COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Azacitidine Stada 25 mg/ml, powder for suspension for injection (azacitidine)

NL/H/4713/001/DC

Date: 3 December 2025

This module reflects the scientific discussion for the approval of Azacitidine Stada 25 mg/ml, powder for suspension for injection. The procedure was finalised on 26 March 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Azacitidine Stada 25 mg/ml, powder for suspension for injection, from Stada Arzneimittel AG.

The product 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.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Vidaza 25 mg/ml, powder for suspension for injection, which has been registered in the EEA via a centralised procedure (EU/1/08/488) since 17 December 2008.

The concerned member state (CMS) involved in this procedure was Germany.

Scientific advice from the Medicines Evaluation Board confirmed the applicability of the biowaiver criteria.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Azacitidine Stada and the current orphan products authorised in the EU, based on designation EU/3/07/509. These orphan products are:

Indicated in the treatment of acute myeloid leukemia (AML):

- Mylotarg (gemtuzumab ozogamicin), Pfizer Europe MA EEIG, EU/1/18/1277
- Rydapt (midostaurin), Novartis Europharm Limited, EU/1/17/1218
- Vyxeos (liposomal combination of cytarabine an daunoribicin), Jazz Pharmaceuticals, EU/1/18/1308
- Dacogen (decitabine), Janssen-Cilag International NV, EU/1/12/792
- Xospata (gilteritinib), Astellas Pharma Europe B.V., EU/1/19/1399

For the assessment report, the therapeutic indication, mechanism of action and molecular structure of Azacitidine Stada and the orphaned products were compared. The (updated)

similarity assessment report was completed in March 2020, concluding Azacitidine Stada and the orphaned products Mylotarg, Rydapt and Xospata were not similar, Azacitidine Stada and the orphaned product Dacogen were not similar based on principal molecular structure, partly similar based on indication and similar based on mechanism of action, Azacitidine Stada and the orphaned product Vyxeos were not similar based on mechanism of action. It was concluded that the existence of any market exclusivity for the orphaned products in the treatment of AML, does not prevent the granting of the marketing authorisation of Azacitidine 25 mg/ml.

II. QUALITY ASPECTS

II.1 Introduction

Azacitidine Stada is a white to off-white powder for suspension for injection, packed in a vial. Each vial contains as active substance 100 mg azacitidine. After reconstitution, each ml of suspension contains 25 mg azacitidine as active substance.

The excipient is mannitol (E421).

The powder for suspension for injection is packed in a colourless, glass type I closed vial with bromobutyl rubber stoppers, grey, secured by caps, aluminium seals with green polypropylene disk.

II.2 Drug Substance

The active substance is azacitidine, an established active substance not described in the European or British Pharmacopoeia (Ph.Eur.). Azacitidine is a white to off-white powder and is slightly soluble in water. For this product, one polymorphic form is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of two steps. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Potential carry-over of impurities has adequately been evaluated. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three process validation batches and five annual stability batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
Formulation development is based on the formulation of the reference product.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Particle size distribution and particle morphology are adequately controlled in the drug product release specification.
The manufacturing process of the drug product has been described in detail.
Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipient
The excipient is usual for this pharmaceutical form and similar to the reference product. As the excipient is from pharmacopeial quality and dissolved during the manufacturing process, no further assessment is required. Same reference standards as for the drug substance are used. These specifications are acceptable.

Microbiological attributes
The primary packaging consists of type I clear glass vials (Ph.Eur. 3.2.1) of 50 ml nominal capacity and 20 mm bromobutyl stoppers. Clear specifications for the glass vial and stopper, including test methods and requirements applied by the MAH have been submitted. The integrity of the container closure system to prevent microbial contamination is acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. A very low risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies have been performed in line with the ICH Guideline. The only trend observed is a slight decrease in pH when the product is exposed to light. On basis of the data submitted, a shelf life was granted of two years, in unopened glass vial with rubber stopper. The unopened vial does not require any special storage conditions.

The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. When it is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than 8 hours at 2 °C to 8 °C when reconstituted using water for injections that has not been refrigerated or not longer than 22 hours when reconstituted using refrigerated (2 °C to 8 °C) water for injections.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Azacitidine Stada has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Azacitidine Stada is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Vidaza which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Azacitidine is a well-known active substance with established efficacy and tolerability. As per Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), there is no recommendation given for suspensions for injections. A biowaiver has been requested and a clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Azacitidine Stada 25 mg/ml, powder for suspension for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Azaciditine CF is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Biowaiver

The biowaiver for clinical equivalence studies based on *in vitro* equivalence of test- and reference product (Vidaza) has adequately been substantiated and is acceptable. To show *in vitro* bioequivalence, a comparison of reference product with generic product has been performed. The composition and physico-chemical characteristics assay, particle size distribution, particle morphology, viscosity, pH, osmolality, and solubility and time to clear solution on warming to 36°C on water bath (to mimic clinical subcutaneous administration) were compared. Both products had comparable values for all parameters, only some slight differences in viscosity and pH were observed. It has adequately been justified that these slight differences will have no impact on the efficacy and safety of the drug product compared to the reference product. As requested the MAH has included a test and requirement for

polymorphic form and a test for particle size distribution to the drug product specification. The specification limits for these tests are acceptable.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Azacitidine Stada. At the time of approval, the most recent version of the RMP was version 1.1, signed 13 September 2019.

Table 1. Summary table of safety concerns as approved in RMP

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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Vidaza. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Azacitidine Stada 25 mg/ml, powder for suspension for injection has a proven chemical-pharmaceutical quality and is a generic form of Vidaza 25 mg/ml, powder for suspension for injection. Vidaza is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted based on results of comparative *in vitro* testing.

In the Q-consultation of 26 February 2020, advice was given by CMD(h) members regarding a risk evaluation of nitrosamine impurities in the product. Due to changed CMD(h) guidelines, missing a fully adequate risk evaluation was now considered a major objection. MAH was requested to provide a risk evaluation concerning the presence of nitrosamine impurities in the product in question and applying the principles outlined in the notice “Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)”. MAH provided the risk evaluation that is in line with EMA/CHMP/428592/2019 Rev. 2 and appropriate. The point was resolved.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Azacitidine Stada with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 March 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4713/001 /IB/001	Changes in the manufacturing process of the active substance - Minor change to the restricted part of an Active Substance Master File. Change in control of the active substance - Other variation Change in the specification parameters and/or limits of the immediate packaging of the active substance - Tightening of specification limits Change in the specification parameters and/or limits of the immediate packaging of the active substance - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) Change in test procedure for the immediate packaging of the active substance - Other changes to a test procedure (including replacement or addition)	No	10-11-2020	Approved	N.A.
NL/H/4713/001 /II/002	Change in the specification parameters and/or limits of the finished product - Change outside the approved	No	5-4-2022	Approved	N.A.

	specifications limits range				
NL/H/4713/001/IB/003	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	Yes	13-5-2022	Approved	N.A.
NL/H/4713/001/IA/005	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging site	No	20-6-2022	Approved	N.A.
NL/H/4713/001/IB/004	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH (in order to update the Product information texts (SmPC, PIL) of Azacitidine in line with the reference product Vidaza, including topics concerned in EMEA/H/C/PSUSA/00000274/202105.)	Yes	12-7-2022	Approved	N.A.
NL/H/4713/001/IA/007/G	Deletion of manufacturing sites (including for an active substance, intermediate or finished	Yes	25-10-2022	Approved	N.A.

	product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)). Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place	No			
NL/H/4713/001 /IB/006	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH (update section 4.2 and 4.6 of the SmPC and section 2 of the PL in alignment with reference product Vidaza).	Yes	3-1-2023	Approved	N.A.
NL/H/4713/001 /II/008	Other variation ASMF-update	No	10-1-2023	Approved	N.A
NL/H/4713/001 /IA/009	Change in test procedure for the finished product - Minor changes to an approved test procedure	No	25-10-2023	Approved	N.A.
NL/H/4713/001 /IB/010	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation (To update the SmPC and PL in accordance with PRAC recommendation on signals, topic: Cutaneous vasculitis,	Yes	13-2-2024	Approved	N.A.

	EMA/PRAC/416581/2023).				
NL/H/4713/001/R/001	Renewal	No	26-8-2024	Approved	N.A.