30 January 2020
EMA/CHMP/36881/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Azacitidine Mylan

International non-proprietary name: azacitidine

Procedure No. EMEA/H/C/004984/0000

Note

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

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List of abbreviations

AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
API	Active Pharmaceutical Ingredient
AS	Active substance
ASMF	Active Substance Master File
AUC	Area under the curve
BUN	Blood urea nitrogen
CMML	Chronic myelomonocytic leukaemia
CYPs	Cytochrome P450 isoenzymes
DOSEai	Maximum daily dose consumed per patient
DSC	Differential Scanning Calorimetry
Fpen	Fraction of market penetration
GC	Gas chromatography
GSTs	Glutathione transferases
HPLC	High performance liquid chromatography
HSCT	Haematopoietic stem cell transplantation
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IPSS	International Prognostic scoring system
IR	Infra-red
KF	Karl Fischer titration
LDPE	Low-density polyethylene
MAH	Marketing Authorisation holder
MDD	Maximum daily dose
MDS	Myelodysplastic syndromes
MS	Mass spectroscopy
Nd	Number of days per year
NLT	Not less than
NMR	Nuclear magnetic resonance
PEC	Predicted environmental concentration
Ph. Eur.	European Pharmacopoeia
Pregion	Highest regional prevalence
RH	Relative Humidity
RMP	Reference Medicinal product
SmPC	Summary of Product Characteristics
SULTs	Sulfotransferases
UGTs	UDP-glucuronosyltransferases
ULN	Upper limit of normal
USP	United States Pharmacopoeia
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction
WBC	White blood cells

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 8 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Azacitidine Mylan, 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 25 January 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 Mylan 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 has received scientific advice from the CHMP prior to start of the procedure (EMEA/H/SA/3878/1/2018/II). Advice was sought on the demonstration of bioequivalence between the test and reference products by comparison of particle size distribution and other physicochemical characteristics, as well as dissolution of the drug product.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kolbeinn Gudmundsson

The application was received by the EMA on	8 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	25 June 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019

The applicant submitted the responses to the CHMP consolidated List of Questions on	10 October 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	18 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on a list of outstanding to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	06 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 January 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
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 Mylan on	30 January 2020
The CHMP adopted a report on similarity of Revlimid, Vyxeos, Dacogen, 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 Mylan 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 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 vial sealed with butyl rubber stopper and aluminium seal with plastic button 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-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-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):

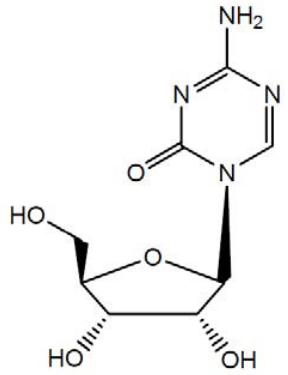

Figure 1: active substance structure

The chemical structure of azacitidine was elucidated by a combination of ^{1}H and ^{13}C NMR, MS, IR, UV and elemental analysis. The obtained spectra are in agreement with the assigned structure. The solid state properties of the active substance were measured by P-XRD and DSC.

Azacitidine is a white to off white crystalline powder, sparingly soluble in water, it is non-hygroscopic.

Azacitidine exhibits stereoisomerism due to the presence of four chiral centres, but it is synthesized as a single enantiomer. Enantiomeric purity is controlled routinely by specific optical rotation as shown 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.

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 manufactured by non-sterile and non-aseptic process by a single manufacturer. The active substance is synthesized in three main steps, using commercially available, well-defined starting materials. Adequate in-process controls are applied during the synthesis. The impurity profile of each intermediate has been thoroughly investigated and specified impurities identified. The specifications and control methods for intermediate products, starting materials and reagents were set in line with the impurity profiles updated during the evaluation procedure, and found acceptable. The specification limits for specified, unspecified and total impurities, as well as purity and assay of the proposed starting materials have been adequately set. 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.

Detailed information on the reprocessing procedures has been provided.
Azacitidine is packaged in transparent LDPE bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended, as well as with Ph.Eur. 3.1.3.

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), during the evaluation procedure the Applicant has been asked to review the azacitidine product for potential presence of nitrosamine impurities and to conduct risk evaluation/risk assessment as appropriate. On the basis of the results of the risk assessment performed both on the active substance and the finished product, the risk for formation of nitrosamines in the API manufacturing process, in the API itself, as well as in the finished product, is concluded to be negligible, therefore no action is required.

Specification

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

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 acceptable from a safety point of view. 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 and the draft USP monograph for the active substance. Forced degradation studies demonstrated that the methods for control of related substances and assay are stability indicating. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three batches at commercial scale of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The Applicant demonstrated that the active substance can be manufactured consistently within tight quality margins.

Stability

Stability data from three batches at the initial batch size of active substance from the proposed manufacturer stored in the intended commercial packaging and container closure system representative of that intended for the market, for up to 60 months under long term conditions (5°C±3°C) and for up to 6 months under accelerated conditions (25°C±2°C / 60%±5% RH), according to the ICH guidelines were provided. The temperature conditions chosen by the Applicant are in line with those authorized for the innovator Vidaza. This is considered acceptable. In addition, stability data for three batches at commercial size, for up to 24 months at long term conditions, and for up to 6 months under accelerated conditions were provided.

Photostability was investigated during forced degradation studies, on one batch of active substance. The active substance did not show signs of degradation after exposure to light without the protection of the primary packaging material. Hence, the active substance was not considered to be photosensitive. Stress conditions were as follows: acid, alkali, oxidation, thermal stress, UV and fluorescent light, humidity.

The stability indicating parameters tested were: description, identification (IR and XRD), water content (KF), related substances (HPLC), assay (HPLC) and microbial quality (microbial count and BET). On the batches at commercial scale, optical rotation and related substances (Method II) tests were also conducted. The analytical methods used were the same as for release.

The active substance was generally stable at accelerated and long-term conditions. All tested parameters were within the specifications

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 42 months at the proposed storage conditions in the proposed container.

With respect to all ongoing stability studies, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished medicinal product

Description of the product and 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 product is reconstituted with 4 mL of water for injections as mentioned in SmPC. After reconstitution each mL of suspension will contain 25 mg of azacitidine and 25 mg of mannitol.

The finished product azacitidine powder for suspension for injection (100 mg/vial) was developed to be identical to reference product Vidaza, currently marketed in Europe. The finished product manufacturer has performed a panel of comparative studies to demonstrate that the finished product is comparable to the reference product. The following quality attributes were investigated: (on neat finished product) description, water content, assay and related substances; (on reconstituted finished product) osmolality, pH, viscosity, particle morphology and particle size distribution. No differences in the physiochemical profiles of the test and reference products are claimed.

A comparison of the *in vitro* release of the active substance between the test and the reference product was conducted. The dissolution experiments were conducted in the flow-through cell with phosphate buffer pH 7.2 as dissolution medium. Quantification was conducted by HPLC. All batches of the test and reference products show complete dissolution within the first 10 minutes. All batches of the test and reference products show a difference of less than 10% of the mean release at all tested time-points.

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 **) does not provide guidance. 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. Therefore, the biowaiver for the BE studies is considered to be 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. All other excipients are commonly used in medicinal products and comply with pharmacopoeial standards, except for acetonitrile which is controlled according to adequate in-house specification.

The finished product is filled in a clear 30 mL Type I glass vial. The vials are closed with 20 mm grey chlorobutyl flurotec coated single slot rubber stoppers and aluminium seals with flip-off seals. The packaging materials 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.

Manufacture of the product and process controls

The finished product is manufactured by a single manufacturer. The process consists of a simple preparation of a bulk solution, followed by sterile filtration, filling and subsequent lyophilisation; it is considered a non-standard process.

A summary of the in-process information during manufacture was provided to confirm that the proposed Azacitidine powder for suspension for injection can be manufactured according to the proposals in the dossier. All process parameters as discussed in the pharmaceutical development section and verified during process validation were found to be within acceptable ranges and according to acceptance criteria. The description also included additional details related to the filters, and maximum acceptable holding times and holding temperatures of the bulk solution before filtration were clearly stated. Results from media fill runs demonstrated 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 (UV and HPLC), water content (Ph.Eur), uniformity of dosage units (weight variation) (Ph.Eur), particulate contamination (Ph.Eur), foreign particles, BET (Ph.Eur), sterility (Ph.Eur), assay (HPLC), related

substances (HPLC), residual solvents (GC), appearance of suspension, pH (Ph.Eur), syringeability, osmolality (Ph.Eur), reconstitution time, particle size distribution (Laser diffraction), particle morphology (Ph.Eur).

The maximum daily dose (MDD) for Azacitidine Mylan 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. Crystal morphology and PSD are the key parameters and are tested routinely to assure that each batch is similar to the originator.

Analytical methods were adequately described and validated. The limits of quantitation for the specified and unspecified impurities by the uHPLC method for related substances were established below the ICH Q3B identification threshold of 0.1%. This is acceptable. Forced degradation studies were performed in connection with the HPLC methods for assay and related substances (methods I, II and III). The highest degradations occurred under acidic and alkali conditions. Peak purity was investigated and mass balance was demonstrated. All methods are considered as stability indicating.

Batch analysis results from batches of each proposed batch size were presented. The tested batches correspond to the batches used for process validation. The batch analysis results originate from recent batches manufactured between January 2014 and June 2018, in line with all proposed batch sizes. All results comply with the proposed specifications. Overall, the results confirm 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 in the finished product specification. The information on the control of elemental impurities is satisfactory.

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.

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 for all proposed batch sizes for up to 36 months under long term conditions (25 ºC / 60% RH) and for up six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided for the 100 mg/vial powder for suspension.

The process validation batches were included in the stability study. All selected batches were packed in the primary packaging proposed for marketing.

Samples were tested for description, identification, water content, foreign particles, particulate matter, BET, sterility, assay, related substances (HPLC methods I, II and III), appearance of suspension, pH, syringeability, osmolality, reconstitution time, PSD, and particle morphology. The analytical procedures used are stability indicating. The finished product is generally stable in the proposed container packaging system. .Overall, the observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC. Compatibility data

provided for a reconstituted batch near the end of shelf life supported the in-use shelf life of the reconstituted product.

With respect to all ongoing stability studies, in accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

A photostability study has been performed on one batch of neat Azacitidine finished product in vials, as well as on 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. The finished product was hence not considered to be photosensitive.

Based on available stability data, the proposed shelf-life of 24 months and storage conditions as stated in the SmPC (section 6.3) are acceptable.

[1]6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union.

Adventitious agents

None of the components used in the manufacture of Azacitidine Mylan are of human or animal origin.

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. A major objection was raised during the evaluation of the procedure, regarding the *in vitro* comparative studies required to support the biowaiver of the bioequivalence studies. The requirements set up 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.

2.3. 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 Mylan manufactured by Mylan Ireland Limited 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 Mylan 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 Mylan in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Azacitidine Mylan 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.

2.4.3. 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.

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

2.5. Risk management plan

Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Haemorrhagic events (Bleeding related problems) • Infections
Important potential risks	None
Missing information	None

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Routine risk minimisation measures only.

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. 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.

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 Mylan 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.