabi 25 mg/mL powder for suspension for injection 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 Kabi 25 mg/mL powder for suspension for injection. 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).

List of important risks and missing information	
Important identified risks	• Haemorrhagic events • Infections
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.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 Kabi 25 mg/mL powder for suspension for injection.

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Azacitidine Kabi 25 mg/mL powder for suspension for injection.

EU Risk Management Plan for "Azacitidine Kabi 25 mg/mL powder for suspension for injection"

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 – Specific adverse drug reaction follow-up forms

For proposed specific adverse drug reaction follow-up forms, see attachment.

Annex 5 – Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 – Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.1	Approval date: Procedure number: EMEA/H/C/006154	Not applicable (First version of the RMP)

Annex 4 - Specific adverse drug reaction follow-up forms

[Targeted follow-up questionnaires are proposed as part of routine pharmacovigilance for Haemorrhagic events (thrombocytopenia/bleeding) and Infections [Infection in general (including opportunistic infection, abscess, soft tissue infections including necrotizing fasciitis)]

EU Risk Management Plan

Annex 4a – Targeted Follow-Up Questionnaire for Haemorrhagic events (thrombocytopenia/bleeding)

1) Please provide location of the bleeding/haemorrhage.

2) Relevant medical history: Does the patient have:

a) History of anaemia? Was patient transfusion dependent? If yes, since when and how frequent?

b) Episodes of hypotension? Hypertension? Gingivorrhagia or epistaxis? Headaches? Pallor? Dyspnoea? Weakness? Please describe.

c) History of bleeding/haemorrhage? Coagulation disorder? Please describe.

3) Please provide relevant concomitant medications, including thromboprophylaxis (type/dose/ dates as well as corresponding lab monitoring values if applicable), and possible platelet transfusion need to prevent haemorrhagic event.

4) Please provide date of diagnosis of underlying disease, stage at the time of diagnosis and stage of the patient's disease at the time of the event.

5) Please provide the following lab values at baseline, onset of the event (worst), and recovery:

Test	Range w/ Units	Baseline/ Date	Worst/ Date	Recovery/ Date
Platelets				
PT				
aPTT				
INR				
ESR				
LFTs				
Factor VIII				
Factor IX				

6) Please include bone marrow studies/ x-ray / CT scan results for the event of thrombocytopenia/bleeding/haemorrhage.

7) What treatments were given for the thrombocytopenia/ bleeding/ haemorrhage? Please include dates/dose.

EU Risk Management Plan

Annex 4b – Targeted Follow-Up Questionnaire for Infections [Infection in general (including opportunistic infection, abscess, soft tissue infections including necrotizing fasciitis)]

See also specific questions targeted to opportunistic infections below.
See also specific questions targeted to Necrotizing fasciitis below

1. Please provide the type and source of infection (e.g., bacterial, fungal, viral, etc.).

2. Has the patient had a history of recurrent infection?
☐ Yes
☐ No
If yes, please explain.

3. What was the stage of the underlying disease at the time of the infection onset?

4. Any history of bone marrow involvement, bone marrow transplantation or radiotherapy? If so, please provide approximate dates.

5. Please indicate one or more of the following
☐ De novo infection
☐ Recurrent infection
☐ Relapse

6. Did the patient receive infection prophylaxis?
☐ Yes
☐ No
If yes, please specify antibiotic, including dose and dates of treatment

7. Did the patient receive colony stimulating factors?
☐ Yes
☐ No
If yes, please specify (including type and dates).

8. Please provide the following lab values: at baseline, at onset of the event (worst lab value), and at the time of recovery:

Test	Range w/ Units	Baseline lab value/ Date (*prior to Azacitidine product*)	Worst lab value/ Date	Recovery lab value/ Date
WBC				

ANC				

9. Please provide relevant culture/serology and chest x-ray results with dates.

Opportunistic infections *(only if appropriate)*

1. Please indicate whether there is any suspicion or evidence of the following types of infections (partial list):

Viral:
☐ Epstein Barr virus (EBV)
☐ Hepatitis B (HBV)
☐ Cytomegalovirus (CMV)
☐ Herpes simplex (HSV)
☐ Varicella zoster virus (VZV)
☐ Progressive multifocal leukoencephalopathy (PML)
☐ Other (please specify):

Protozoal:
☐ Pneumocystis carinii (PCP)
☐ Toxoplasmosis
☐ Other (please specify):

Malignancies
☐ Kaposi sarcoma (KS) - associated herpes virus
☐ Other (please specify):

Fungal:
☐ Candidiasis
☐ Aspergillosis
☐ Histoplasmosis
☐ Cryptococcosis
☐ Other (please specify):

Bacterial:
☐ Tuberculosis (TBC)
☐ Mycobacterium avium (MAI)
☐ Salmonellosis
☐ Other (please specify):

Parasitic:
☐ Visceral leishmaniasis (VL)
☐ Other (please specify):

2. If the answer to any of the above is yes, please indicate whether this diagnosis has been confirmed and if so how?

3. Please indicate whether the patient's travel history includes geographical areas associated with parasitic infections such as VL (i.e. Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, Sudan, etc.). If so, please provide dates of travel.

4. Please indicate whether the patient experienced symptoms of VL including: slow progression of malaise, fever, weight loss, and splenomegaly (abdominal discomfort and fullness localized to left upper quadrant), skin hyperpigmentation over a period of months. If so, please provide dates and details below.

Soft tissue infections including necrotizing fasciitis (NF) (*only if appropriate*)

1. Please provide the site of the body that was initially affected by the soft tissue infection:

2. If the soft tissue infection was due to a local precipitating event(s), please indicate the cause of the event (e.g. traumatic including surgery, minor invasive procedures [e.g. joint aspirations], and penetrating injuries [e.g. insect and animal bites] and nontraumatic including soft tissue burns):

3. If the suspect drug is an injectable form, please specify the route of administration:
☐ Subcutaneous (SC)
☐ Intravenous (IV)

4. Please specify if the starting point of the soft tissue infection was at the injection site.

5. Please specify if any of the below risk factors have been identified:
☐ Diabetes
☐ Chronic disease (please specify):
☐ Immunosuppressive drugs (including corticosteroids), if yes specify:
☐ Malnutrition,
☐ Age >60 years
☐ Peripheral vascular disease
☐ Alcohol /drug abuse (please specify):

☐ Renal failure
☐ Obesity
☐ Recent childbirth
☐ Recent infection with rash (e.g. varicella)
☐ Recent stay in health care facility
☐ Recent dental work
☐ Others (please specify):

6. Please provide the identified infectious causative pathogen and source of identification (e.g. skin or blood culture/serology results with dates).

7. Please provide any additional diagnostic test results if available (e.g. Scan; MRI; Skin biopsy; Muscle biopsy, etc.).

8. Please provide additional lab data including:

Test	Range w/ Units	Baseline lab value/Date (*prior to Azacitidine product*)	Worst lab value/ Date	Recovery lab value/ Date
CPK MM				
CPK				
lactate				
BUN				
Creatinine				
glucose				
INR				
PT				
D-Dimer				
Serum C-reactive protein				

9. Please provide post-surgery pathology results including cultures from deep specimen samples during the intervention.

10. Please provide any available information concerning the patient's hobbies/occupation (fishing, weightlifting/heavy work-out/gardening, etc.).