27 June 2019
EMA/CHMP/445484/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Azacitidine Celgene

International non-proprietary name: azacitidine

Procedure No. EMEA/H/C/005300/0000

Note

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

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Administrative information

Name of the medicinal product:	Azacitidine Celgene
Applicant:	Celgene Europe BV Winthonlaan 6N 3526 KV Utrecht NETHERLANDS
Active substance:	AZACITIDINE
International Non-proprietary Name/Common Name:	azacitidine
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agents, pyrimidine analogues (L01BC07)
Therapeutic indication(s):	Azacitidine Celgene 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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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe BV submitted on 04 April 2019 an application for Marketing Authorisation (MA) to the European Medicines Agency (EMA) for Azacitidine Celgene, through the centralised procedure. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 January 2019.

The applicant applied for the following indication:

Azacitidine Celgene 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:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product

The application submitted is composed of administrative information with a letter from the MAH Celgene Europe BV allowing cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Vidaza authorised on 17 December 2008 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

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.

New active Substance status

The applicant indicated the active substance azacitidine contained in the above medicinal product to be considered as a known active substance.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Jorge Camarero Jiménez

The application was received by the EMA on	4 April 2019
The procedure started on	29 April 2019
The Rapporteur's first CHMP and PRAC Assessment Report was circulated to all CHMP members on	3 June 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 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 Celgene on	27 June 2019

2. Scientific discussion

2.1. Problem statement

Disease or condition

MDS (myelodysplastic syndrome) 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.

MDS encompasses a group of haematological disorders that is characterised by clonal haematopoietic stem cell disorder, usually of the granulocytic, erythroid or platelet lineage, that results in abnormalities in proliferation, differentiation and maturation of the myeloid lineage. This leads to one or more peripheral cytopenias and progressive bone marrow failure. As a result, patients with MDS are at risk for symptomatic anaemia, infection and bleeding.

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.

The diagnosis and classification of MDS can be based on two classification systems, the French-American-British (FAB) classification system and the WHO classification system (table 1).

Table 1 FAB and WHO classification systems for MDS

FAB	Blast count in bone marrow	Blast count in peripheral blood	WHO
Refractory anaemia (RA)	< 5%	≤ 1%	Refractory anaemia (RA)
	< 5%	≤ 1%	del(5q) syndrome
Refractory Anaemia with Ringed Sideroblasts (RARS)	< 5% with 15% ringed sideroblasts	≤ 1%	Refractory Anaemia with Ringed Sideroblasts (RARS)
	< 5%		Refractory Cytopenia with Multilineage Dysplasia (RCMD)
Refractory Anaemia with Excess Blasts (RAEB)	5-20	< 5	Refractory anaemia with excess blasts-1 (RAEB-1)
			Refractory Cytopenia with Multilineage Dysplasia and Ringed Sideroblasts (RCMD-RS)
	10-19		Refractory Anaemia with Excess Blasts-2 (RAEB-2)
Refractory Anaemia with Excess Blasts in Transformation (RAEB-T)	21-30	> 5	AML with multilineage dysplasia
AML	> 30		AML
Chronic MyeloMonocytic Leukaemia (CMMoL)	≤ 20	< 5	Myelodysplastic (WBC< $12x10^9$/l) Myeloproliferative disease (WBC > $12x10^9$/l)

The International Prognostic Scoring System issued in 1997 provides a method for evaluating clinical prognostic risk factors for patients with MDS. The 3 critical factors include risk-based cytogenetic subgroups (good, intermediate, and poor), bone marrow blast percentage and cytopenias. Patients are grouped into 4 risk categories based on total scores from these prognostic factors (table 2).

Table 2 IPSS for MDS - Prognostic risk based survival and AML evolution

	Total Score Value			
	0	0.5-1.0	1.5-2.0	≥ 2.5
Clinical outcome	Low	Intermediate-1	Intermediate-2	High
Overall Survival (median in years)	5.7	3.5	1.2	0.4
25% AML evolution (median in years)	9.4	3.3	1.1	0.2

Total Score Value is determined based on the combination of individual score of bone marrow blasts, karyotype and cytopenia

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. Otherwise, low-dose chemotherapy or standard combination chemotherapy may be used for the various subclasses of MDS but without a standard approach of care. Only intensive chemotherapy followed by allo HSCT was shown to result in improved survival in patients with Intermediate-2 or high risk MDS or AML that progressed from MDS (AML-MDS) when compared with non-intensive treatment or supportive care only (actuarial survival at 4 years of 26% vs. 10%).

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.

About the product

Azacitidine belongs to the group '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 application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.

Accordingly, the MAH of the reference product, Vidaza, has provided consent to allow access to Module 2 to Module 5 of the initial dossier and any subsequent post-marketing procedures submitted, assessed and approved. The complete assessment history of Vidaza is available on the EMA website.

The proposed indication for Azacitidine Celgene is the same as the approved indication for the reference product.

2.2. Quality aspects

Since this application is an informed consent of the Vidaza application, the quality data in support of the Azacitidine Celgene application are identical to the up-to-date quality data of the Vidaza dossier, which have been assessed and approved.

2.3. Non-clinical aspects

No non-clinical data have been submitted in the Azacitidine Celgene dossier. Since this application is an informed consent of the Vidaza application, the non-clinical data in support of the Azacitidine Celgene application are identical to the up-to-date non-clinical data of the Vidaza dossier, which have been assessed and approved.

2.3.1. Ecotoxicity / environmental risk assessment

An environmental Risk Assessment has been provided, which is identical to the one that was submitted for Vidaza.

Azacitidine Celgene is submitted as an informed consent application intended to be administered at the same dose levels as Vidaza and for the same indication as already approved in the EU. Based on the assumption that the product is to be substituted for the identical product Azacitidine Celgene, the approval of the product does not result in an increase of the total quantity of the active ingredients released into the environment.

2.4. Clinical aspects

No clinical data have been provided within this application. Since this application is an informed consent of the Vidaza application, the clinical data in support of the Azacitidine Celgene application are identical to the up-to-date clinical data of the Vidaza dossier, which have been assessed and approved by the CHMP.

Following the signal of Progressive Multifocal Leukoencephalopathy for Azacitidine - VIDAZA (EPITT ref. No. 19422), the PRAC has agreed that the MAH for Vidaza (Celgene) should submit by 28 August 2019, a cumulative review of all cases of progressive multifocal leukoencelopathy associated with azacitidine. The outcome of this post-authorisation commitment should be implemented in Azacitidine Celgene.

2.5. Risk Management Plan

2.5.1. Safety Specification

Table 3. Summary of the Safety Concerns

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

2.5.2. Pharmacovigilance Plan

Only routine risk pharmacovigilance activities are applicable. As part of routine pharmacovigilance activities, targeted questions have been developed in the current follow-up questionnaires for Haemorrhagic Events and Infections.

2.5.3. Risk Minimisation Measures

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

Table 4. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Haemorrhagic events	*SmPC* *Section 4.8 Undesirable effects: details on haemorrhagic ADRs.* *PL* *This document details the risks associated with azacitidine use, their symptoms, and any actions to be taken by the patient.* *Routine risk minimisation activities recommending specific clinical measures to address the risk:* *SmPC* *Section 4.2 Posology and method of administration: recommendations on dose adjustments and delay based on haematology laboratory values including platelet count, to reduce the risk.* *Section 4.4 Special warnings and precautions for use: dose recommendations and advice for monitoring of complete blood counts are provided. Warnings regarding thrombocytopenia and how to monitor this risk.* *Section 4.8 Undesirable effects: advice that patients should be monitored for signs and symptoms of*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	bleeding, particularly those with pre-existing or treatment-related thrombocytopenia. *Other routine risk minimisation measures beyond the Product Information:* *Legal status: prescription only medicine and treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents.*	
Infections	*<u>SmPC</u>* *Section 4.8 Undesirable effects: ADRs of infections, including necrotising fasciitis, are listed.* *<u>PL</u>* *This document details the risks associated with azacitidine use, their symptoms, and any actions to be taken by the patient.* *Routine risk minimisation activities recommending specific clinical measures to address the risk:* *SmPC* *Section 4.2 Posology and method of administration: recommendations on dose adjustments and delay based on haematology laboratory values including ANC, to reduce the risk.* *Section 4.4 Special warnings and precautions for use: dose recommendations and advice for monitoring of complete blood counts are provided. Warnings regarding neutropenia and how to monitor this risk. Warnings regarding necrotising fasciitis.* *Section 4.8 Undesirable effects: advice regarding management of infections is provided.* *Other routine risk minimisation measures beyond the Product Information:* *Legal status:* *Prescription only medicine and treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents.*	*None*

The submitted Risk Management Plan (version 15.0), is identical to the latest approved RMP for the reference product.

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

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

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. New Active Substance

The CHMP, based on the available data, considers that azacitidine is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Azacitidine is contained in the marketing authorisation Vidaza which was authorised in the European Union on 17 December 2008.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The Patient Information Leaflet for the reference product, Vidaza, was the subject of a user testing study, which was completed successfully in January 2008.

As the Patient Information Leaflet for Azacitidine Celgene is identical (with the exception of the product name) to that of the reference product, the user testing of the Patient Information Leaflet for the reference product can be taken to apply equally to Azacitidine Celgene.

3. Benefit-Risk Balance

The application has been submitted in accordance with Article 10c of Directive 2001/83/EC as amended (Informed consent Application) under automatic access to the centralised procedure.

Azacitidine Celgene is identical to Vizada, previously approved by the CHMP. The quality, non-clinical, efficacy and safety data for Azacitidine Celgene is therefore considered satisfactory and the benefit-risk profile for Azacitidine Celgene is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Azacitidine Celgene is not similar to Revlimid, Dacogen, Rydapt, Mylotarg or Vyxeos within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

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 Celgene is favourable in the following indication:

Azacitidine Celgene 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 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.