9 November 2023
EMA/71813/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Azacitidine Kabi

International non-proprietary name: Azacitidine

Procedure No. EMEA/H/C/006154/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AML	Acute myeloid leukaemia
AP	Applicant´s part of active substance master file
API	Active pharmaceutical ingredient
AR	Assessment report
AS	active substance
ASMF	Active substance master file = drug master file
CoA	Certificate of analysis
CQA	critical quality attribute
CMML	Chronic myelomonocytic leukaemia
DNA	Deoxyribonucleic acid
DMF	Drug master file = Active substance master file, ASMF
DSC	Differential scanning calorimetry
EEA	European Economic Area
FAB	French American British group
FP	finished product
GC	gas chromatography
HR	Hazard ratio
HR-MDS	Higher-risk myelodysplastic syndromes
HPLC	High performance liquid chromatography
IC	ion chromatography
IPC	In-process control test
GC	Gas chromatography
IC	Standard induction chemotherapy
IPSS	International prognostic scoring system
ICH	International conference on harmonisation
IR	Infra-red
KF	Karl Fischer titration
LoA	Letter of access
MAH	Marketing authorisation holder
MS	Mass spectroscopy
MDS	Myelodysplastic syndromes
MO	Major objection
NLT	Not less than

NMR	Nuclear magnetic resonance
NMT	Not more than
OS	Overall survival
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
QOS	Quality overall summary
QTPP	Quality target product profile
RH	Relative humidity
RP	Restricted part of active substance master file
Rt	Retention time
Rt	Room temperature
RNA	Ribonucleic acid
sc	subcutaneous
SmPC	Summary of product characteristics
TGA	Thermo-gravimetric analysis
UV	Ultraviolet
vs	versus
WHO	World Health Organization
WPSS	WHO prognostic scoring system
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Deutschland GmbH submitted on 25 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Azacitidine Kabi, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2022.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Azacitidine Kabi 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and literature references instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Vidaza, 25 mg/mL, powder for suspension for injection
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 17-December-2008
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/488/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Vidaza, 25 mg/mL, powder for suspension for

injection

- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 17-December-2008
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/488/001

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Tomas Radimersky

The application was received by the EMA on	25 November 2022
The procedure started on	28 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 July 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	16 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023

The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	10 October 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Azacitidine Kabi on	9 November 2023
The CHMP adopted a report on similarity of Azacitidine Kabi with Rebrozyl, Dacogen, Mylotarg, Rydapt, Vyxeos liposomal, Xosprata, Daurismo and Tibsovo on (Appendix on similarity)	9 November 2023

2. Scientific discussion

2.1. Introduction

Myelodysplastic syndromes (MDS) are acquired haematopoietic disorders, characterised by ineffective haematopoiesis, disturbed proliferation, and maturation of myeloid cell lineages as well as frequent progression to acute myeloid leukaemia (AML). The median age at diagnosis is approximately 70 years, and the yearly incidence rate increases to 25 per 100,000 in people aged 65 years and older. MDS are more common in men compared with women (with yearly incidence rates of approximately 5.4 vs 2.9 per 100,000). The disease has prognostic heterogeneity, with some patients showing slow clinical course over many years and others progressing rapidly to overt leukaemia or dying from the consequences of bone marrow failure or AML development within a few months after diagnosis. These occur more frequently in older males and in individuals with prior exposure to cytotoxic therapy. It may develop after exposure to toxins such as benzene, chemotherapy drugs, or high doses of radiation, though its aetiology is unknown in more than 80% of patients. Most patients with high-risk MDS (i.e., French-American-British [FAB] subtypes with excess blasts) die within 1 year from progressive bone marrow failure attributable to haemorrhage or infection. In 35% to 40% of patients, transformation to acute leukaemia occurs, which is often refractory to present therapy. The primary goal of treatment for higher-risk MDS is prolonging overall survival (OS) by changing the natural disease course. Because treatment related effects on OS may require years to measure, haematologic response has been the primary end point in most MDS clinical studies. Using treatment experience from AML, the general view has been that complete or partial remission (CR or PR) is a criterion for prolonged OS (Aul2002; Bennett1982; Bennett1985; Cheson2000; Garcia2020; Gore2013; Harris1999; Public Assessment Report, Vidaza2009; Santini2010; Sekeres2022b; Seymour2010; Silverman2002; Uchida2011).

Azacitidine (5-azacytidine or 5-aza) is a pyrimidine nucleoside analogue of cytidine, a constituent of RNA. Due to its similarity to cytidine, azacitidine blocks the synthesis of DNA and RNA and thus inhibits the growth of tumour cells. Metabolites such as azacitidine are also associated with inhibition of DNA-methylation (hypo-methylation) and can inhibit tumour growth. High-risk MDS shows a high prevalence of tumour suppressor gene hypermethylation, which induces inactivation of tumour

suppressor genes. By re-establishing cell cycle control by restoring suppressor gene function and anti-proliferative signals, this could contribute to re-establish cell differentiation pathways required for appropriate cellular function.

This Marketing authorisation application (MAA) is based on 'essential similarity' to the original product in accordance with article 10(1) of Directive 2001/83/EC. The medicinal product is a generic of the reference medicinal product, which has been authorised within the community, in accordance with community provisions in force, for not less than eight years in a member state or in the community. The reference product is Vidaza powder for suspension for injection manufactured/marketed by Celgene Europe BV, Netherland. The indications sought for Azacitidine Kabi are the same as those for Vidaza powder for suspension for injection:

Proposed indication

Azacitidine Kabi 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.

According to the proposed SmPC (section 4.2) the posology and method of administration of Azacitidine Kabi is as follows:

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.

Posology

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 (see section 4.4); a delay in starting the next cycle or a dose reduction as described below 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. Healthcare professionals are recommended to verify the name of the medicinal product, dose and administration route.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for suspension for injection, 25 mg/mL containing azacitidine as active substance.

Other ingredients are: mannitol.

The product is available in glass vial sealed with chlorobutyl rubber stopper and sealed with aluminium flip-off-seal.

2.2.2. Active substance

2.2.2.1. General Information

The active substance (AS) azacitidine present in this formulation is stated to be a known active substance. Active substance master file approach is used for this compound, therefore information about the active substance has been made separately for control of azacitidine by the active substance manufacturer (ASMF sent separately) and by the finished product manufacturer (in the dossier for the application of the finished product).

The AS is a white to off white powder, soluble in dimethyl sulphoxide, sparingly soluble in water and insoluble in n-hexane. Based on the X-ray diffraction studies it is concluded that the manufacturing process followed by the AS supplier, consistently produces the same crystalline form of azacitidine.

Azacitidine is not described in the Ph. Eur.

The chemical name of azacitidine is 4-amino-1-(β-D-ribofuranosyl)-1,3,5-triazin- 2(1H)-one corresponding to the molecular formula $C_8H_{12}N_4O_5$. It has a relative molecular mass of 244.20 g/mol and the following structure:

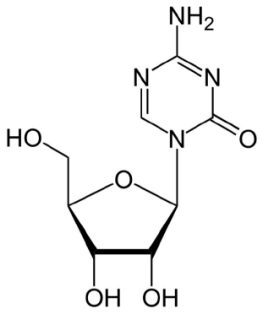

Figure 1: Active substance structure

The structure of azacitidine was confirmed by infrared spectroscopy, mass spectroscopy, Nuclear Magnetic Resonance Spectroscopy (1H-NMR and 13C-NMR), X-Ray Powder Diffraction (XRPD),Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), elemental analysis, UV spectroscopy and specific optical rotation.

Azacitidine is non-hygroscopic in nature. Azacitidine AS was found to be stable (with no significant changes) in presence of light. Azacitidine may exist in two isomeric (regiomers) forms, however, only one form is bio-active and approved as antineoplastic drug; this bio-active form is manufactured by the AS supplier.

Azacitidine contains 4 chiral centres, but it is synthesised as a single enantiomer. Enantiomeric purity is routinely controlled in the active substance through specific optical rotation.

Polymorphism has been observed for azacitidine.

2.2.2.2. Manufacture, characterisation and process controls

Azacitidine is synthesised in 5 main steps using welldefined starting materials with acceptable specifications. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The characterisation of the active substance azacitidine has been studied by infrared spectroscopy, mass spectroscopy, nuclear magnetic resonance spectroscopy (proton nuclear magnetic resonance spectroscopy (1H-NMR) and carbon-13 nuclear magnetic resonance (13C-NMR)), X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), elemental analysis, UV spectroscopy and specific optical rotation.

Potential and actual impurities were generally well discussed with regards to their origin and characterised.

The AS container closure system has been descried and is acceptable. The packaging complies with EC 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for: appearance (visual), identification (IR, HPLC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), specific optical rotation (Ph. Eur.), residual solvents (GC, HPLC, IC), related substances (HPLC), assay (HPLC), bacterial endotoxins (Ph. Eur.), microbial limits (Ph. Eur.) and dissolution (in-house).

The specification covers all relevant parameters. The finished product manufacturer uses the same controls as the active substance manufacturer. Justification of specification is based on ICH and Ph. Eur. requirements.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data four production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three batches of active substance from the AS stored in the intended commercial package for up to 18 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, IR, specific optical rotation, water, related substances, assay, dissolution, bacterial endotoxins, microbial limit testing. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. Degradation products increased under accelerated conditions but remained within the specification.

Photostability testing following the ICH guideline Q1B was performed. Azacitidine is not light sensitive.

Stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product (FP) is a powder for suspension for injection, 25 mg/mL containing azacitidine as active substance. The product is available in glass vial sealed with chlorobutyl rubber stopper and sealed with aluminium flip-off-seal.

The finished product has been developed to be a generic equivalent to the reference medicinal product Vidaza 25 mg/mL Powder for Suspension for Injection by Bristol-Myers Squibb Pharma EEIG, authorised since 22 December 2008 via the centralised procedure. Consequently, the objective was to prepare a powder for suspension for injection which is essentially similar to the reference medicinal product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Pharmaceutical development

The physicochemical properties of active substance have been listed. The section addresses all important attributes of the active substance. They are either satisfactorily controlled or omission of their control has been satisfactorily justified.

The selected excipient, solvent and process aid are the same as in the reference product and in the same amount. All of them are of Ph. Eur. quality.

The target of the formulation development was to develop product pharmaceutically equivalent to the reference product Vidaza 25 mg/mL Powder for Suspension for Injection. After analysis of reference product, the applicant presented the Quality Target Product Profile (QTPP) for the generic product. Based on the QTPP, critical quality attributes (CQA) were identified.

The formulation development is short, but the finished product is simple, containing only active substance and one excipient, same as in reference product.

Physicochemical and biological properties have been briefly discussed. Conclusion has been provided regarding impact of parameters.

Since, the proposed product is powder for suspension for injection comparative in-vitro studies have been performed between Fresenius Kabi's Azacitidine 25 mg/mL powder for suspension for injection and European Reference Product (ERP) VIDAZA for demonstrating the bioequivalence. Relevant physicochemical properties between the reference and test medicinal products were compared. The generic product can be concluded as similar to Vidaza.

Regarding dissolution method used for in vitro dissolution comparison sufficient details have been provided. The dissolution method development has been provided.

Detailed manufacturing process development has been described. The critical steps, consequent critical process parameters and their controls are clearly highlighted and accepted. Detailed development of the lyophilisation process has been provided taking into account the thermal behaviour of the substance. The applicant has presented good knowledge of the process and influence of the process variables for the finished product quality. The manufacturing process development is accepted.

The choice of the materials for the container closure system has been satisfactorily described. The container closure system commonly used for this pharmaceutical form has been chosen. The suitability is also confirmed by the stability of the finished product.

The product is for parenteral administration (subcutaneous injection), it is preservative free. The microbiological attributes as controlled throughout the process are clearly stated and accepted.

The in-use stability study in line with the instructions for reconstitution in SmPC have been conducted.

The results of thermal cycling study confirm that the product can be exposed to temperature excursions without negative impact on the product quality.

The primary packaging is Type I tubular clear colourless glass vials stoppered with chlorobutyl (Lyo) rubber stopper and sealed with aluminium flip-off over seals.

The material complies with Ph. Eur. and EC requirements. The specifications of parts of the primary packaging contain dimensions as well. The specification of vials and rubber stopper presented by finished product manufacturer contain the dimensions. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing and testing are provided. In response to a Major Objection during the procedure the applicant provided an updated satisfactory GMP certificate for the finished product manufacturing site; MIAs and GMP certificates were provided in Module 1.

The batch size is clearly stated as volume of the bulk solution and as well as equivalent number of vials. Satisfactory batch formula has been provided including vehicle and nitrogen as a processing aid. Satisfactory formula for calculation of actual quantity of active substance has been provided.

The manufacturing process consists of following main steps: compounding, filtration, filling and partial stoppering, lyophilisation, stoppering, sealing, external decontamination, inspection, packaging.

Generally acceptable flow chart and narrative description of the manufacturing process has been provided. In-process controls are identified. Most of the relevant process parameters are laid down in the process description with set points or ranges. The set points and ranges are justified by pharmaceutical development. The sterilisation conditions applied for the rubber stoppers and aluminium seal have been included in the dossier. The test for bioburden with acceptable limit is included as in-process control. This is satisfactory.

The processing time from AS addition to the end of lyo loading is proposed. The additional information regarding the time of the complete manufacture and filling step has been presented.

Satisfactory list of in-process controls for monitoring of the process is provided. Information on test methods used for in process control has been described.

The filter validation data are provided. All validation parameters according to the EMA/CHMP/CVMP/QWP/850374/2015 Guideline on the sterilisation of the medicinal product, active

substance, excipient and primary container were considered. The filter was subject of the validation. Sufficient process validation data regarding the filter used has been presented.

The manufacturing process validation has been provided for three batches of proposed commercial scale size. The process is non-standard, so the results of commercial scale batches are needed in the dossier. This has been fulfilled. According to the presented data, the process is capable to produce the product of consistent quality and hence considered validated. The container closure integrity has been confirmed for the validation batches. The results were satisfactory.

The bulk holding study has been provided. The full-scale size batches were used. The Applicant clearly discussed and justified the storage of the bulk solution.

Process validation studies were performed on 3 production scale batches of azacitidine 25 mg/mL powder for suspension for injection. Media fill as a part of the validation has been performed. This is satisfactory. Different vial size and filling volume were used than proposed for commercial manufacture. The applicant´s justification that this is a worst case covering also the proposed vial size and filling is fully acceptable. It has been confirmed that the growth promotion test has been conducted and aummary of results has been provided, which were satisfactory.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.2.3.3. Product specification(s)

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), Water (KF), uniformity of dosage units (Ph. Eur.), colour and appearance of reconstituted suspension (in house), pH of reconstituted suspension (Ph. Eur.), reconstitution time (in house), particulate contamination (Ph. Eur.), related substances (HPLC), assay (HPLC), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), particle size distribution (laser diffraction), crystal morphology (in-house), seal integrity test (in-house) and viscosity (Ph. Eur.).

Specification has been provided for the finished product. One specification is proposed, the same limits are applied for release and shelf-life except for the impurities. References to the analytical methods are listed in the table, they refer to the specific general Ph. Eur. monographs or to the in-house method.

The specification contains all tests relevant for this particular pharmaceutical form (such as appearance of suspension, pH of suspension, subvisible particles, reconstitution time and uniformity of dosage units, sterility and bacterial endotoxins). The limits for these tests are set according to the relevant Ph. Eur. monograph. The test for mass variation is conducted to confirm uniformity of dosage units, which is in line with the requirement of the Ph. Eur. monograph 2.9.40 for this pharmaceutical form and dose. Generally required tests such as identification by two independent methods, assay and related substances are included. Omission of certain parameters from the specification has been justified.

Particle size distribution test is included as one of the key parameters to assure the similarity with the reference medicinal product. The limits for PSD in the finished product specification have been updated to be a range as requested and the specification for span has been added.

The limits for pH and water are set according to the batch results and are acceptable.

The crystal morphology test has been included in the specification as part of the finished product specification. Acceptable acceptance criteria are proposed.

For impurities, the acceptance criteria have been set in line with the ICH Topic Q 3 B (R2). The maximum daily dose of the product is 100 mg/m^2 per day. Considering the average body surface 1.8 m^2, the daily dose 180 mg. The limit proposed for the any unspecified degradation product is in line with the ICH Q3B and is accepted. The limits proposed for total impurities are acceptable.

All impurities above the ICH limit are necessary to be identified and qualified. The release and shelf-life limits for certain impurities are above the qualification threshold but have been adequately justified. Overall, the justification for the proposed limits seems to be acceptable when considering the ICH S9 Guideline and genotoxic potential of the AS itself. The limit for assay at release as well as at shelf-life is acceptable.

The limit for bacterial endotoxins has been proposed. Detailed calculation has been provided and accepted.

The absence of the dissolution test in the specification is considered acceptable as the data in the section 3.2.P.2 clearly showed very rapid dissolution.

The degradation products potentially present in the finished product are clearly stated, the structure of two specified impurities has been satisfactorily confirmed by spectral analysis. According to the stability results, no additional degradation products are observed in the finished product above the identification threshold.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. The elemental impurities risk assessment has been provided, confirming the risk is low and all results are below 30 % of PDE for the concerned EI, thus it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Potential sources are identified and discussed. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The container closure integrity (CCI) test is included in the specification as a seal integrity test. This is satisfactory. Implementation of a validated CCIT method before the release and as part of the routine stability programme provides an additional assurance that integrity of the container closure system is maintained from the manufacture throughout the shelf-life.

The finished product contains only one excipient, which remains a part of the finished product. Other two excipients are used during the manufacture and are not a part of the finished product composition. All these three excipients comply with the current version of Ph. Eur. monograph, which has been satisfactorily supported by exemplary certificates of analysis. As the methods strictly according to the respective Ph. Eur. monograph are used, no description and validation are necessary to be provided. Satisfactory assurance has been given that the used excipients are BSE/TSE risk free.

The test methods are generally well addressed. For the simple methods the reference to the respective Ph. Eur. monograph is acceptable. For some methods such as bacterial endotoxins and sterility, the

product specific setting has been presented. The method description for seal integrity test has been provided.

The in-house methods were validated, and validations were carried out according to ICH-Guideline Q2 (R1). The test methods for related substances and assay were shown to be satisfactorily stability indicating. Also, the microbiological methods are confirmed to be suitable for the testing of the proposed product. The methods validations as performed by the finished product manufacturing site are provided and concluded as satisfactory. The method transfer from the sending to the receiving laboratory is also confirmed to be successful. Information regarding the testing for EU release is sufficient.

As there is no Ph. Eur. monograph for the substance, in-house reference standards are used. which are fully characterised and are concluded as acceptable. Satisfactory chromatographic purity for the purpose of methods validation and transfer has been confirmed. Reference standard of acceptable quality was used for the methods validation.

Satisfactory overview of batch results of three batches of the proposed commercial batch size were presented. The results comply with the proposed specification, which is satisfactory The results confirm, that the process is capable to produce the product of the consistent quality.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 18 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Other specified as well as unspecified impurities do not show significant trends. Based on the results it can be concluded that the product shows similar trends as the reference product.

Results of photostability confirms that the product is not sensitive to the light.

The results of the in-use stability study of the proposed product are lower or comparable to the results of reference product. This is acceptable. The age of the batches used in the in-use stability study has been stated. In the section 3.2.P.8 additional in-use stability study is presented and batches after 6 months of storage at 30°C are presented. As the in-use results of the proposed product are confirmed by the results of reference product, they are acceptable. The proposed shelf life and storage of the reconstituted product as stated in the SmPC (section 6.3) is acceptable.

Based on available stability data, the proposed shelf-life for the unopened vials of 2 years without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information about active substance azacitidine via ASMF has been provided. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The chemical-pharmaceutical documentation (Module 3) and Quality Overall Summary in relation to Azacitidine Kabi 25 mg/mL powder for suspension for injection,

is of sufficient quality in view of the present European regulatory requirements. The MO raised during the procedure regarding the GMP certification of the finished product manufacturing site was resolved following the provision of an updated GMP certificate.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment studies were submitted. This was justified by the applicant as the introduction of Azacitidine Kabi manufactured by Fresenius Kabi Deutschland GmbH is considered unlikely to result in any significant increase in the combined sales volumes for all azacitidine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the CHMP agreed that no further non-clinical studies are required.

The impurity profile of applicant’s azacitidine is comparable to that of Vidaza. Thus, additional toxicology studies to qualify the impurity profile of the drug product are not required.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.3.4. Conclusion on the non-clinical aspects

The CHMP is of the opinion that the applicant has justified the absence of non-clinical studies based on the literature review and the claim that Azacitidine Kabi is a generic of the reference product Vidaza. The literature data presented in the dossier is considered acceptable and sufficient for the assessment of non-clinical aspects of Azacitidine Kabi in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The applicant has provided a clinical overview where pharmacology, efficacy and safety of azacitidine were discussed. The active substance of Azacitidine 25mg/mL is not considered a new active substance. Pharmacodynamic, pharmacokinetic, efficacy and safety profiles of azacitidine are well known. As azacitidine is a widely used, well-known active substance, no further studies are required. An overview based on literature review is, thus, appropriate. Information stated in the clinical overview is up-to-date and adequately supported with the scientific literature.

The proposed indication and posology of test product are in line with the reference product Vidaza.

Exemption

No bioequivalence study was submitted to support the application. The CHMP considered that a biowaiver for a generic azacitidine powder for suspension for injection product is acceptable considering that the test and reference product have the same qualitative and quantitative composition in active substance and the same qualitative and very similar quantitative composition in excipients, that the provided in vitro data demonstrate high aqueous solubility of azacitidine, rapid and similar dissolution rate between the test and reference products and that the reconstitution instructions for the products by healthcare professionals prior to administration, which requires vigorous shaking, are common between test and reference product.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

The proposed product represents powder for suspension for injection containing the same active substance, dosage form and route of administration (s.c.) as the currently approved product. The suspension of azacitidine does not show characteristics of prolong release formulation after s.c. administration.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

No bioequivalence study was submitted to support the application which is in line with the CHMP view that a biowaiver for BE studies for azacitidine generics is acceptable.

Azacitidine Kabi is considered essentially similar to Vidaza, Bristol Myers Squibb

2.4.4. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Azacitidine Kabi was provided and was accepted by the CHMP. This is in accordance with the relevant guidelines, WPs positions and additional clinical studies were not considered necessary. Azacitidine Kabi is considered essentially similar to Vidaza.

2.5. Risk Management Plan

2.5.1. Safety concerns

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

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities are planned.

2.5.3. Risk minimisation measures

No additional risk minimisation activities are planned.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of azacitidine 25 mg/mL powder for suspension for injection. The reference product, Vidaza, 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Azacitdine Kabi is not similar to Rebrozyl, Dacogen, Mylotarg, Rydapt, Vyxeos liposomal, Xosprata, Daurismo and Tibsovo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Azacitidine Kabi is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.