COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5204/001/DC

Date: 8 March 2022

This module reflects the scientific discussion for the approval of Azacitidine Zentiva 25 mg/ml powder for suspension for injection. The procedure was finalised on 11 November 2021. 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
WHO	World Health Organisation

I. INTRODUCTION

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

The product is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- Intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System.
- Chronic myelomonocytic leukaemia with 10 – 29% marrow blasts without myeloproliferative disorder.
- Acute myeloid leukaemia with 20 – 30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification.
- Acute myeloid leukaemia 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. Vidaza has been registered in the EEA by Celgene Europe B.V. since December 2008 by centralised procedure EMEA/H/C/000978.

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Poland, Portugal and Slovakia.

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

<u>Assessment of orphan similarity</u>
The MAH has submitted an orphan similarity assessment report that addresses the possible similarity between Azacitidine Zentiva and the orphan medicinal products which have received a marketing authorisation.

For the similarity assessment the following criteria were considered:

- principal molecular structural features
- mechanism of action
- therapeutic indications

Currently authorised orphan medicinal products in myelodysplastic syndromes and acute myeloid leukaemia are:

- Mylotarg (gemtuzumab ozogamicin), Pfizer Europe MA EEIG
- Rydapt (midostaurin), Novartis Europharm Limited
- Dacogen (decitabine), Janssen-Cilag International NV
- Vyxeos (daunorubicin hydrochloride/Cytarabine), Jazz Pharmaceuticals Ireland Ltd
- Xospata (gilteritinib fumarate), Astellas Pharma Europe B.V.
- Reblozyl (luspatercept), Celgene Europe B.V
- Daurismo (glasdegib maleate), Pfizer Europe MA EEIG

It has been agreed that Azacitidine Zentiva is not similar, as defined in Article 3 of Commission Regulation (EC) No. 847/2000, to these authorised orphan medicinal product.

II. QUALITY ASPECTS

II.1 Introduction

Azacitidine Zentiva is a white lyophilised 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 a type-I clear glass vial sealed with a 20 mm dark grey chloro-butyl single slotted rubber stopper and 20 mm aluminium flip off seal.

The excipient is mannitol (E421).

II.2 Drug Substance

The active substance is azacitidine, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). A draft United States Pharmacopeia (USP) monograph for azacitidine is pending. Azacitidine is a white to off white crystalline powder with a solubility of about 10 mg/mL across the physiological pH range at 37°C. Azacitidine is a stable chemical compound with low tendency for degradation in the solid state. The drug substance is non-hygroscopic. Azacitidine contains four chiral centres; however it is manufactured as a single enantiomer. Different polymorphic forms of azacitidine are declared in the literature; the drug substance manufacturer consistently produces polymorphic form I.

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 consecutive synthetic stages, followed by one purification stage. Two chemical transformation steps in the sense of ICH Q11 separate the proposed starting materials from the final active substance, which is considered sufficient. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The drug substance specification of the drug product manufacturer contains tests for description, solubility, identification, water content, specific optical rotation, residue on ignition, related substances, assay, residual solvents, microbial limits, and bacterial endotoxins. The drug substance specification of the drug product manufacturer is identical to that of the ASMF holder, and is acceptable.

Batch analysis data of two drug substance batches used to manufacture the drug product demonstrate compliance with the drug substance specification. Batch analysis data of three commercial scale batches have additionally been provided by the ASMF holder.

Stability of drug substance

Stability data on the active substance have been provided for six batches stored at 25°C/60% RH (up to 60 months) and 25°C/60% RH (six months) in accordance with applicable European guidelines. The batches were packed in a transparent LDPE bag, in a continuous liner, in a triple laminated sunlight barrier bag inside a HDPE container. The active substance is generally stable at both storage conditions. Assay remains constant and no conversion of the polymorphic form is observable.

Photostability testing performed in accordance with ICH Q1B showed that the drug substance is not sensitive to light exposure. The proposed re-test period of 42 months with the special storage condition “Store at 2 to 8°C” is acceptable. Storage in the refrigerator would not be necessary, but storage in the refrigerator is accepted as it has no implications for the related drug product on a patient level.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the development was to formulate a robust, essentially similar, stable, bioequivalent and generic formulation of the reference product Vidaza. Formulation development has been adequately described.

After reconstitution, the drug product corresponds to a suspension which is administered subcutaneously. A waiver for a bioequivalence study has been requested, which will be discussed in section IV on Clinical aspects. To support the biowaiver, comparative *in vitro* data on three batches of the test and three batches of the reference product have been

provided. The data include comparisons of physicochemical characteristics, particle morphology, particle diameter, and dissolution. The data have been assessed based on the FDA draft guidance on azacitidine products and the scientific advice obtained from the EMA for this product. The comparative particle size distribution data were evaluated using an average bioequivalence approach, which showed equivalence.

Due to the lack of discriminatory power of the dissolution method, other means are needed to ensure batch-to-batch consistency of future batches with development batches that were shown to be pharmaceutically equivalent with the reference product. Therefore, tests for particle size distribution and particle morphology have been added to the drug product specification as these are considered the most relevant parameters for this type of drug product.

Manufacturing process

The manufacturing process includes the preparation of the bulk solution, sterile filtration, filling, and lyophilisation. The manufacturing process is adequately described. The manufacturing process is regarded as a non-standard process due to the aseptic processing and lyophilisation steps. The batch sizes are acceptable based on the provided process validation data. The manufacturing process was adequately validated on three batches of all proposed batch sizes. The filters used for sterile filtration were adequately validated as well.

Control of excipient

The excipient mannitol is commonly used in medicinal products and complies with pharmacopoeial standards. The specifications are acceptable.

Microbiological attributes

The drug product is sterile. Sterility, bacterial endotoxins and bioburden tests are critical. The drug product is tested for sterility at release and during stability studies. A justification has been provided for the acceptance criterion for the bacterial endotoxins test. Bioburden test is the pharmacopoeial recommendation for the input materials and in process product solution. Hence, all raw material specifications shall have this parameter to control microbial load.

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, identification of the active substance, water content, uniformity of dosage units, particulate contamination, foreign particles, bacterial endotoxins, sterility, assay, related substances, residual solvent, appearance of suspension, pH of suspension, syringe ability, osmolality of the reconstituted suspension, reconstitution time, extractable volume of the reconstituted suspension, particle size distribution, and particle morphology. The release and shelf life specification differs with regard to the acceptance criteria for assay and related substances. The proposed drug product specification is acceptable.

Analytical methods were adequately described and validated. The limits of quantitation for the specified and unspecified impurities by the HPLC method for related substances were established below the ICH Q3B identification threshold of 0.1%. This is acceptable. Forced degradation studies were performed in connection with the methods for assay and related substances. All methods are considered as stability indicating. Batch analysis results from batches of each proposed batch size are presented. The tested batches correspond to the batches used for process validation. All results comply with the proposed release specification.

A risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided. No risk has been identified. Confirmatory testing is therefore not needed.

Stability of drug product

Stability data on the powder product have been provided for three batches per batch size stored at 25°C/60% RH (six to 36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. 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 in the primary packaging. No significant changes have been observed during the formal stability studies. Based on the provided stability data, a shelf life of two years has been granted for the unopened powder vial. No special storage conditions are needed.

When the product is reconstituted using water for injections that has not been refrigerated, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 25 °C for 60 minutes and at 2 – 8 °C for 8 hours.

When the product is reconstituted using refrigerated (2 – 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 – 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 – 8 °C when reconstituted using water for injections that has not been refrigerated or not longer than 22 hours when reconstituted using refrigerated (2 – 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 Zentiva 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 Zentiva 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

Azacitidine Zentiva is a parenteral formulation and therefore fulfils the exemption mentioned in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr), 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. The quantitative compositions of Azacitidine Zentiva is entirely the same as the originator and does not contain excipients that may affect the pharmacokinetics.

Therefore, Azacitidine Zentiva 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 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 Zentiva.

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 deemed necessary since both the reference and current product are intended for parenteral use. A biowaiver has been granted. 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 followed by one round with ten participants. 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 Zentiva 25 mg/ml powder for suspension for injection has a proven chemical-pharmaceutical quality and is a generic forms 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 Zentiva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 November 2021.

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