Risk Management Plan

for

Azacitidine Accord 25 mg/mL powder for suspension for injection

Azacitidine Accord 200 mg film-coated tablets

Azacitidine Accord 300 mg film-coated tablets

(Azacitidine)

RMP version to be assessed as part of this application:

RMP Version number	2.0
Data lock point for this RMP	25-Jun-2024
Date of final sign off	12-Jul-2024

Rationale for submitting an updated RMP: The Risk Management Plan (RMP) has been updated to add Azacitidine Accord 200 mg/300 mg film-coated tablets for line extension of formulation.

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part I, Part II (SVII), Part VI and Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number	Approved with procedure	Date of approval (opinion date)
1.1	EMEA/H/C/0005147	12-Dec-2019

[redacted]

QPPV name: Agata Gesiewicz

QPPV signature: (on behalf of QPPV)

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Azacitidine
Pharmacotherapeutic group(s)(ATC Code)	**Pharmacotherapeutic group:** Antineoplastic agents, antimetabolites, pyrimidine analogues **ATC code:** L01BC07
Marketing Authorisation Holder	Accord Healthcare S.L.U.
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Azacitidine Accord 25 mg/mL powder for suspension for injection Azacitidine Accord 200 mg film-coated tablets Azacitidine Accord 300 mg film-coated tablets
Marketing authorisation procedure	Centralized Procedure (EMEA/H/C/0005147)
Brief description of the product	**Chemical class:** Azacitidine is a pyrimidine nucleoside analogue of cytidine with antineoplastic activity.
	Summary of mode of action: Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Incorporation of azacitidine into the DNA of AML cells, modified epigenetic pathways through the inhibition of DNA methyltransferases, and reduction of DNA methylation. This led to alteration of gene expression, including re-expression of genes regulating tumour suppression, immune pathways, cell cycle, and cell differentiation. Incorporation of azacitidine into the RNA of AML cells, inhibited RNA methyltransferase, reduced RNA

[redacted]

	methylation, decreased RNA stability, and decreased protein synthesis.
	Important information about its composition: Azacitidine Accord 25 mg/mL powder for suspension for injection **100 mg/vial:** Each vial contains 100 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine. **150 mg/vial:** Each vial contains 150 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine Azacitidine Accord 200 mg film-coated tablets Each film-coated tablet contains 200 mg of azacitidine. *Excipient with known effect* Each film-coated tablet contains 3.61 mg of lactose (as lactose monohydrate). Azacitidine Accord 300 mg film-coated tablets Each film-coated tablet contains 300 mg of azacitidine. *Excipient with known effect* Each film-coated tablet contains 5.42 mg of lactose (as lactose monohydrate).
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC.
Indication(s) in the EEA	*Current* Azacitidine Accord 25 mg/mL powder for suspension for injection Azacitidine Accord is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with:

[redacted]

	• 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 <u>Azacitidine Accord 200 mg/300 mg film-coated tablets</u> Azacitidine Accord 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, hematopoietic stem cell transplantation (HSCT).
Dosage in the EEA	*Current* <u>Azacitidine Accord 25 mg/mL powder for suspension for injection</u> **<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 as long as the patient continues to benefit or until disease progression.

[redacted]

	Method of administration: Reconstituted Azacitidine Accord 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.
	Proposed Azacitidine Accord 200 mg/300 mg film-coated tablets **Posology:** The recommended dose is 300 mg azacitidine orally once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment free period of 14 days (28-day treatment cycle). **Method of administration:** Azacitidine Accord is for oral use.
Pharmaceutical form(s) and strengths	*Current* Powder for suspension for injection 25 mg/mL
	Proposed Film-coated Tablets 200 mg and 300 mg
Is the product subject to additional monitoring in the EU?	No

[redacted]

Part II: Safety specification

Module SI – Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII – Non-clinical part of the safety specification

Not applicable

Module SIII – Clinical trial exposure

Not applicable

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

Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable

[redacted]

Module SVII – Identified and potential risks

The safety concerns for this Risk Management Plan (RMP) have been considered as per European Public Assessment Report (EPAR) – Risk-management-plan of Vidaza (azacitidine) version 16.0, dated 26-May-2021, published on EMA website on 15-Jun-2023. There is no change proposed by MAH in these safety concerns mentioned in Module SVIII which is in-line with RMP summary.

Hence, this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2 Presentation of the missing information

Not applicable

[redacted]

Module SVIII – Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Haemorrhagic events* • Infections
Important potential risks	• None
Missing information	• None

* for injection formulation only

[redacted]

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in "Module SVIII – Summary of the safety concerns".

In addition, in-line with the reference product Vidaza, MAH has proposed targeted follow-up questionnaires for following risks with azacitidine and they are appended in Annex 4 of this RMP.

- Haemorrhagic events
- Infections

Purpose: For collection and reporting of safety information while use of azacitidine.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable

[redacted]

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

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

V.1 Routine Risk Minimisation Measures

Not applicable

V.2 Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets (Azacitidine)

This is a summary of the risk management plan (RMP) for Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets. The RMP details important risks of Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablet's risks and uncertainties (missing information).

Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablet's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets should be used.

This summary of the RMP for Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets 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 Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablet's RMP.

I. The medicine and what it is used for

Azacitidine Accord 25 mg/mL powder for suspension for injection

Azacitidine Accord 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),

[redacted]

- 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 the active substance and it is given by subcutaneous route.

Azacitidine Accord 200 mg/300 mg film-coated tablets

Azacitidine Accord 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, hematopoietic stem cell transplantation (HSCT).

It contains azacitidine as the active substance and it is given by oral route.

Further information about the evaluation of Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablet's benefits can be found in Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablet's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/azacitidine-accord.

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

Important risks of Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets together with measures to minimise such risks and the proposed studies for learning more about Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablet'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;

[redacted]

- 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 signal management activity, 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 Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered/taken. 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 Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets. 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 risks	• Haemorrhagic events* • Infections
Important potential risks	• None
Missing information	• None

* for injection formulation only

II.B Summary of important risks

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

[redacted]

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 Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets.

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

There are no studies required for Azacitidine Accord 25 mg/mL powder for suspension for injection and Azacitidine Accord 200 mg/300 mg film-coated tablets.

[redacted]

Annex 4 – Specific adverse drug reaction follow-up forms

In addition, in-line with the reference product Vidaza, MAH has proposed targeted follow-up questionnaires for following risks with azacitidine.

- Haemorrhagic events
- Infections

Purpose: For collection and reporting of safety information while use of azacitidine

[redacted]

Targeted Follow Up Questionnaire For Haemorrhagic Events

THROMBOCYTOPENIA/BLEEDING

1) Please provide location of the bleeding/hemorrhage.

2) Relevant medical history. Does the patient have:
   a. History of anemia? Was patient transfusion dependent? If yes, since when and how frequent?

   b. Episodes of hypotension? Hypertension? Gingivorrhagia or epitaxis? Headaches? Pallor? Dyspnea? 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 hemorrhagic 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.

[redacted]

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/hemorrhage.

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

[redacted]

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

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

Has the patient had a history of recurrent infection?

☐ Yes

☐ No

If yes, please explain.

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

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

Please indicate one or more of the following

☐ De novo infection

☐ Recurrent infection

☐ Relapse

Did the patient receive infection prophylaxis?

☐ Yes

☐ No

If yes, please specify antibiotic, including dose and dates of treatment.

[redacted]

Did the patient receive colony stimulating factors?

☐ Yes

☐ No

If yes, please specify (including type and dates)

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				

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

[redacted]

Opportunistic infections (only if appropriate)

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):

[redacted]

Parasitic:

☐ Visceral leishmaniasis (VL)

☐ Other (please specify):

*Please refer to targeted questionnaire for viral reactivation as needed

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

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.

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.

[redacted]

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

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

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):

If the suspect drug is an injectable form, please specify the route of administration:

☐ Subcutaneous (SC)

☐ Intravenous (IV)

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

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 (eg varicella)

☐ Recent stay in health care facility

☐ Recent dental work

☐ Others (please specify):

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

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

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				

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

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

[redacted]