COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Azacitidine STADA Arzneimittel 25 mg/ml, powder for suspension for injection

(azacitidine)

NL/H/4889/001/DC

Date: 28 January 2021

This module reflects the scientific discussion for the approval of Azacitidine STADA Arzneimittel 25 mg/ml, powder for suspension for injection. The procedure was finalised at 18 November 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
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
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 Arzneimittel 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Vidaza 25 mg/ml powder for suspension for injection which has been registered in the EEA by Celgene Europe B.V. since 17 December 2008 via a centralised procedure (EU/1/08/488/001).

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

<u>Orphan similarity</u>

The MAH has compared in this module the product applied for with the authorised orphan medicinal products:

- Mylotarg (gemtuzumab ozogamicin)
- Rydapt (midostaurin)
- Dacogen (decitabine)
- Vyxeos (liposomal combination of cytarabine an daunoribicin)
- Daurismo (glasdegib)
- Reblozyl (luspatercept)
- Xospata (gilteritinib)

With reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Dacogen, Rydapt, Mylotarg, Vyxeos, Xospata, Daurismo and Reblozyl does not prevent the granting of the marketing authorisation of for Azacitidine STADA Arzneimittel 25

mg/ml, powder for suspension for injection. This finding was without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Introduction

Azacitidine STADA Arzneimittel is a white lyophilised cake or powder for suspension for injection. Each vial contains 100 mg azacitidine. After reconstitution, each ml of suspension contains 25 mg azacitidine.

The powder for suspension for injection is packed in colourless type I glass vial sealed with bromobutyl rubber stopper and aluminium seal with polypropylene plastic disc, containing 100 mg of azacitidine. The vials may be placed in a polypropylene vial guard (with bottom and top components and the grooves are aligned) if required or may be directly packed in a clean carton box.

The only excipient is mannitol (E421).

II.2 Drug Substance

The active substance is azacitidine, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.). A draft monograph is available for the drug substance in the United States Pharmacopeia (USP). Azacitidine is a pyrimidine nucleoside analogue of cytidine. It is a white to off-white solid, sparingly soluble in water. Azacitidine contains 4 chiral centres but it is synthesised as a single enantiomer. It is not hygroscopic but it hydrolyses quickly in water (reaction pH and temperature dependent). Nine solid-state forms have been identified: five polymorphic forms, three pseudopolymorphic forms and an amorphous form. The manufacturing process of the active substance manufacturer results in crystalline form-I. Even if the active substance is fully solubilised during manufacture of the finished product, polymorphism could be of importance since the speed of dissolution of azacitidine could affect its degradation. However, all the polymorphs have been shown to convert quickly to a single bioavailable pseudopolymorphic form in presence of water via rapid surface hydration and therefore in this case the physical form of the active substance is not expected to impact either on the stability or on the performance of the finished product.

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 three main stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance
The active substance specification has been established in-house by the MAH and includes tests for description, solubility, identification, water content, specific optical rotation, sulphated ash, related substances, assay, residual solvents, bacterial endotoxins, and microbial limits. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 36 months without a maximum storage temperature.

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. Azacitidine rapidly degrades in aqueous solution via hydrolysis. Due to this instability, an aqueous formulation was not a viable option. Thus, a lyophilised dosage form was developed to minimize water activity in the medicinal product. The use of the excipients is justified and its function explained.
The type I glass vials and the siliconized rubber stopper used as primary packaging material meet the Ph.Eur. requirements. They are compatible with the product and capable to protect it from excessive moisture in relation to the proposed specification. Acceptable closure integrity studies (dye penetration and microbial challenge studies) have been performed.
No bioequivalence study was conducted, but comparative *in vitro* data have been provided. The comparative data *in vitro* data, among which comparative particle size distribution data of three batches of the test and three batches of the reference product evaluated according to the average bioequivalence approach, support equivalence between the test and the reference product.

Manufacturing process
The manufacturing process involves the following operations: compounding, sterile filtration, aseptic filling, lyophilisation and packaging. It has been validated according to relevant European guidelines. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. The maximum holding time has been

adequately justified based on azacitidine degradation data and microbiological data. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipient mannitol complies with the Ph.Eur. The specification is acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description (before/after reconstitution), identification, pH, uniformity of dosage units, water content, assay, organic impurities, sterility, bacterial endotoxins, extractable volume, residual solvents, particle size distribution, and particulate morphology. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scaled 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 batches stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years without any special storage conditions. The storage conditions after reconstitution of the medicinal product can be found in the SmPC section 6.3.

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 Arzneimittel 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 Arzneimittel is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is 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 is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

In the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), there is no recommendation given for the pharmaceutical form 'suspension for injection'. However, a biowaiver can be requested. No bioequivalence study was conducted, but comparative *in vitro* data have been provided. The comparative *in vitro* data, among which comparative particle size distribution data of three batches of the test and three batches of the reference product evaluated according to the average bioequivalence approach, support equivalence between the test and the reference product.

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 Arzneimittel.

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. No new clinical studies were conducted. 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 test consisted of: a pilot test with 2 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 Arzneimittel 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.

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 Arzneimittel with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 November 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