30 January 2020
EMA/CHMP/91461/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Azacitidine betapharm

International non-proprietary name: azacitidine

Procedure No. EMEA/H/C/005075/0000

Note

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

Administrative information

Name of the medicinal product:	Azacitidine betapharm
Applicant:	betapharm Arzneimittel GmbH Kobelweg 95 86156 Augsburg GERMANY
Active substance:	AZACITIDINE
International non-proprietary name/Common name:	azacitidine
Pharmaco-therapeutic group (ATC Code):	antimetabolites, pyrimidine analogues (L01BC07)
Therapeutic indication(s):	Azacitidine betapharm 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% to 29% marrow blasts without myeloproliferative disorder, • acute myeloid leukaemia (AML) with 20% to 30% blasts and multi-lineage dysplasia, according to World Health Organization (WHO) classification, • AML with > 30% marrow blasts according to the WHO classification.
Pharmaceutical form(s):	Powder for suspension for injection
Strength(s):	25 mg/ml

Route(s) of administration:	Subcutaneous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AUC	Area under the curve
BUN	Blood urea nitrogen
CMML	Chronic myelomonocytic leukaemia
CYPs	Cytochrome P450 isoenzymes
DOSEai	Maximum daily dose consumed per patient
Fpen	Fraction of market penetration
GSTs	Glutathione transferases
HSCT	Haematopoietic stem cell transplantation
IPSS	International Prognostic scoring system
MDS	Myelodysplastic syndromes
Nd	Number of days per year
PEC	Predicted environmental concentration
Pregion	Highest regional prevalence
RMP	Reference Medicinal product
SULTs	Sulfotransferases
UGTs	UDP-glucuronosyltransferases
ULN	Upper limit of normal
WBC	White blood cells

1. Background information on the procedure

1.1. Submission of the dossier

The applicant betapharm Arzneimittel GmbH submitted on 9 January 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Azacitidine betapharm, 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 31 May 2018.

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 in the Union 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 betapharm 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.

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 10 years in the EEA:

- Product name, strength, pharmaceutical form: Vidaza, 25 mg/mL, powder for suspension for injection
- Marketing authorisation holder: Celgene Europe B.V.
- 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: Celgene Europe B.V.
- Date of authorisation: 17-December-2008
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/488/001

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

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.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Ondřej Slanař

The application was received by the EMA on	9 January 2019
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 May 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	29 May 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	24 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	17 October 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	7 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	27 November 2019
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in	4 December 2019

an oral explanation to be sent to the applicant on	
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	3 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 January 2020
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 betapharm on	30 January 2020
The CHMP adopted a report on similarity of Azacitidine betapharm with Revlimid, Dacogen, Ceplene, Rydapt, Mylotarg and Xospata	30 January 2020

2. Scientific discussion

2.1. Introduction

Myelodysplastic syndrome (MDS) is a rare and life-threatening disease that can affect children and adults, although the highest prevalence occurs in those over 60 years of age. The incidence of MDS has been estimated as 4.1/100,000 population. The incidence rises with increasing age: 4.9 for people aged 50 to 70 years and 22.8 for people older than 70 years.

The clinical presentation of MDS is generally non-specific. However, initial findings of MDS can usually be attributed to the underlying cytopenias. MDS can arise de novo (primary MDS) or following treatment with chemotherapy, radiation therapy or chemical injury (secondary MDS). Depending on the subtype of myelodysplasia, there is a risk of approximately 50% for development of acute myeloid leukaemia (AML), which is often refractory to standard treatment.

Despite current treatment strategies, approximately half of the patient population with MDS dies within 4 years. Cure may be achieved only in patients who can receive allogeneic haematopoietic stem cell transplantation (allo HSCT). However, depending on a patient' s age and general health condition, best supportive care (BSC), consisting in transfusions, growth factors, iron chelation therapy, is most frequently applied.

AML evolving from MDS is often less responsive to standard treatment than de novo AML. The usually higher age at diagnosis makes these patients more vulnerable to toxic effects from induction and consolidation chemotherapy (with e.g., cytarabine, etoposide and idarubicin) and the HSCT.

Acute myeloid leukaemia (AML) is an aggressive, clonal myeloid neoplasm with maturation arrest of myelopoiesis, leading to an accumulation of myoblasts in bone marrow (BM) and/or blood. AML is the most frequent form of leukaemia, accounting for approximately 25% of all leukaemias in adults in the Western world. Worldwide, the incidence of AML is the highest in the United States (US), Australia and Western Europe. The overall annual crude incidence of AML is 3.7 per 100, 0000 people. More than half of the subjects with newly diagnosed AML in developed countries are over 65 years of age, with a median age at diagnosis of 67.

AML can arise de novo, through transformation of existing myelodysplasia, or be secondary to previous therapy (e.g. cytotoxic chemotherapy). AML is a heterogeneous disease in terms of response to treatment and overall survival (OS). Prognostic factors that contribute to this heterogeneity can be both patient- and disease-related.

Patient-related prognostic factors include age, performance score and comorbidities. Disease-related prognostic factors include high leukocyte count, existence of prior MDS or myelodysplasia-related changes, previous cytotoxic therapy, and cytogenetic and molecular/genetic changes in the leukaemic cells at diagnosis. Overall, the 5-year survival rate for AML is 19%, whereas for elderly only 5% of the patients achieve a 5-year survival.

About the product

Azacitidine belongs to the group of 'anti-metabolites'. Azacitidine is an analogue of cytidine, which means that it is incorporated into the genetic material of cells (RNA and DNA). It is thought to work by altering the way the cell turns genes on and off and also by interfering with the production of new RNA and DNA. These actions are thought to correct the problems with the maturation and growth of young blood cells in the bone marrow that cause myelodysplastic disorders, and to kill cancerous cells in leukaemia.

This Marketing Authorization 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 authorized 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 betapharm are the same as those for Vidaza powder for suspension for injection:

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 Leukemia (10%-29% marrow blasts without Myeloproliferative Disorder),

- Acute Myeloid Leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO),

- AML with >30% marrow blasts according to the WHO classification.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for suspension for injection containing 100 mg per vial of azacitidine as active substance, to be reconstituted in 4 mL of solvent (25 mg/mL).

The only other ingredient is mannitol (E 421).

The product is available in glass vials (type I) sealed with bromobutyl rubber stopper and flip-off-seal as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of azacitidine is 4-amino-1-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2-one corresponding to the molecular formula $C_8H_{12}N_4O_5$. It has a molecular weight of 244.207 g/mol and the following structure:

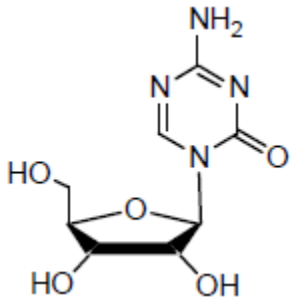

Figure 1: active substance structure

The chemical structure of the active substance was elucidated by a combination of thermal analysis (differential scanning calorimetry), UV spectrophotometry, specific optical rotation, FT-IR spectroscopy, NMR spectroscopy, and high-resolution mass spectrometry (HRMS). The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD).

The active substance is a white to off-white non-hygroscopic powder, soluble in dimethyl sulphoxide, sparingly soluble in water and insoluble in acetone and ethanol.

Azacitidine exhibits stereoisomerism due to the presence of four chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation in the active substance specifications.

Azacitidine exhibits polymorphism. Based on XRPD studies conducted, it is concluded that the manufacturing process consistently produces Form I of azacitidine.

Nonetheless, since the active substance is dissolved during the compounding step of the manufacturing process of the finished product, the potential presence of polymorphic forms is not considered relevant for the performance of the product.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Azacitidine is sourced from a single manufacturer and it is synthesized in a two-stage synthesis with four chemical transformation steps and one isolated intermediate using well defined starting materials with acceptable specifications. The CHMP raised concerns during the procedure regarding the justification of selection of one of the starting materials, however the updated discussion regarding controls and carry-over of potential impurities supported the initially proposed starting material.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

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

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

Azacitidine is packed under nitrogen atmosphere. The active substance is packaged in polyethylene bag, tied with strip. This bag is placed inside a continuous liner bag along with silica gel packet and tied both sides with strip. This bag is kept in a triple laminated bag along with silica gel pouch in between triple laminated bag and continuous liner and sealed with sealer. This sealed triple laminated bag is kept in HDPE container with a HDPE lid and this outer container is also sealed with tamper evident seal. The polyethylene bags in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC, XRD), solubility (in-house), loss on drying (in-house), sulphate ash (Ph. Eur.), specific optical rotation (in-house), related substances (HPLC), assay (HPLC), residual solvents (GC), bacterial endotoxin (in-house) and microbial test (Ph. Eur.).

The manufacturing process of starting materials and final active substance, azacitidine have been evaluated for potential sources of elemental impurities and it is observed that no Class-1, Class-2A, Class-2B and Class-3 elemental impurities were intentionally added during the complete manufacturing process.

Azacitidine is sensitive to moisture and several compounds are possible degradants. During the procedure, additional information on the control strategy of the impurities were requested by CHMP which was amended and is considered acceptable.

From the specificity studies, in acid hydrolysis, base hydrolysis, oxidation and in water stress conditions, two major unknown impurities were identified by LCMS/MS.

The existing related substances by HPLC method is capable of detecting relevant impurities in azacitidine.

Further 48 months long term stability study data was examined and no significant increase in known and unknown impurities was observed. This information was sufficient to resolve the raised concerns.

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 on three consecutive production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 9 production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25 °C / 60% RH) and from 3 commercial scale batches for up to 12 months under intermediate conditions (30 °C / 65% RH) and from 3 commercial scale batches for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification, loss on drying, related substances and assay. The analytical methods used were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions: heat/thermal, photolytic exposure, humidity/moisture/ acidic solution/ basic solution, oxidation and metallic ions were also provided on one batch. Based on the provided photostability study it can be concluded that azacitidine is photostable. Results of stress degradation study show that the active substance is stable for heat, humidity and photolytic conditions. The active substance is highly sensitive to acid, base, water hydrolysis, oxidation and metal ion degradation.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored in the proposed container at a temperature below 25° C (excursions permitted between 15 and 30° C).

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Azacitidine 25 mg/mL Powder for Suspension for Injection is a sterile lyophilized powder packed in 30 mL/20 mm tubular type-I glass vials, stoppered with 20 mm rubber stoppers and sealed with 20 mm flip-off seals.

Mannitol, used as a bulking agent for the lyophilization process, is the only excipient in the formulation. There is no overage used in the formulation and there are no accompanying reconstitution diluents provided with the finished product.

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 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 formulation development is concise, since the finished product is relatively simple, containing only the active substance and one excipient, same as in reference 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 2.1.1 of this report.

Physicochemical and biological properties have been discussed. The pharmaceutical equivalency has been shown comparing product characteristics such as dosage form, strength, reconstitution solutions, storage etc. and the results of the specification parameters testing.

The morphology of reconstituted suspension, Particle Size Distribution (PSD) of the API, solubility, XRD pattern and *in vitro* dissolution profile has been evaluated for Dr. Reddy's product and reference medicinal product. pH, osmolality and viscosity were also evaluated. The substance is quickly solubilized even after adding a small amount of diluent.

The finished product is a suspension for subcutaneous injection, for which the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) requires bioequivalence studies versus the reference product, unless a biowaiver is applicable as per Appendix III. While Appendix III is not applicable, during the evaluation procedure the CHMP agreed that a biowaiver for BE studies specifically for azacitidine powder for suspension for injection generic products could be justified based on *in vitro* data provided 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. Considering the specific nature of the product and how it is used in practice, the parameters that are considered most relevant for the performance of the product are the PSD and the crystal morphology of the active substance immediately prior to use. In order to support therapeutic equivalence based on *in vitro* data, when reconstituted in accordance with the recommended instructions, these parameters should be similar to the reference product and should be part of the finished product specification. In addition the biowaiver request should be supported with results comparing osmolality, pH and viscosity, and with results from a suitably designed test for the reconstituted product measuring and comparing "time/temperature to clear solution" after reconstitution between test and reference products. An MO was consequently raised in relation to the above. Comparative results between test and reference product have been provided and specifications for PSD and for particle morphology were included in the finished product to assure that the performance of each batch is similar to the originator, on the basis of the *in vitro* comparability studies performed. The equivalence of the test product to the reference product has been proved based on the physical and chemical parameters. The biowaiver was therefore accepted. Moreover, due to the high solubility of the active substance azacitidine in water at 37 °C (i.e. at biorelevant conditions), it is recognized that developing a discriminatory dissolution method for the proposed product is very difficult.

Detailed manufacturing process development has been described. The critical process parameters and their impact on product performance were identified. The possibility of risk mitigation for these steps has been described and satisfactory controls were set, based on this analysis.

The process time and temperature were identified as critical parameters in the bulk solution manufacturing, as they directly affect assay and purity of the final product. The holding time of filled vials is critical and should be minimized.

The selection of sterilization method has been discussed and data after exposure 121 ° C for 30 minutes were presented. The selected method is aseptic processing and filtration followed by lyophilization. The lyophilization cycle has been developed.

The chosen container closure system (Type I glass vials) is widely used for this pharmaceutical form. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The compatibility studies confirm, that the product quality is not affected by contact with filter membranes, silicon gasket, rubber stopper, containers and tubing.

Manufacture of the product and process controls

The manufacturing process consists of eleven main steps: dispensing of raw materials, preparation of primary packaging, sterilisation, compounding of bulk solution, first filtration, second filtration + filling and partial stoppering, lyophilisation, sealing and external decontamination, visual inspection of sealed decontaminated

vials, coding of sealed vials and labelling/packing. The process is considered to be a non standard manufacturing process.

The in-process control tests have been described and are deemed satisfactory. Major steps of the manufacturing process have been validated by a number of studies. Three process validation reports are provided – one report including three batches of each proposed batch size. The filter validation includes all generally required studies – bacterial retention study, filter compatibility study and extractable study.

The media fill summary has been provided. The results of the container closure integrity have been provided. 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.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (UV, HPLC), reconstitution time (in-house), color of the solution (in-house), particulate contamination (Ph. Eur.), uniformity of dosage units (Ph. Eur.), assay (in-house), related substances (HPLC), water content (KF), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), particle size distribution of reconstituted suspension (laser diffraction), solubility (in-house), pH (in-house), osmolality (in-house), viscosity (in-house) and crystal morphology (in-house).

Most of the tests relevant for the pharmaceutical form powder for suspension for injection and subcutaneous administration are included in the specification. A test for dissolution is omitted, however, during the development studies it has been shown, that the product is rapidly dissolved. The particle size distribution and the crystal morphology are the key parameters and are tested routinely to assure that each batch is similar to the originator from this point of view. The limits for the individual percentiles of the PSD are considered adequate.

The general tests are considered satisfactorily justified. Impurities were justified by results of lab batches, submission batches and reference product. Satisfactory discussion related to the impurity profile has been provided confirming, that the presented impurities are the same in refence and generic product.

A summary of the product risk assessment prepared in accordance to the requirements set forth in ICH Q3D: Elemental Impurities has been provided. It has been concluded that there is no risk from container closure system and excipient and sufficient controls are proposed for active substance and for impurities sourced from equipment.

The analytical methods used have been adequately described and 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 results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 9 commercial scale (3 of each proposed batch size) batches of finished product stored for up to 48 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 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.

Samples were tested for appearance, color of solution, water content, assay, related substances, bacterial endotoxins, sterility and particulate contamination. The analytical procedures used are stability indicating.

In addition, one lab scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed that the finished product is not photosensitive.

When Azacitidine betapharm 25 mg/mL Powder for Suspension for Injection 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 45 minutes and at 2° C to 8° C for 8 hours.

The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2° C to 8° C) water for injections. When Azacitidine 25 mg/mL Powder for Suspension for Injection 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.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

The product has been developed as a generic of Vidaza.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Major Objections that were raised during the procedure on designation of regulatory starting material, discussion regarding active substance impurities and regarding the *in vitro* comparative studies required to support the biowaiver of the bioequivalence studies, by CHMP were satisfactorily addressed. 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

In the context of the obligation of the MAHs to take due account of technical and scientific progress and to investigate the risk of presence of nitrosamine in their medicinal products, the CHMP recommends the following point for investigation:

It is recommended that an updated risk evaluation on the potential presence of nitrosamine impurities in Azacitidine betapharm active substance and finished product is conducted within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

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 betapharm manufactured by betapharm Arzneimittel 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.

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 betapharm 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 betapharm in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Azacitidine betapharm 25 mg/mL powder for suspension for injection containing azacitidine.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

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. Pharmacodynamics

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

2.4.2. 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 WPs view that a biowaiver for BE studies for azacitidine generics is acceptable.

Azacitidine betapharm is considered essentially similar to Vidaza, Celgene Europe B.V.

2.4.3. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Azacitidine betapharm 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 betapharm is considered essentially similar to Vidaza, Celgene Europe B.V.

2.5. Risk management plan

Safety concerns

List of important risks and missing information	
Important identified risks	• Haemorrhagic events • Infections
Important potential risks	• None
Missing information	• None

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

No additional risk minimisation measures.

Conclusion

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

2.6. Pharmacovigilance

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.

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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

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.

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.

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

4. Recommendation

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

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.

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 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