CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214120Orig1s000

OTHER REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

Consult Memorandum

Date:	08/17/2020
To:	Emily Jen FDA/OC/CDER/OND/OOD/DHMI
From:	Jacqueline M Cleary CDRH/OPEQ/OHT7/DIHD/IMFB
Through:	Ying Katelin Mao (Branch chief) and Lea Carrington (Division Director)
Subject:	NDA 214120
Drug Name:	Azacitidine
Drug Sponsor	Celgene Corp
Biomarker(s):	Minimal Residual Disease (MRD)
Device Name:	Laboratory Developed Test
Device Sponsor:	(b) (4)
CDRH Tracking Number:	ICC2000416
Related Submissions:	

I. BACKGROUND and PURPOSE

(b) (4)

CDER requested CDRH to review the analytical validity of the assay used to determine MRD.

The clinical trial (NCT01757535) was an international, multicenter, placebo-controlled, Phase 3 study with a double-blind, randomized, parallel-group design which evaluated the safety and efficacy of Azacitidine versus placebo as maintenance therapy in AML patients. Patients were enrolled with de novo acute myelogenous leukemia (AML), AML secondary to prior diagnosis of myelodysplastic syndromes (MDS), or chronic myelomonocytic leukemia (CMML); the patients were aged 55 years or older, and had achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) within 4 months +/- 7 days after intensive induction chemotherapy with or without consolidation therapy. The decision about induction and consolidation therapy regimens was an investigator choice prior to study enrollment. Patients were not candidates for transplant at the time of randomization, which included patients who were not eligible for hematopoietic stem cell transplantation (HSCT), who did not have a transplant donor, or who chose not to proceed to HSCT.

Patients who achieved a CR/CRi after completion of intensive induction therapy with or without consolidation were administered ONUREG 300 mg or placebo orally on Days 1 through 14 of each 28-day cycle. In the event of disease relapse (5% to 15% blasts in peripheral blood or bone marrow), the

dose schedule was extended to 21 days of repeated 28-day treatment cycles. Treatment continued until disease progression (more than 15% blasts were observed in peripheral blood or bone marrow) or until unacceptable toxicity.

Specifically, the CDER seeks advice on:

1. Please assess the analytical validity of the assay used to assess MRD in CC-486-AML-001. The document provided for review of the device is Module 5.3.1.4 (b) (4)

II. BIOMARKER/ANALYTE

(b) (4) .

III. DEVICE USE IN THE TRIAL

The assay applied for the analyses has been designed (b) (4)

(b) (4)

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(b) (4)

VII. Final Recommendation from CDRH to CDER:

We think it is important to note (b) (4) Many modifications have been made to the original assay that was validated (b) (4) The current version of the assay used in the clinical trial has not been analytically validated. CDRH recommends that the sponsor provide the analytical validation performance data to support the analytical validity of a reliable result being obtained (b) (4) (b) (4) for the MRD measurement in patients with AML in remission as part of the AML 001 study.

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/s/

RACHEL S MCMULLEN
08/17/2020 04:50:39 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD, 20993

CLINICAL OUTCOME ASSESSMENT (COA) REVIEW MEMORANDUM

RE: NDA 214120

FROM: Julia Ju, PharmD., PhD.
Clinical Outcome Assessment (COA) Reviewer
Division of Clinical Outcome Assessment (DCOA)

Elektra Papadopoulos, MD. MPH.
Acting Division Director
DCOA

SUBJECT: Division of Hematologic Malignancies 1 consult to DCOA requesting review of the FACIT-Fatigue scale used in trial CC-486-AML-001

DRUG SPONSOR: Celgene

COA TRACKING NUMBER: C2020149

Please check all that apply:

☐ Rare Disease/Orphan Designation
☐ Pediatric

We are closing this consult request with this review memo since the review division and sponsor have both agreed (b) (4) for the FACIT-F and there was also no validity or reliability information to review in the submission. The clinical outcome assessment (COA) consult request was filed in DARRTS by Division of Hematologic Malignancies 1 (DHM1) on April 10, 2020 (DARRTS Reference ID: 4591366) for NDA 214120 regarding azacitidine (b) (4)

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/s/

JING JU
08/17/2020 02:16:02 PM

ELEKTRA J PAPADOPOULOS
08/17/2020 02:25:37 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 14, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214120
Product Name and Strength:	Onureg (azacitidine) Tablets, 200 mg, 300 mg
Applicant/Sponsor Name:	Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb (Celgene)
OSE RCM #:	2020-419-2
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on August 12, 2020 for Onureg. We review the revised container labels for Onureg (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] The revisions are also in response to the proprietary name request decision letter stating that the proprietary name, Onureg is conditionally acceptable. (b) (4)

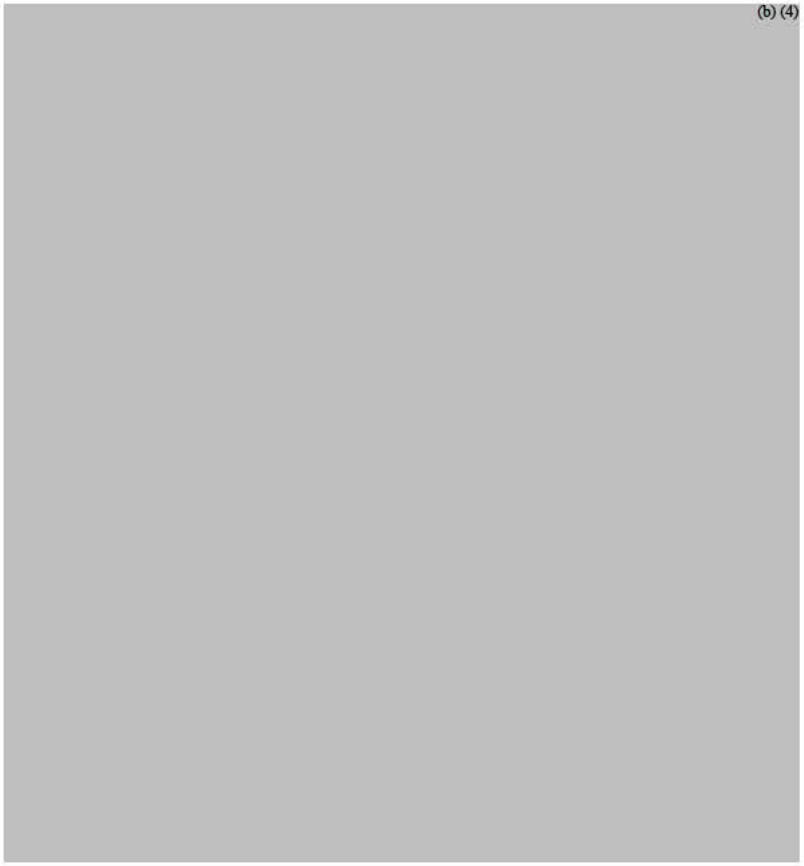
2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Iverson N. Label and Labeling Review for Onureg (NDA 214120). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 29. RCM No.: 2020-419-2.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 12, 2020

Container labels



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/s/

NICOLE F IVERSON
08/14/2020 04:01:42 PM

HINA S MEHTA
08/17/2020 11:15:54 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 3, 2020
To:	Rachel McMullen, MPH, MHA Senior Regulatory Project Manager **Division of Hematologic Malignancies I (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachel Conklin, MS, RN **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (azacitidine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214120
Applicant:	Celgene Corporation

1 INTRODUCTION

On March 3, 2020, Celgene Corporation submitted for the Agency's review an original New Drug Application (NDA) 214120 for TRADENAME (azaciditine) tablets. The proposed indication for TRADENAME (azaciditine) is (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 1 (DHM1) on April 14, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (azaciditine) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (azaciditine) tablets PPI received on March 4, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 28, 2020.
- Draft TRADENAME (azaciditine) tablets Prescribing Information (PI) received on March 3, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 28, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
08/03/2020 02:32:24 PM

RACHAEL E CONKLIN
08/03/2020 03:05:10 PM

SHARON R MILLS
08/03/2020 03:14:23 PM

LASHAWN M GRIFFITHS
08/03/2020 03:35:29 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 07/30/20

To: Rachel McMullen, Regulatory Project Manager, DHM1

Stacy Shord, Associate Director for Labeling, OOD

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, Team Leader, OPDP

Subject: OPDP Labeling Comments for [TRADENAME] (azacitidine) tablets, for oral use

NDA: 214120

In response to DHM1's consult request dated April 9, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA submission for [TRADENAME] (azacitidine) tablets, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling emailed to OPDP on July 28, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

Section	Statement from Draft (if applicable)	OPDP Comment
6.1 Clinical Trials Experience	(b) (4) [redacted]	Is it standard to include (b) (4) [redacted] OPDP is concerned that inclusion (b) (4) [redacted] and we suggest considering deletion of this information. However, we defer to the review team as to whether this information is considered informative for prescribers and should be retained.
14 CLINICAL STUDIES	"A subgroup analysis showed consistency in the OS benefit for patients in either CR or CRi."	OPDP would like to confirm that the study was adequately powered to show consistency of effect in these subgroups.
14 CLINCIAL STUDIES	(b) (4) [redacted]	(b) (4) [redacted] We defer to the review division regarding the appropriateness of inclusion of this information in the labeling.

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RACHAEL E CONKLIN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 29, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214120
Product Name and Strength:	azacitidine* Tablets, 200 mg, 300 mg
Applicant/Sponsor Name:	Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb (Celgene)
OSE RCM #:	2020-419-1
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, (b) (4) received on June 15, 2020 for azacitidine. We reviewed the revised container labels, (b) (4) (b) (4) for azacitidine (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] In addition, we note the Applicant (b) (4)

2 CONCLUSION

The revised container labels, (b) (4) are unacceptable from a medication error perspective. We acknowledge revisions (b) (4)

* The proposed proprietary name, Onureg was withdrawn by the Applicant and the proposed proprietary name submission is currently under review.

[a] Iverson N. Label and Labeling Review for azacitidine (NDA 214120). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 27. RCM No.: 2020-419.

[redacted] We note the labels and labeling contain the word, [redacted] which is inconsistent with current terminology recommended in labeling for hazardous drugs. We also note [redacted]

3 RECOMMENDATIONS FOR CELGENE CORPORATION, A WHOLLY OWNED SUBSIDIARY OF BRISTOL-MYERS SQUIBB (CELGENE)

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels & Carton Labeling)

1. We acknowledge that you have reviewed approved product labeling. However, we recommend revising the word, [redacted] to "hazardous" on the labels and labeling to reflect alignment with current terminology recommended in labeling for hazardous drug. Revise [redacted] to "**CAUTION: Hazardous Agent**".

B. Container labels

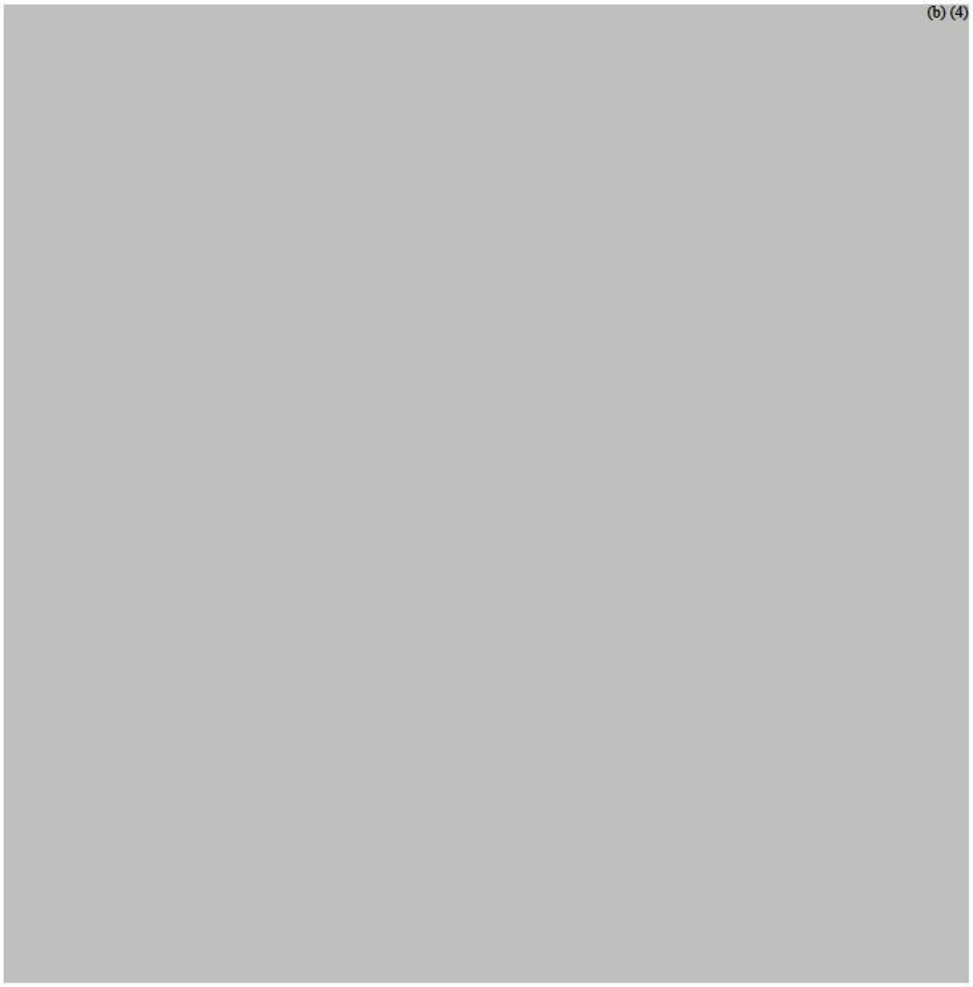
1. We note revisions to the product codes in the National Drug Code (NDC) number [redacted]

C. [redacted]

1. [redacted]

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 15, 2020

Container labels



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/s/

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HINA S MEHTA
06/30/2020 01:14:34 PM

CLINICAL INSPECTION SUMMARY

Date	June 30, 2020
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Emily Jen, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader (Acting) R. Angelo de Claro, M.D., Director Rachel McMullen, MPH, MHA, Regulatory Project Manager Division of Hematology Malignancy 1 (DHM1/OOD)
NDA	214120
Applicant	Celgene Corporation
Drug	Onureg™ (azacitidine)
NME	No (505b2)
Division Classification	Cytotoxic cytosine nucleoside analogue, via induction of antineoplastic activity
Proposed Indication	(b) (4)
Consultation Request Date	March 16, 2020 (Priority Review)
Summary Goal Date	July 6, 2020
Action Goal Date	September 3, 2020
PDUFA Date	September 3, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor, Celgene Corporation, was inspected in support of NDA 214120. The sponsor appeared to maintain adequate oversight of the clinical trials. Based on the results of the inspection, Study CC-486-AML-001 appears to have adequate oversight by the sponsor. An inspection assignment was issued and plans to conduct these GCP inspections were scheduled by the Office of Regulatory Affairs (ORA). The COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, inspections of Andrew Wei, M.D. (Australia Site 500) and Christopher Pocock, M.D. (UK Site 902) were not conducted. Remote data investigation of source records from Drs. Wei and Pocock by ORA was not feasible due to local restriction, to obtain remote access at source records. Therefore, OSI is unable to determine if Study CC-486-AML-001 at both Dr. Andrew Wei and Dr. Christopher Pocock sites was conducted adequately, and whether the study data from those sites are reliable in support of the proposed indication.

II. BACKGROUND

Azacitidine (5-azacytidine, CC-486), primarily excreted by the kidneys, is a chemical analogue of the cytosine nucleoside used in DNA and RNA. Azacitidine may induce antineoplastic activity by inhibition of DNA methyltransferase at low doses and cytotoxicity through incorporation into RNA and DNA at high doses.

The sponsor proposes azacytidine [redacted] (b) (4)

A single study, Study CC-486-AML-001, will form the basis for the regulatory decision-making process for this application.

Study CC-486-AML-001

Study CC-486-AML-001 was a multicenter, placebo-controlled, Phase 3 study with a double-blind, randomized, parallel-group design in subjects with de novo AML or AML secondary to prior diagnosis of myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). The study consisted of 3 phases: the Pre-randomization Phase (Screening Phase), the Treatment Phase, and the Follow-up Phase. The study was amended to include an Extension Phase (EP).

Best supportive care may have been used in combination with study treatment as deemed necessary in both treatment groups. These supportive treatments may have included the following: red blood cell (RBC) and platelet transfusions, use of erythropoiesis stimulating agents (ESAs), antibiotic, antiviral, and antifungal therapy, nutritional support, and granulocyte colony stimulating factors (G-CSFs) for subjects experiencing neutropenic infections.

The primary study objective was to evaluate whether maintenance therapy with CC-486 improved overall survival (OS) compared with placebo in subjects with acute myeloid leukemia (AML), over 55 years of age, who had achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) after induction with intensive chemotherapy with or without consolidation chemotherapy.

The primary efficacy endpoint was overall survival. This endpoint was defined as time from randomization to death from any cause.

Study CC-486-AML-001 was conducted at 147 investigational sites in Europe, North America, Asia, and South America. The first subject first visit date was May 10, 2013. The data cutoff date was July 15, 2019.

Of the 555 study patients screened, a total of 472 subjects were randomized to treatment. There were 238 subjects randomized in the CC-486 group and 234 study patients in the placebo group.

Compared to placebo, randomized patients on azacitidine (CC-486) most frequently reported the following treatment-emergent adverse events: nausea, vomiting, diarrhea, neutropenia, constipation, thrombocytopenia, and fatigue.

The most frequently reported serious adverse events for azacytidine (CC-486) relative to placebo were febrile neutropenia, pneumonia, sepsis, and fever.

III. RESULTS

Celgene Corporation [Sponsor]
86 Morris Avenue
Summit, NJ 07901

Inspection dates: May 26 to June 3, 2020

This inspection evaluated compliance with the sponsor's responsibilities concerning the conduct of Study CC-486-AML-001 which had 472 enrolled study subjects.

The inspection included review of organizational charts, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. Monitoring files for the following study sites were evaluated and found to be adequate: 401, 902, 972, 252, 530, 652, 860, and 500. Monitoring was conducted frequently, and 100% source data verification was performed. Underreporting of significant adverse events to the Agency was not found in this sponsor audit. A noncompliant site, Site 401 (e.g., delay in timely sign offs of laboratory documents), was eventually brought into compliance.

A Form FDA 483 was not issued at the end of the study inspection. In general, the sponsor appeared to be in compliance with Good Clinical Practice. Clinical trial oversight and monitoring by the sponsor appeared to be adequate.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

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KASSA AYALEW
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 27, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214120
Product Name, Dosage Form, and Strength:	azacitidine* Tablets, 200 mg, 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb (Celgene)
FDA Received Date:	March 3, 2020, March 20, 2020, and May 14, 2020
OSE RCM #:	2020-419
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

* The proposed proprietary name, Onureg was withdrawn by the Applicant and the proposed proprietary name submission is currently under review.

1 REASON FOR REVIEW

As part of the approval process for NDA 214120 azacitidine tablets this review evaluates the proposed container label, (b) (4) Prescribing Information (PI) and Patient Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Celgene submitted a 505(b)(1) application to obtain marketing approval of azacitidine tablets. Azacitidine is proposed (b) (4)

We performed a risk assessment of the proposed container labels, (b) (4) (b) (4) Prescribing Information (PI) and Patient Information for azacitidine tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note (b) (4)

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we note that the PI and Patient Information lacks clarity on the recommended dosage, administration, and storage instructions. We also noted the use of sequential product codes in the National Drug Code (NDC) numbers. For the Applicant, we note the labels and labeling lack clarity in the package type, dosage form, product codes in the NDC numbers, strength, and special handling precautions. We also note lack of clarity of the administration instructions, a graphic in front of the proprietary name, prominence of the Rx only statement, and inconsistency in the terminology used for the recommended dosage. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We have identified areas in the proposed PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Celgene to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Highlights of Prescribing Information

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[a] McMullen R. FDA Communication: Information Request for Azacitidine (NDA 214120). Silver Spring (MD): FDA, CDER, OOD, DHM1 (US); 2020 MAY 05. \\cdsesub1\evsprod\nda214120\0008\m1\us\resp-to-fda-req-dated-05may2020.pdf

1. We note your submission received April 30, 2020 requesting a withdrawal for the proposed proprietary name "Onureg". Replace the proprietary name "Onureg" in the Prescribing Information with "Tradename" as a placeholder until a proprietary name is found conditionally acceptable.
2. Revise the statement, [redacted] (b) (4) to "Recommended dosage: 300 mg taken orally once daily on Days 1 to14 of each28-day cycles."
3. ONUREG should not be split or cut. To prevent administration errors, consider including the statement, "Swallow tablets whole. Do not cut, crush, or chew the tablets."

B. Prescribing Information

1. Dosage and Administration Section

   a. Section 2.1 *Recommended Dosage*

      i. Revise the statement, [redacted] (b) (4) to "The recommended dosage of ONUREG is 300 mg orally once daily on Days 1 to 14 of each 28-day cycles."

   b. Section 2.2 *Administration*

      i. Onureg should not be split or cut and the statement lacks clarity. To prevent administration errors, revise the statement, [redacted] (b) (4) to "Swallow tablets whole. Do not cut, crush, or chew the tablets."

      ii. It is not clear within how many hours after a dose is missed that a patient can still take the dose. It is recommended to clarify this instruction to avoid potential overdoses.

      iii. Since this statement is in the Prescribing Information, [redacted] (b) (4) it would be important to indicate if Onureg can be substituted for other Azacitidine products to help mitigate

the risk of substitution errors. Thus, we recommend including a statement to indicate if Onureg is substitutable.

iv. ONUREG is a hazardous drug and requires special handling procedures. Therefore, we recommend including the statement, "ONUREG is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

c. Section 2.4 *Dosage Adjustment for Adverse Reactions.*

i. For the table containing dosage adjustments due to adverse reactions lacks clarity on resumption of dose. We recommend modifying the statement to state "resume at reduced dose of 200 mg" throughout the table.

2. How Supplied/Storage and Handling Section

a. (b) (4) *How Supplied*

i. As currently presented, the product codes *(middle 3-4 digits)* in the NDC numbers (b) (4) We recommend revising the product code in the NDC numbers (b) (4)

b. (b) (4) *Storage*

i. Users are advised to store ONUREG tablets supplied in bottles in the original packaging; however the two desiccant canisters, should remain in place. To minimize the risk of administering a degraded product, we recommend revising the storage to, "Store bottles at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Keep bottle tightly closed. Store and dispense in the original bottle (with two desiccant canisters)."

c. (b) (4) Handling and Disposal

i. Revise the word, (b) (4) to "hazardous" to reflect alignment with terminology recommended in labeling for hazardous drugs.

3. Section 17 Patient Counseling Information

    a. Administration and Storage Instructions

        i. Onureg should not be split or cut and the statement lacks clarity. To prevent administration errors, revise the statement, (b) (4) to "Swallow tablets whole. Do not cut, crush, or chew the tablets."

C. Patient Information

1. We note your submission received April 30, 2020 requesting a withdrawal for the proposed proprietary name "Onureg". Replace the proprietary name "Onureg" in the Patient Information with "Tradename" as a placeholder until a proprietary name is found conditionally acceptable.

2. How should I take ONUREG

    a. Onureg should not be split or cut and the statement lacks clarity. To prevent administration errors, revise the statement, (b) (4) to "Swallow tablets whole. Do not cut, crush, or chew the tablets."

    b. Users are advised to store the tablets supplied in bottles in the original packaging; however the two desiccant canisters, should remain in place. To minimize the risk of administering a degraded product, we recommend including the statement, "Keep the bottles tightly closed with both desiccant cannisters inside. Do not to eat the desiccant cannisters."

4.2 RECOMMENDATIONS FOR CELEGENE CORPORATION

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. We note your submission received April 30, 2020 requesting a withdrawal for the proposed proprietary name "Onureg". Replace the proprietary name "Onureg" on all container labels and carton labeling with "Tradename" as a placeholder until a name is found conditionally acceptable.

2. The placement of the graphic in front of the first letter "O" in the proprietary name is prominent. Placement of the graphic in front of the first letter in the proprietary name competes with readability of the proprietary name, which may

lead to misinterpretation of the proprietary name as "OOOONUREG" or "Conureg". We recommend moving or decreasing the prominence of the graphic in front of the proprietary name as it may lead to misinterpretation of the proprietary name.

3. ONUREG is a hazardous drug; however the principal display panel of the carton labeling does not convey this information. Hazardous products require special handling procedures. We recommend adding the statement, "**CAUTION: Hazardous Agent**" in bold red font on the principal display panel of the labels and labeling.
4. The Rx Only statement appears prominent in bold font. Decrease the prominence by debolding the Rx Only statement.
5. The font color (blue) of the 200 mg strength is difficult to read against the orange background and overlaps with the font color (blue) used for the proprietary name. Lack of adequate differentiation may contribute to product selection errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. Revise the font color of the 200 mg strengths to improve readability and the color does not overlap with any other colors utilized in highlighting the strengths.
6. To ensure consistency with the terminology in the Prescribing Information, revise the recommended dosage statement from, (b) (4) to "Recommended Dosage: See Prescribing Information."
7. As currently presented, the product codes (b) (4) Revise the product code in the NDC numbers (b) (4)

B. Container Labels

1. To minimize the risk of administering a degraded product, we recommend revising and bolding the storage statement on the container labels to, **"Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to**

86°F) [See USP Controlled Room Temperature]. Keep bottle tightly closed. Dispense in the original bottle (with two 1 g desiccant canisters)."

2. If space permits, consider adding the statements, "Swallow tablets whole. Do not cut, crush, or chew the tablets." on the principal display panel of the container labels. We recommend this revision to mitigate the risk of product administration errors.

3. The linear barcode is presented in a horizontal position on the container label. Barcodes placed in a horizontal position may not scan due to container curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode. Reorient the linear barcode on the container label to a vertical position to improve the scannability of the barcode.

(b) (4)

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for azacitidine received on March 3, 2020 from Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb (Celgene).

Table 2. Relevant Product Information for azacitidine	
Initial Approval Date	N/A
Active Ingredient	azacitidine
Indication	(b) (4) [redacted]
Route of Administration	Oral
Dosage Form	Tablets
Strength	200 mg, 300 mg
Dose and Frequency	The recommended (b) (4) dose is 300 mg orally once daily on Day 1 through Day 14 of repeated 28-day treatment cycles.
How Supplied	Bottles of 14 with two desiccant cannisters • 200 mg • 300 mg (b) (4) [redacted]
Storage	Bottles • Store bottles at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Keep bottle tightly closed. Store in the original bottle (with two desiccant canisters). (b) (4) [redacted]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 14, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Onureg. Our search did not identify any previous label and labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following azacitidine labels and labeling submitted by Celgene.

- Container label received on March 20, 2020
- (b) (4) labels received on March 20, 2020
- (b) (4) labeling received on March 20, 2020
- Prescribing Information (Image not shown) received on March 3, 2020, available from \\cdsesub1\evsprod\nda214120\0001\m1\us\proposed.docx

G.2 Label and Labeling Images

Container label

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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06/01/2020 10:33:22 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memorandum

Date: May 26, 2020

Reviewer: Connie Cheng, PharmD, BCOP
Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Team Leader: Afrouz Nayernama, PharmD
DPV II

Division Director: S. Christopher Jones, PharmD, MPH, MS
DPV II

Subject: QT prolongation

Application Type/Number:

Oral azacitidine (b) (4) (CC-486)	Vidaza® (azacitidine)
NDA 214120	NDA 050794
	NDA 208216
	ANDA 201537
	ANDA 204949
	ANDA 207234
	ANDA 207475
	ANDA 207518
	ANDA 209540
	ANDA 210748

OSE RCM #: 2020-828

EXECUTIVE SUMMARY

This memorandum provides a high-level analysis of cardiac adverse events related to QT prolongation reported with azacitidine in the FDA Adverse Event Reporting System (FAERS) and the applicant's periodic safety report (PSR). We further provide a sub-analysis of more selective, relevant preferred terms (PTs), including *electrocardiogram QT prolonged and torsade de pointes* (TdP). In anticipation of the non-New Molecular Entity (non-NME) New Drug Application (NDA) review of the oral azacitidine (b) (4) formulation (CC-486), the Division of Hematology Malignancies 1 (DHM1) and the Division of Clinical Pharmacology I (DCP I) requested the Division of Pharmacovigilance II (DPV II) provide a high-level summary of postmarketing safety data for QT prolongation with the existing injectable formulation, Vidaza® (azacitidine). Of note, DCP I acknowledged that no formal concentration-QT assessment has been conducted with Vidaza® (azacitidine). (b) (4)

DPV II identified 135 FAERS cases that reported cardiac related PTs with azacitidine use. The majority of these events were consistent with the Vidaza® product label and the cases evaluated by the applicant. Most of these cases reported concomitant administration of medications that are associated with cardiotoxicity and/or confounding medical conditions, including cardiac disorders. Additionally, 14 of the 135 FAERS cases reported *electrocardiogram QT prolonged* or TdP as a PT, or QTc value greater than 450 milliseconds (ms). The severity of the event was evidenced by the QT/QTc interval exceeding 500 ms or presence of grade 3-4 QT prolongation per Common Terminology Criteria for Adverse Events (CTCAE) in nine of the 14 cases (64%). However, the majority of these cases, including those with a fatal outcome (n=6), reported administration of azacitidine in combination with other antineoplastic agents. These cases also involved critically ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities, and concomitant medications that are associated with QT prolongation. The applicant's PSR data analysis of QT effect was consistent with the FAERS data.

We recognize the presence of confounding factors in most cases from the FAERS database and the applicant's PSR, and general limitations of spontaneous postmarketing data that prevent us from establishing or excluding a causal association between azacitidine and QT prolongation. Although we are unable to determine to what extent QT prolongation is attributed to other risk factors, we also cannot determine the contributory role, if any, of azacitidine to QT prolongation and other reported cardiac events in these postmarketing cases. (b) (4)

1 INTRODUCTION

This memorandum provides a high-level analysis of cardiac adverse events related to QT prolongation reported with azacitidine in the FDA Adverse Event Reporting System (FAERS) and the applicant's periodic safety report (PSR). We further provide a sub-analysis of more selective, relevant preferred terms (PTs) including *electrocardiogram QT prolonged and torsade de pointes* (TdP). In anticipation of the non-New Molecular Entity (non-NME) New Drug Application (NDA) review of the oral azacitidine (b) (4) formulation (CC-486), the Division of Hematologic Malignancies 1 (DHM1) and the Division of Clinical Pharmacology I (DCP I) requested the Division of Pharmacovigilance II (DPV II) provide a high-level summary of postmarketing safety data for QT prolongation with the existing injectable formulation, Vidaza® (azacitidine). Of note, DCP I acknowledged that no formal concentration-QT assessment has been conducted with Vidaza® (azacitidine).[1] (b) (4)

1.1 REGULATORY HISTORY

Vidaza® (azacitidine)

FDA approved Vidaza® (NDA 050794, azacitidine), a nucleoside metabolic inhibitor, on May 19, 2004. It is indicated for the treatment of patients with the following FAB myelodysplastic syndrome (MDS) subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL). It is noteworthy that FDA approved two routes of administration for Vidaza®, including intravenous (IV) infusion and subcutaneous (SC) injection.[2]

Oral azacitidine (b) (4) formulation (CC-486)

Celgene, the applicant of the oral azacitidine (b) (4) formulation, CC-486 (NDA 214120), and Vidaza®, is requesting a priority review designation for this non-NME NDA. Notably, azacitidine received orphan drug designation approval for the treatment of acute myeloid leukemia (AML) on June 18, 2008.[3] The proposed indication for this non-NME NDA is (b) (4) [1,3] The Prescription Drug User Fee Act (PDUFA) goal date for this non-NME NDA review is September 3, 2020.

1.2 RELEVANT U.S. PRODUCT LABELING

The Vidaza® label does not contain any data regarding QT prolongation. However, labeled cardiac adverse events for Vidaza® include *atrial fibrillation*, *cardiac failure*, *cardiac failure congestive*, *cardiorespiratory arrest*, and *congestive cardiomyopathy* under the *Adverse Reactions in Clinical Trials* section (6.1).[2]

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV II searched the FDA Adverse Event Reporting System (FAERS) database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	April 23, 2020
Time period of search	May 19, 2004† - April 22, 2020
Search type	FBIS – Quick Query
Product terms	Product active ingredient – azacitidine
MedDRA search terms (Version 22.1)	Standardised MedDRA Query (SMQ): *Torsade de pointes/QT prolongation* – Narrow Preferred Terms (PT): *Cardiac arrest, Cardiac death, Cardiac fibrillation, Cardio-respiratory arrest, Electrocardiogram repolarization abnormality, Sudden cardiac death, Sudden death, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia*
* See **Appendix A** for a description of the FAERS database. † U.S. approval date	

2.2 SEVERITY ASSESSMENT OF QT PROLONGATION

DPV II characterized the severity of QT prolongation reported in FAERS cases according to the Common Terminology Criteria for Adverse Events (CTCAE) Grade 1-4 electrocardiogram QT corrected (QTc) interval prolonged. **Table 2** lists the severity grading criteria.[4]

Table 2. Classification of Electrocardiogram QTc Interval Prolonged per CTCAE Criteria	
Grade	***Description***
1	Average QTc 450 - 480 ms
2	Average QTc 481 - 500 ms
3	Average QTc ≥ 501 ms; > 60 ms change from baseline
4	TdP; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia
Abbreviations: ms = milliseconds; TdP = torsade de pointes	

2.3 APPLICANT DATA

DPV II screened the following PSR for the applicant's assessment of QT prolongation with azacitidine use:[5]

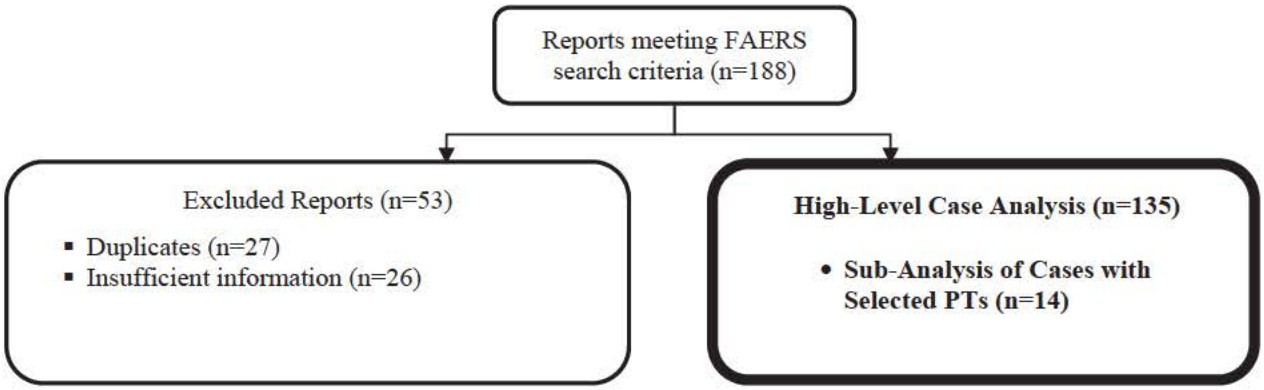
- Periodic Safety Update Report (PSUR) for Vidaza (NDA 050794), Reporting Period: May 19, 2018 – May 18, 2019

3 RESULTS

3.1 FAERS Case Selection

The FAERS search strategy in **Table 1** retrieved a total of 188 reports of cardiac events with azacitidine use. After excluding a total of 53 reports that were duplicates (n=27) or did not provide patient-specific information (n=26), 135 cases remained for further high-level analysis (see **Figure 1**). It is noteworthy that 25 of the 26 cases with insufficient information were reported in published clinical studies. Additionally, 18 of the 25 cases reported azacitidine was administered in combination with other antineoplastic agents.

Figure 1. FAERS Case Selection



3.2 Overall FAERS Assessment of Cases Reporting Cardiac Events with Azacitidine

For the purpose of this memo, we did not apply a case definition or causality assessment. **Table 3** summarizes the case characteristics for 135 cases with relevant cardiac events reported with azacitidine.

Table 3. Descriptive Characteristics of Cardiac Events Reported with Azacitidine Use, Received by FDA from May 19, 2004 through April 22, 2020 (N=135)

Age (years)	
Mean	70
Median	71
Range	1-96
Not reported	13
Sex	
Male	91
Female	41
Not reported	3
Country	
United States	38
Foreign	97

Table 3. Descriptive Characteristics of Cardiac Events Reported with Azacitidine Use, Received by FDA from May 19, 2004 through April 22, 2020 (N=135)	
Report type	
Expedited	131
Non-expedited	1
Direct	3
Time to onset from first azacitidine dose (days)	
Mean	127
Median	71
Range	0 (same day) – 728
Not reported	24
Serious outcomes*	
Death	107
Life-threatening	34
Hospitalization	78
Disability	3
Other serious	48
Indications for azacitidine use	
ALL	1
AML	51
AML/MDS	1
CMMoL	3
MDS	61
Multiple myeloma	1
NSCLC	1
T-cell lymphoma	1
Unspecified leukemia	2
Not reported	13
Azacitidine administered as monotherapy	
No	61†
Yes	32
Not reported	42

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case can have more than one serious outcome.
† 42 of these 61 cases reported concomitant antineoplastic therapies that are labeled for cardiotoxicity or QT prolongation.
Abbreviations: ALL=acute lymphoblastic leukemia, AML=acute myeloid leukemia, CMMoL=chronic myelomonocytic leukemia, MDS=myelodysplastic syndrome, NSCLC=non-small cell lung cancer

Table 4 summarizes the presence of confounding concomitant medications that are labeled for cardiotoxicity, QT prolongation, or electrolyte imbalance. Confounding medications were identified in 84 cases. This information was not provided in 43 cases. The remaining eight cases did not report relevant concomitant medications; however, these cases were confounded by a medical history, comorbidities, or did not report sufficient information to assess for risk factors.

Table 4. Presence of Confounding Concomitant Medications Among FAERS Cases of Cardiac Events with Azacitidine from May 19, 2004 through April 22, 2020 (N=84)	
Medication	**Number of Cases***
All-trans-retinoic acid (ATRA)	1
Antiarrhythmics	3
Anthracyclines	4
Azithromycin	2
Azole antifungals	23
Cyclophosphamide	2
Digoxin	1
Diuretics	27
Erythropoietin	4
Escitalopram	1
Everolimus	2
Fluoroquinolones	15
Gemtuzumab	1
Gilteritinib	2
Glasdegib	3
Histone deacetylase (HDAC) inhibitors	5
Immune checkpoint inhibitors	2
Ivosidenib	3
Lenalidomide	15
Ondansetron	11
Ranitidine	1
Raloxifene	1
Risperidone	1
Rituximab	1
Verapamil	1
* Each case may report one or more confounding medication.	

Table 5 summarizes the presence of confounding medical conditions that may be an independent predisposing factor for cardiotoxicity. Confounding comorbidities were identified in 101 cases. Seventy-one of these 101 cases were also confounded by concomitant medications. The medical history was not provided in 28 cases. The remaining six cases did not report confounding medical history or comorbidities; however, these cases were confounded by concomitant medications or did not report sufficient information to assess for risk factors.

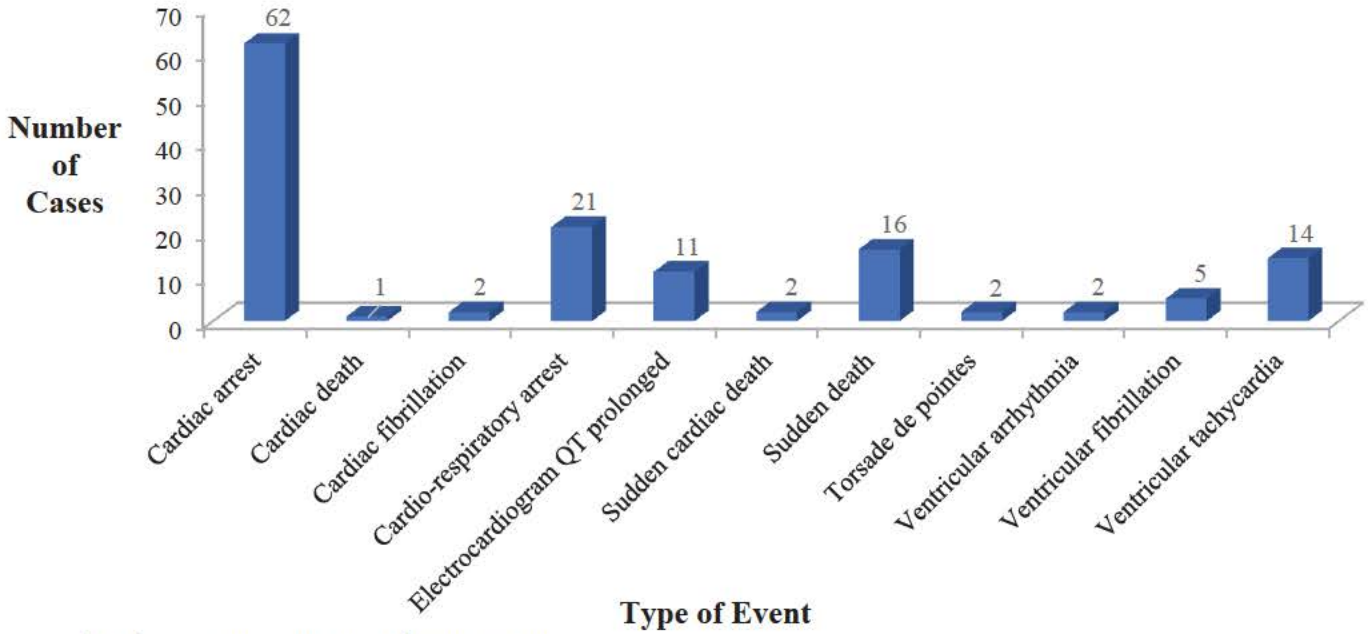
Table 5. Presence of Confounding Comorbidities Among FAERS Cases of Cardiac Events with Azacitidine from May 19, 2004 through April 22, 2020 (N=101)	
Medical History/Comorbidity	**Number of Cases***
Cardiac disorder	**56***
Arrhythmia	18
Cardiac condition NOS	5
Cardiac failure or CHF	14

Table 5. Presence of Confounding Comorbidities Among FAERS Cases of Cardiac Events with Azacitidine from May 19, 2004 through April 22, 2020 (N=101)	
Medical History/Comorbidity	**Number of Cases***
Cardiomyopathy	5
Coronary artery disease	25
Heart valve disease	7
History of ECG abnormality/QT prolongation	4
Deep vein thrombosis/pulmonary embolism	4
Disease progression	9
Disseminated infection	5
Electrolyte abnormality	13
Hemorrhage†	10
Multi-system organ dysfunction/failure	24
Sepsis/septic shock	13

* Each case may report more than one medical condition or cardiac disorder.
† Reported hemorrhagic events involved brain, gastrointestinal tract, lung, rectum.
Abbreviations: NOS = not otherwise specified; CHF = congestive heart failure; ECG = electrocardiogram

Figure 2 shows the reported cardiac events or PTs among the 135 cases retrieved from the FAERS search strategy described in **Table 1**. The majority of the reported PTs are consistent with the current Vidaza® (azacitidine) product label.[2]

Figure 2. Reported Cardiac Events*



*Each case may report more than one event

In 8.9% (n=12) of the cases, *electrocardiogram QT prolonged* or *torsade de pointes* (TdP) was reported as a PT. We identified two additional cases in which QTc value exceeded 450 ms; however, these cases did not report *electrocardiogram QT prolonged* or TdP as a PT.

3.3 ASSESSMENT OF FAERS CASES WITH ELECTROCARDIOGRAM QT PROLONGED/TDP REPORTED AS A PT OR QTC VALUE > 450 MS (N=14)

Overall, we identified 14 FAERS cases that reported *electrocardiogram QT prolonged* or TdP as a PT, or QTc value that exceeded 450 ms. **Table 6** summarizes the case characteristics for these FAERS cases. **Appendix B** lists the corresponding FAERS case numbers, FAERS version numbers, and manufacturers.

Table 6. Case Characteristics of Electrocardiogram QT Prolonged/TdP as a PT or QTc Value > 450 ms with Azacitidine, Received by FDA from May 19, 2004 through April 22, 2020 (N=14)

Age (years)	
Mean	68
Median	69
Range	47-81
Not reported	1
Sex	
Male	6
Female	8
Country	
United States	7
Foreign	7
Report type	
Expedited	14
Serious outcomes[*]	
Death	6
Life-threatening	2
Hospitalization	11
Other serious	10
Reported causes of death (n=6)	
Acute myocardial infarction	1
Acute respiratory failure	1
Cardiac and respiratory failure	1
Cardio-respiratory arrest/leukemia	1
Sudden death	1
Torsade de pointes/ventricular tachycardia	1
Indications for azacitidine use	
AML	9
MDS	4
Unspecified leukemia	1
Azacitidine administered as monotherapy	
No	12[†]
Yes	1
Not reported	1

Table 6. Case Characteristics of Electrocardiogram QT Prolonged/TdP as a PT or QTc Value > 450 ms with Azacitidine, Received by FDA from May 19, 2004 through April 22, 2020 (N=14)	
Azacitidine dosage regimen	
75 mg/m^2/day x 7 days	5
75 mg/m^2 at unspecified frequency	3
Other or unspecified dosage regimen	6
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case can have more than one serious outcome. † Eight of these 12 cases reported concomitant antineoplastic therapies that are labeled for QT prolongation.	

Table 7 summarizes the event characteristics for the 14 FAERS cases of *electrocardiogram QT prolonged* or TdP reported as a PT, or QTc value > 450 ms with azacitidine use.

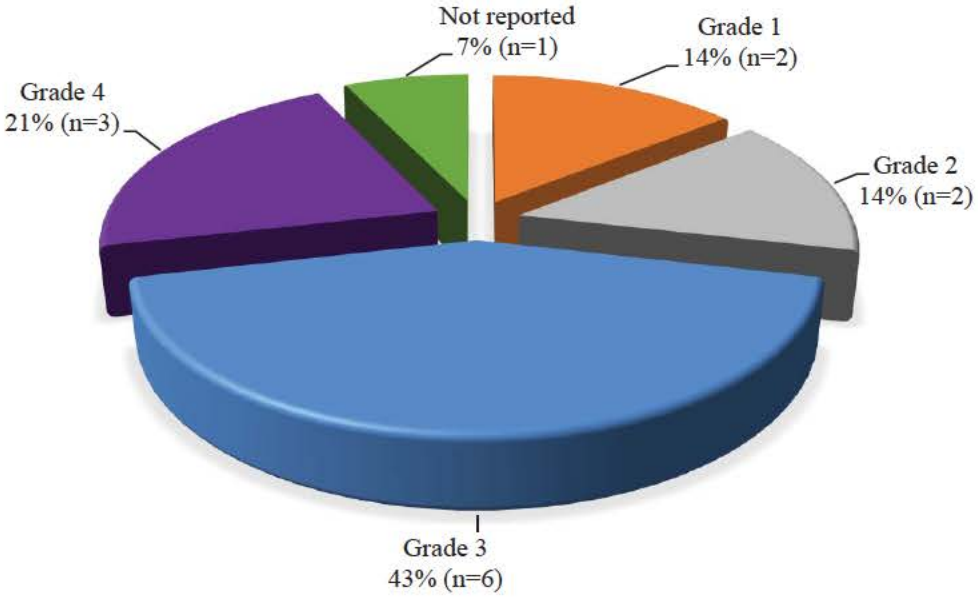
Table 7. Event Characteristics of Electrocardiogram QT Prolonged/TdP as a PT or QTc Value > 450 ms with Azacitidine, Received by FDA from May 19, 2004 through April 22, 2020 (N=14)	
Time to onset from first azacitidine dose (days)	
Mean	54
Median	37
Range	7-166
Time to onset from last azacitidine dose (days)	
Mean	12
Median	5
Range	0 (same day) – 32
Not reported	3
Azacitidine disposition	
Discontinued	7*
Interrupted/resumed	1
Continued	4
Not reported	2
Clinical outcomes	
Death	3
Recovered/recovering	8
Not recovered	2
Not reported	1
Treatment†	
Amiodarone	1
Defibrillation	2
Electrolyte repletion	3
Not reported	9
QT/QTc > 500 ms at event onset	
Yes	8
No	4
Not reported	2
QT/QTc increase > 60 ms from baseline at event onset	

Table 7. Event Characteristics of Electrocardiogram QT Prolonged/TdP as a PT or QTc Value > 450 ms with Azacitidine, Received by FDA from May 19, 2004 through April 22, 2020 (N=14)	
Yes	3
No	1
Not reported	10
Clinical manifestation‡	
Asymptomatic	1
Dyspnea/palpitations/syncope/vertigo	5
Hemodynamic collapse/loss of consciousness	2
Not reported	8
Concomitant QT prolonging medications (n=13§**)**	
Antineoplastic agents‖	8
Azole antifungals	8
Fluoroquinolones	5
Medical history/comorbidity (n=11¶**)**	
Arrhythmia	2
Cardiac failure	1
Coronary artery disease	4
Heart valve disease	1
History of QT prolongation	1
Hypokalemia	3
Hypomagnesemia	2
Sepsis	1

* One case reported azacitidine was discontinued > 1 month prior to event onset due to relapsed disease.
† More than one treatment may have been reported per case.
‡ More than one clinical manifestation or signs/symptoms of serious arrhythmia may have been reported per case.
§ Thirteen cases reported confounding concomitant QT prolonging medications. The remaining case did not report concomitant QT prolonging medications; however, this case reported concurrent atrial flutter in setting of grade 4 anemia and hyperkalemia that may contribute to cardiac instability. A case may report more than one concomitant QT prolonging medication.
‖ Reported concomitant QT prolonging antineoplastic agents include: entinostat (n=1), gilteritinib (n=1), glasdegib (n=2), ivosidenib (n=3), sorafenib (n=1).
¶ Eleven cases reported confounding medical conditions that may be an independent predisposing risk factor for QT prolongation. Of note, 10 out of 11 cases were also confounded by concomitant QT prolonging medications. Three other cases did not report relevant medical conditions; however, these three cases were confounded by concomitant QT prolonging medications. A case may report more than one confounding medical history/comorbidity.

Figure 3 shows the severity of QT prolongation according to the CTCAE Grade 1-4. Overall, the severity was assessed as grade 3-4 in nine of the 14 cases (64%).

Figure 3. Severity of QT Prolongation



3.4 APPLICANT DATA

We reviewed Celgene's PSUR that covered the reporting interval between May 19, 2018 and May 18, 2019 because the applicant evaluated azacitidine's effect on the QT interval during this reporting period.[5] Our findings for this report are summarized below.

- The applicant categorized "effect on QT interval" as missing information for azacitidine in the European Union (EU) Risk Management Plan (RMP) Version 13.0 because no specific studies have been conducted to evaluate the effect of azacitidine use on the QT interval.
- The applicant conducted a search of the safety database utilizing the MedDRA broad scope of SMQ *Torsade de pointes/QT prolongation*. This search strategy retrieved 227 cases of "effect on QT interval" with azacitidine, cumulatively through May 18, 2019. For the current reporting interval (May 19, 2018 – May 18, 2019), the applicant identified 21 cases of "effect on QT interval," including 15 initial and six follow-up cases. **Table 8** shows the PTs reported among the 15 initial cases; one of them reported *electrocardiogram QT prolonged* as a PT, and five other cases reported a fatal outcome due to either cardiac arrest or sudden death.

Table 8. Reported PTs Among Initial Cases of Effect on QT Interval Identified by Applicant from May 19, 2018 through May 18, 2019 (N=15)

Reported PTs	Number of Cases
Syncope	5

Table 8. Reported PTs Among Initial Cases of Effect on QT Interval Identified by Applicant from May 19, 2018 through May 18, 2019 (N=15)	
Reported PTs	**Number of Cases**
Cardiac arrest	4
Sudden death	2
Cardio-respiratory arrest	1
Electrocardiogram QT prolonged	1
Loss of consciousness	1
Multiple organ dysfunction syndrome	1

- Overall, the applicant's analysis of the 15 initial cases, including those with a fatal outcome, acknowledged that limited clinical information was reported regarding the circumstances leading to cardiac arrest or sudden death. Additionally, the applicant determined that these cases were confounded by underlying cardiovascular disease, advanced age, concomitant medications, severe anemia that may contribute to cardiac instability, or did not provide sufficient information to assess the presence of risk factors. The applicant's review of the six follow-up cases also did not identify any new significant data regarding azacitidine's effect on the QT interval. The FAERS cases that we reviewed were similar to those described by the applicant in the PSUR.
- The applicant concluded that their "risk evaluation during this reporting interval did not reveal any new relevant information with respect to the severity, nature, and apparent risk level of azacitidine's effect on the QT interval in the approved indications." In addition, the applicant determined the reporting rates for the effect on QT interval with azacitidine use "have remained stable over time with no remarkable increase." Therefore, the applicant considers the current risk minimization activities to be adequate at this time.
- Given no safety signal for QT prolongation has been identified in clinical trials with azacitidine treatment, the applicant no longer considers "effect on QT interval" to be missing information (b) (4)

Patient Exposure

- The overall cumulative exposure to azacitidine worldwide through May 18, 2019 is estimated to be 464,771 patients, including 21,293 patients from clinical trials and 443,478 patients from commercial exposure.

Reviewer's Comments

- *The discrepancy between the number of FAERS reports versus the applicant's data could be attributed to differences in the time period of search, MedDRA search terms (e.g., broad vs narrow scope of SMQ Torsade de pointes/QT prolongation), and data sources.*
- *In the 15 initial cases identified by the applicant during this PSUR reporting interval, the PTs were consistent with the cardiac events reported in the 135 FAERS cases (see **Figure 2**). In addition, the applicant provided manufacturer case control numbers for these 15 cases only. We retrieved eight of these 15 cases in our FAERS search, including the five*

fatal cases and one case that reported electrocardiogram QT prolonged as a PT. Our assessment of these cases is consistent with the applicant's findings.

4 CONCLUSION

Overall, the majority of cardiac events or PTs reported in 135 FAERS cases were consistent with the Vidaza® product label and applicant-identified cases. Most of these cases reported concomitant administration of medications that are associated with cardiotoxicity and/or confounding medical conditions, including cardiac disorders. We could not unequivocally tease out any specific event that could clearly be attributed to azacitidine use alone.

Among 14 FAERS cases that reported *electrocardiogram QT prolonged* or TdP as a PT, or QTc value greater than 450 ms, the severity was evidenced by the QT/QTc interval exceeding 500 ms or presence of grade 3-4 QT prolongation (per CTCAE criteria) in nine cases (64%). However, the majority of these cases, including those with a fatal outcome (n=6), reported administration of azacitidine in combination with other antineoplastic agents. These cases also involved critically ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities, and concomitant medications that are associated with QT prolongation (see **Tables 6** and **7**). The applicant's PSR data analysis of QT effect was consistent with the FAERS data.

We recognize the presence of confounding factors in most cases from the FAERS database and the applicant's PSR, and general limitations of spontaneous postmarketing data that prevent us from establishing or excluding a causal association between azacitidine and QT prolongation. Although we are unable to determine to what extent QT prolongation is attributed to other risk factors, we also cannot determine the contributory role, if any, of azacitidine to QT prolongation and other reported cardiac events in these postmarketing cases. (b) (4)

5 REFERENCES

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6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.2 APPENDIX B. FAERS LINE LISTING OF CASES WITH ELECTROCARDIOGRAM QT PROLONGED/TDP REPORTED AS A PT OR QTC VALUE > 450 MS (N=14)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	7/17/2015	11281174	3	TW-GLAXOSMITHKLINE-TW2015095222	Expedited (15-Day)	81	M	TWN	DE,HO,OT
2	9/18/2015	11522831	5	US-009507513-1509USA007040	Expedited (15-Day)	60	F	USA	DE,HO,OT
3	2/1/2018	14474184	5	US-CELGENEUS-USA-20180110997	Expedited (15-Day)	69	F	USA	HO,LT,OT
4	5/14/2018	14892369	1	FR-CELGENEUS-FRA-20180500558	Expedited (15-Day)	59	F	FRA	HO
5	10/23/2018	15542681	2	BE-CELGENEUS-BEL-20181005687	Expedited (15-Day)	68	F	BEL	OT
6	8/2/2019	16660303	2	US-ASTELLAS-2019US030766	Expedited (15-Day)	74	M	USA	DE,OT
7	8/6/2019	16674218	15	FR-CELGENEUS-FRA-20190704612	Expedited (15-Day)	69	M	FRA	HO,OT
8	8/28/2019	16750864	1	DE-CELGENEUS-DEU-20190808585	Expedited (15-Day)	78	M	DEU	HO
9	3/17/2020	17552119	3	CN-CELGENEUS-CHN-20200305440	Expedited (15-Day)	67	F	CHN	HO,LT
10	12/1/2006	6201395	1	AZAUS200600352	Expedited (15-Day)	47	F	USA	HO
11	4/6/2010	7345434	6	PHHY2010US20569	Expedited (15-Day)	NR	M	USA	DE,HO,OT
12	8/20/2012	8732147	2	US-CELGENEUS-163-50794-12072618	Expedited (15-Day)	81	M	USA	HO,OT
13	12/28/2016	13068312	6	ES-CELGENEUS-ESP-2016124174	Expedited (15-Day)	62	F	ESP	DE,HO,OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
14	7/24/2018	15188070	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-069029	Expedited (15-Day)	70	F	USA	DE,OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: NR=not reported, M=male, F=female, TWN=Taiwan, USA=United States of America, FRA=France, BEL=Belgium, DEU=Germany, CHN=China, ESP=Spain, DE=death, HO=hospitalization, LT= life-threatening, OT=other medically significant

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