12 December 2019
EMA/CHMP/22245/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Azacitidine Accord

International non-proprietary name: azacitidine

Procedure No. EMEA/H/C/005147/0000

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 Accord
Applicant:	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona S/N Edifici Est, 6a Planta 08039 Barcelona SPAIN
Active substance:	azacitidine
International non-proprietary name/Common name:	azacitidine
Pharmaco-therapeutic group (ATC Code):	antimetabolites, pyrimidine analogues (L01BC07)
Therapeutic indication(s):	Azacitidine Accord 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.
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

API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File = Drug Master File
BET	Bacterial Endo Toxin
CHMP	Committee for Medicinal Products for Human use
CoA	Certificate of Analysis
DMAP	4-dimethylaminopyridine
EC	European Commission
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
GC	Gas chromatography
ICH	International conference on harmonisation
ICP-OES	Inductively coupled plasma - optical emission spectrometry
IR	Infra-red
KF	Karl Fischer titration
LOD	Limit of Detection
LOQ	Limit of Quantitation
LDPE	Low Density Polyethylene
MDD	Maximum daily dose
NIOSH	National Institute for Occupational Safety and Health
NMT	Not more than
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
SmPC	Summary of Product Characteristics
WFI	water for injections
TAMC	Total Aerobial Microbial Count
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 12 January 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Azacitidine Accord, 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 20 September 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 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 Accord 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 6/10 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: Kolbeinn Gudmundsson

Co-Rapporteur: N/A

The application was received by the EMA on	12 January 2019
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 April 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	22 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	31 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	14 November 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 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, 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 Accord on	12 December 2019

2. Scientific discussion

2.1. Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of disorders that manifest as bone marrow failure with the risk of life-threatening infections and bleeding. In a third of cases it may transform to acute myeloiod leukemia. Due to age and co-morbidities treatment options are limited; the only curative modality to date is allogeneic stem cell transplantation. The advent of targeted therapy has increased the choice of therapeutic options. The methyl transferase inhibitor azacitidine, which targets epigenetic changes in MDS, has been shown to be effective in a Phase III randomized controlled trial comparing it with best supportive care (Raj K et al. 2006).

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.a.iii 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 Accord are the same as those for Vidaza powder for suspension for injection:

- 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 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 (E421)

The product is available in colourless type I glass vials sealed with butyl rubber stopper and aluminium seal with plastic button, containing 100 mg of azacitidine, as described in section 6.5 of the SmPC.

2.2.2. Active substance

The chemical name of azacitidine is (2R,3R,4S,5R)-4-amino-1-(3,4-dihydroxy-5-hydroxymethyltetrahydrofuran-yl)-1H-[1,3,5]triazin-2-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:

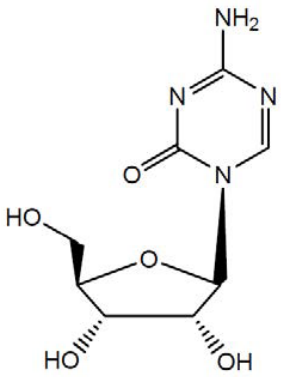

Figure 1: active substance structure

The chemical structure of azacitidine was elucidatedby a combination of IR, UV, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. The solid-state properties of the active substance were measured by XRD.
Azacitidine is a white to off-white solid, moderately soluble in water (13.41 mg/ml at 25 C), it is non-hygroscopic.

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.

Based on the literature survey, azacitidine active substance exhibits polymorphism. It was adequately demonstrated that the manufacturing process consistently results in the same polymorphic form, as shown by P-XRD analysis.

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

Manufacture

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 manufactured by non-sterile and non-aseptic process by a single manufacturer. The active substance is synthesized in four main steps using 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 manufacturing process has been validated. 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.

The active substance is packaged in LDPE bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended, placed inside a triple laminated bag with silica gel pouches and stored inside a HDPE drum.

In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products (https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf, https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf), MAHs of products containing chemically-synthesized active substances are being asked to review their products for potential presence of nitrosamine impurities and to conduct risk evaluations/risk assessments as appropriate.

No risk evaluation has been submitted for azacitidine and Azacitidine Accord within the current procedure. Therefore, it is recommended that a risk evaluation on the potential risk of presence of nitrosamine in azacitidine and Azacitidine Accord is conducted after the marketing authorisation, within six months of the publication of the call for review (19th September 2019). 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 3 years of the publication of the call for review (19th September 2019), or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

Specification

The active substance specification includes tests for appearance/description, identity (IR, HPLC), solubility (Ph.Eur.), assay (HPLC), specific optical rotation (Ph.Eur.), impurities (HPLC), residual solvents (GC), sulphated ash (Ph.Eur.), bacterial endotoxins (Ph.Eur.), water content (Ph.Eur.), microbial content (Ph.Eur.), tin content (ICP-OES).

The maximum daily dose (MDD) for azacitidine is 200 mg/day (100 mg/m^2). Therefore the ICH recommended thresholds for reporting, identification and qualification are 0.05%, 0.10% and 0.15%, respectively. The proposed limits for the specified impurities are controlled in-line with ICH Q3A, hence are acceptable from a safety point of view.

A risk assessment for elemental impurities was performed, including an elemental impurities screening by ICP-OES on three batches of azacitidine. The total level of all elemental impurities analyses was below 30 % of ICH Q3D limit.

No Class 1 solvents are employed throughout the synthetic process.

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 for batches at commercial scale of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial size batches of the active substance from the proposed manufacturer, stored in the intended commercial package for up to 60 months under long term conditions and up to 6 months under accelerated conditions were provided. The temperature conditions chosen by the Applicant are in line with those authorized for the innovator Vidaza. This is considered acceptable.

The following parameters were tested: description, identification (IR), appearance (Ph.Eur), water content (KF), related substances (HPLC) and assay (HPLC). Photostability testing following the ICH guideline Q1B was investigated during forced degradation studies. The active substance did not show signs of degradation after exposure to light without the protection of the primary packaging material. The finished product was hence not considered to be photosensitive. Results on stress conditions were also provided.

The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period at the proposed storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical development

Azacitidine, powder for suspension for injection, 25 mg/mL (100 mg/vial) is a white lyophilized powder or cake filled in a clear glass vial.

The finished product azacitidine powder for suspension for injection (100 mg/vial) was developed to be identical to Vidaza by Celgene from the European market. The finished product manufacturer has performed a number of comparative studies to demonstrate that Azacitidine Accord is comparable to the reference product.

The formulation of azacitidine is identical to that of the reference product Vidaza. A comparison of the in-vitro release of the active substance between the test and the reference product was conducted. The finished product is a suspension for subcutaneous injection, and as such it is not covered by the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Moreover, due to the high solubility of the active substance azacitidine in water at 37 ºC (i.e. at biorelevant conditions), it is recognized that developing a discriminatory dissolution method for the proposed product is very difficult. During the evaluation procedure, CHMP agreed that a biowaiver for BE studies for azacitidine generics can be acceptable, provided that some criteria are satisfied. In particular, the two most relevant parameters 'Particle size distribution' and 'Particle morphology' should be included in the specifications for the finished product. In addition, the applicants should demonstrate similarity with regard to pH, osmolality and viscosity, and provide 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. 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 original product, on the basis of the in-vitro comparability studies performed. Similarly, the Applicant showed that time and temperature to clear solution were equivalent to the reference product. In addition, parameters pH, viscosity and osmolality were shown to be similar between test and reference product. Therefore, the biowaiver for the BE studies is considered supported.

The excipient mannitol is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur standards. It is the same as that in the reference product.

The primary packaging is colourless type I glass vial sealed with butyl rubber stopper and aluminium seal with plastic button. 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.

Adventitious agents

None of the components used in the manufacture of Azacitidine Accord is of human or animal origin.

Manufacture of the product

The manufacturing process of azacitidine powder for suspension for injection consists of a simple preparation of a bulk solution, followed by sterile filtration and subsequent lyophilisation; it is considered a non-standard process. A summary of the in-process information during manufacture is provided to confirm that the proposed azacitidine powder for suspension for injection can be manufactured according to the proposals in the dossier. The information provided on the manufacturing process is considered sufficient. All process parameters as discussed in the pharmaceutical development section and verified during process validation are provided. The description also includes additional details related to the filters and maximum acceptable holding times and holding temperatures of the bulk solution are clearly stated. A summary of the in-process information during manufacture is provided to confirm that the proposed azacitidine powder for suspension for injection can be manufactured according to the proposals in the dossier. The proposed maximum acceptable holding time and holding temperature of the bulk solution should be clearly stated. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. Results from media fill runs demonstrate that the aseptic filling process gives a sterile product with high assurance.

Process validation was carried out on several batches at commercial scale. Major steps of the manufacturing process (sterilisation, filtration, lyophilisation and aseptic process steps) 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.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification of the active substance (UV and HPLC), pH of reconstituted suspension, water content (KF), assay (HPLC), uniformity of dosage units (weight variation), related substances (HPLC), sterility (Ph.Eur), BET (Ph.Eur), PSD (laser diffraction), reconstitution time, sub-visible particles(Ph.Eur), particle morphology and osmolarity(Ph.Eur).

The maximum daily dose (MDD) for Azacitidine Accord is 200 mg. Therefore, the ICH recommended thresholds for reporting, identification and qualification in the finished product are 0.1%, 0.2% and 0.2%, respectively. The proposed limits for specified and unspecified impurities are in-line with ICHQ3B and hence acceptable.

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. Forced degradation studies were performed in connection with the HPLC methods for assay and related substances. Peak purity was investigated and mass balance is demonstrated. The methods are considered as stability indicating.

Batch analysis results are provided for batches at commercial scale, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

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 three batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Azacitidine medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for stability indicating parameters. The analytical procedures used are the same as for release. All results remained within specifications and no significant changes were observed.

Compatibility data provided supported the in-use shelf life of the reconstituted product.

A photostability study has been performed on one batch of Azacitidine finished product in vials, as well as vials wrapped and protected by Al-foil. The conditions of the study were selected according to ICH Q1B. The finished product did not show signs of degradation after exposure to light without the protection of the primary and/or secondary packaging materials. Thus, it can be concluded that Azacitidine powder for suspension for injection is photostable when stored in the primary container.

In view of the provided stability data, the Applicant proposes 36 months shelf-life with no special storage conditions for the drug product. All tested quality attributes remain well within the proposed acceptance criteria.

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

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. 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. Recommendation(s) for future quality development

In the context of the review of the potential presence of nitrosamine impurities in human medicinal products and the need for 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:

It is recommended that a risk evaluation on the potential presence of nitrosamine impurities in azacitidine and Azacitidine Accord is conducted after the marketing authorisation, within six months of the publication of the call for review (19th September 2019). 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 3 years of the publication of the call for review (19th September 2019), 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 (please see also above).

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 Accord manufactured by Accord Healthcare S.L.U. 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 (please see also the recommendation in section 2.2.6).

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 Accord 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 Accord in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Azacitidine Accord 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.

For the clinical assessment the CHMP consulted its Pharmacokinetics and Quality Working Parties (please see also below).

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.

2.4.1. Pharmacodynamics

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

2.4.2. 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 WPs view that a biowaiver for BE studies for azacitidine generics is acceptable, please see above.

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

2.4.4. Conclusions on clinical aspects

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

2.5. Risk management plan

Safety concerns

Important Identified Risks:	• Haemorrhagic events • Infections
Important Potential Risks:	• None
Missing Information:	• None

Pharmacovigilance plan

Only routine risk pharmacovigilance activities are applicable. As part of routine pharmacovigilance activities, targeted follow-up questionnaires were implemented for Haemorrhagic Events and Infections.

Risk minimisation measures

Routine risk minimisation activities are sufficient to manage the safety concerns of azacitidine.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vidaza (EMEA/H/C/000978) and Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion (EMEA/H/C/002667). 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

- 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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Azacitidine Accord is not similar to Revlimid, Dacogen, Rydapt, Mylotarg, Vyxeos or Xospata within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

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 Accord is favourable in the following indication:

- 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.