CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208216Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	208216
Priority or Standard	Standard
Submit Date(s)	June 15, 2015
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Division/Office	Division of Hematology Products
Reviewer Name(s)	George Shashaty
Review Completion Date	March 14, 2016
Established Name	Azacitidine
(Proposed) Trade Name	Azacitidine for Injection
Applicant	Actavis Pharmaceuticals
Formulation(s)	Intravenous or subcutaneous
Dosing Regimen	75 mg/M^2 for 7 days every 28 days
Proposed Indication(s)	Treatment of patients with myelodysplastic syndrome
Intended Population(s)	Patients with myelodysplastic syndrome
Recommendation on Regulatory Action	No clinical data have been submitted to this NDA. Approval will require a determination of "sameness" with the reference listed drug. Approval should be denied if "sameness" is not established
Recommended Indication(s)	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

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Glossary

aPTT	activated partial thromboplastin time
AC	advisory committee
AE	adverse event
BE	bioequivalence
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAD	coronary artery disease
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DESI	Drug efficacy and safety investigation
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAB	French-American-British
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GPIIb/IIIa	glycoprotein IIb/IIIa
GRMP	good review management practice
HIT	Heparin induced thrombocytopenia
HITTS	Heparin induced thrombocytopenia with thrombosis syndrome
ICH	International Conference on Harmonization
IND	Investigational New Drug

108	IPSS/IPSS-R	International Prognostic Scoring System (Revised)
109	ISE	integrated summary of effectiveness
110	ISS	integrated summary of safety
111	ITT	intent to treat
112	MedDRA	Medical Dictionary for Regulatory Activities
113	MDS	Myelodysplastic syndrome
114	mITT	modified intent to treat
115	NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
116	NDA	new drug application
117	NME	new molecular entity
118	OCS	Office of Computational Science
119	OPQ	Office of Pharmaceutical Quality
120	OSE	Office of Surveillance and Epidemiology
121	OSI	Office of Scientific Investigation
122	PBRER	Periodic Benefit-Risk Evaluation Report
123	PCI	Percutaneous coronary intervention
124	PD	pharmacodynamics
125	PI	prescribing information
126	PK	pharmacokinetics
127	PMC	postmarketing commitment
128	PMR	postmarketing requirement
129	PP	per protocol
130	PPI	patient package insert
131	PREA	Pediatric Research Equity Act
132	PRO	patient reported outcome
133	PSUR	Periodic Safety Update report
134	PT	prothrombin time
135	PTCA	Percutaneous transluminal coronary angioplasty
136	REMS	risk evaluation and mitigation strategy
137	RCT	randomized controlled trial
138	RLD	reference listed drug
139	SAE	serious adverse event
140	SAP	statistical analysis plan
141	SEALD	Study Endpoints and Labeling Development
142	SGE	special government employee
143	SOC	standard of care
144	STEMI	ST segment elevation myocardial infarction
145	TT	thrombin time
146	TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Azacitidine for Injection contains azacitidine, a pyrimidine nucleoside analog of cytidine, and which functions as a nucleoside metabolic inhibitor. The structural formula is C8H12N405 and the molecular weight is 244. Azacitidine for Injection contains 100 mg of azacitidine as a sterile, (b) (4) powder in a (b) (4) vial for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Azacitidine for Injection also contains 170 mg of sucrose, (b) (4) monosodium phosphate monohydrate and (b) (4) disodium hydrogen phosphate dehydrate as excipients.

Approval for Azacitidine for Injection is being sought by the sponsor via the 505(b)(2) pathway based on information available to FDA for the reference listed drug, VIDAZA (NDA 50794), sponsored by Celgene Corporation, which was approved on May 19, 2004 based on adequate and well-controlled trials. VIDAZA is provided as a lyophilized sterile powder in a (b) (4) vial containing 100 mg of azacitidine and 100 mg of mannitol.

The differences between VIDAZA and Azacitidine for Injection are shown in the following table.

Table 1. Comparison between VIDAZA and Azacitidine for Injection

	Vidaza® 100 mg	Azacitidine for Injection 100 mg
Components	**Formula/ unit dose** **Powder for solution/suspension for injection (100 mg /vial)**	**Formula/ unit dose** **Powder for solution/suspension for injection (100 mg /vial)**
Azacitidine	100.00 mg (b) (4)	100.00 mg* (b) (4)
Mannitol	100.00 mg	Not applicable
Sucrose	Not applicable	170.00 mg
Monosodium phosphate monohydrate	Not listed	(b) (4) mg
Disodium hydrogen phosphate, dihydrate	Not listed	(b) (4) mg

* Manufacturing (b) (4) (b) (4) solution. Please note that as per the SBOA for NDA 050794, the Listed Drug utilizes an (b) (4) as well.
Source: Sponsor submission. Clinical Overview, page 7

Azacytidine for Injection is proposed to be 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). These indications are the same as for the reference listed drug, azacitidine (VIDAZA®).

The initial dose of Azacitidine for Injection is 75 mg/m^2 given intravenously or subcutaneously daily for 7 days. After a 3 week hiatus, similar cycles are administered every 28 days. The dose may be increased to 100 mg/m^2 if no response occurs by the 2nd to 4th cycle. The dose is reduced for neutropenia, thrombocytopenia or an unexplained decrease in serum bicarbonate to < 20 meq/L. The sponsor has not submitted any data from human experience with Azacitidine for Injection. This NDA is a 505(b)(2) application that is based wholly on data submitted for the reference drug, VIDAZA.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sponsor has provided this application as a 505(b)(2) NDA submission under the Federal Food, Drug and Cosmetic Act. No clinical data were submitted with the application. The sponsor has based its conclusions of effectiveness and safety of Azacitidine for Injection on the data already submitted and available to FDA pertinent to the determination of the efficacy and safety of the reference listed drug (RLD), Vidaza (NDA 50794) and has requested that FDA rely on those data to support the approval of Azacitidine for Injection. The sponsor for Azacitidine for Injection has requested a waiver from the need to perform bioequivalence (BE) or bioavailability (BA) studies because it states that the drug will be given intravenously or subcutaneously. The sponsor has submitted data for Azacitidine for Injection that it maintains assures the "sameness" of the drug for subcutaneous use.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

The analysis of benefit and risk for the use of Azacitidine for Injection is based on the benefit and risk of VIDAZA, the RLD. During review of NDA 50794, the efficacy and safety of the use of VIDAZA in patients with MDS were assessed based on clinical data from 4 clinical trials that exhibited the following:

- In Study 1, a randomized, open-label, controlled trial, there were 191 subjects enrolled. Subjects treated with VIDAZA had a complete plus partial response rate of 15.7% compared to best supportive care (control) response rate of 0%. The mean duration of remission for those who experienced remission was 512 days. All subjects who entered remission became transfusion independent.
- In Study 2, a single arm trial of 72 subjects, the response rate was 13.9% with a mean duration of remission of 810 days.
- In Study 3, a single arm trial in 48 subjects, the response rate was 18.8% and the mean duration of remission was 389 days. All subjects in this study received VIDAZA intravenously.
- In Study 4, an international, multi-center, open-label, randomized trial in 358 subjects, the overall survival in the VIDAZA treated subjects was 24.5 months compared to 15.0 months in the best supportive care (control) arm (Hazard ratio 0.58, 95% CI 0.43, 0.77). Of those who were transfusion dependent prior to enrollment, 45.0% in the VIDAZA arm no longer required transfusions, whereas 11.4% of the control arm no longer required transfusions.
- Major adverse events associated with the use of VIDAZA included neutropenia, thrombocytopenia, gastrointestinal symptoms, and renal and hepatic toxicity.

VIDAZA remains a marketed drug in the U.S. Therefore, if Azacitidine for Injection is deemed to be the "same" as VIDAZA despite the fact that the former contains mannitol and the latter contains sucrose, monosodium phosphate monohydrate, and disodium hydrogen phosphate dehydrate as excipients, the efficacy and safety of the use of Azacitidine for Injection for the same indications can be assumed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	MDS is a disorder of bone marrow failure with a propensity to evolve into an acute leukemic state. The cause of MDS is unknown, but may occur after the use of chemotherapy or radiotherapy. There is a wide variability in the severity and duration of different forms of MDS. The main medical problems that occur are due to anemia, neutropenia or a diminished platelet count, and transfusion dependence is common, as are infections and bleeding.	MDS is a marrow failure state that leads to various cytopenias with attendant complications. Most patients with the disease are elderly and this complicates therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Treatment options are very limited. Stem cell transplantation may lead to cure but is not commonly employed. Decitabine is approved for all classifications of MDS. Lenalidomide is approved for transfusion dependent Low and Int-1 risk patients who have a deletion of 5q.	Stem cell transplantation may be curative for MDS. Drug therapies are of limited efficacy.
Benefit	VIDAZA induces a complete or partial remission in 15-20% of patients treated. In addition, patients who are transfusion dependent may no longer require transfusion support. VIDAZA has been shown to improve overall survival in patients with MDS.	Therapy with VIDAZA increases the frequency of remission, leads to a lesser need for transfusions and increases overall survival in MDS.
Risk	VIDAZA may suppress bone marrow function and aggravate various cytopenias. Gastrointestinal side effects are common. VIDAZA may cause liver or kidney dysfunction.	Adverse events associated with VIDAZA are troublesome but tolerable, and can be managed with alteration of the dosing regimen.
Risk Management	Laboratory assessment of blood counts, hepatic and renal function. Dose adjustment in the event of adverse events. No REMS or other special safety requirements. Adverse event reporting per 21CFR314.80-314.81.	Standard assessment of laboratory measures lessens the risks of developing serious side effects.

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2 Therapeutic Context

2.1. Analysis of Condition

Myelodysplastic syndrome (MDS) is a disorder of the bone marrow in which normal erythropoiesis, myelopoiesis and thrombopoiesis are impaired. The primary defect appears to be a clonal mutation of an early marrow precursor. Most commonly, the dyspoietic marrow maturation leads to a variable degree of anemia, leukopenia and/or thrombocytopenia with attendant symptoms and laboratory findings. MDS typically develops as a *de novo* disease in the elderly, but also occurs in persons who have previously received chemotherapy or radiation therapy for malignant disease. In some patients with MDS, the dysplastic process eventually evolves into an acute leukemic disorder. MDS is diagnosed in the U.S. in approximately 13,000 persons annually[1].

MDS is a collection of related diseases with a wide variation in need for treatment and in survival. Over the years there have been several classification schemes devised to permit prognostication for the need of treatment and the likelihood of survival. The original classification was referred to as the French-American-British (FAB) method and consisted of 6 categories. These included refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), acute myelogenous leukemia (AML), and chronic myelomonocytic leukemia (CMML). Subsequent classifications (International Prognostic Scoring System [IPSS]) and the International Working Group for the Prognosis of MDS [IWG-PM]) attempted to assign prognostic features (degree of anemia/thrombocytopenia, transfusion requirement, chromosomal aberrations, etc) to each patient, thereby providing expected lengths of survival by consignment to Good, Intermediate (I/II) and Poor prognostic groups. In recent years, analysis of chromosomal patterns has provided additional prognostic information. Nonetheless, the categorizations are imperfect and prediction of survival and the benefits and risks of treatment often depend on the patient's age and co-morbid conditions. A comparison of the classification of MDS is shown in the following table.

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Table 1. Classification of MDS

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)

Source: Sponsor submission, Clinical Overview, page 4

Prognosis is poor for most patients with MDS, with 3-year survival rates estimated at less than 50% (Rollison, 2008[2]). The standard prognostic tool in MDS is the International Prognostic Scoring System (IPSS), which classifies patients into Low-, Intermediate-1, intermediate-2, and High risk categories on the basis of the percentage of bone marrow blasts, the karyotype, and the number of cytopenias; the respective median survival rates are estimated at 8, 5.3, 2.2, and 0.9 years (Germing, 2005[3]; Greenberg P, 1997[4]). Recently, another Revised International Prognostic Scoring Systems (IPSS-R) has been developed (Greenberg P et al, 2012[5], Adess L, 2012[6], Messa, 2012[7], Mishra A, 2013[8]) to improve the standard IPSS (Greenberg P et al, 1997[4]): it identifies five different prognostic categories based mainly on stratification of cytogenetic risk.

Therapy for MDS is often less than effective. Many patients receive no treatment other than supportive care (transfusions for anemia, antibiotics for infections, platelet transfusions for bleeding, red cell and/or white cell stimulating agents, etc). Stem cell transplantation may be curative but is not commonly used in MDS because of the clinical characteristics of the patients

involved, particularly advanced age and co-morbid conditions. Specific therapy approved for the treatment of some forms of MDS includes the immunomodulatory agent, lenalidomide, and the hypomethylating agents, azacitidine and decitabine.

Azacitidine was approved as VIDAZA (NDA 50794) in 2004 based on adequate and well-controlled trials in patients with several of the morphologic types of MDS, which showed a greater frequency of complete plus partial remissions (approximately 15-20% compared to 0% in subjects treated with best supportive care) plus a lessening of the need for red cell transfusion therapy in patients treated with VIDAZA compared to those treated with best supportive care. In this 505(b)(2) NDA, the sponsor seeks to gain approval of its azacitidine product based on the findings of the efficacy and safety of VIDAZA for the same indications. The sponsor states that, other than for a difference in excipient ingredients, VIDAZA and its Azacitidine for Injection product are identical.

2.2. Analysis of Current Treatment Options

As noted above, the treatments available for MDS are not entirely satisfactory. Other than for stem cell transplantation, no curative therapy is available. Supportive therapy plays a major role in the condition. Specific approved therapies to manage the underlying cause of the disease itself are shown in the following table.

Table 2. Therapies Used in the Treatment of Myelodysplastic Syndromes

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Decitabine (Dacogen®) (NDA 21790) Nucleoside metabolic inhibitor Hypomethyl-ator 50 mg/vial	All FAB MDS subtypes, and IPSS Int-1, Int-2 and High Risk	2006	15 mg/M² IV over 3 hr every 8 hours for 3 days every 6 weeks Or 20 mg/M² IV over 1 hour daily for 5 days every 4 weeks	Complete Response plus Partial Response =17% compared to 0% for best supportive care. Duration of response – 288 d	Cytopenias, fever, hepatic and renal dysfunction, gastrointestinal symptoms, fatigue	Similar efficacy and safety reported in a single arm study
Azacitidine (VIDAZA®) (NDA 50794)	All FAB MDS subtypes	2004	75 mg/M² subQ or IV daily for 7 days every 4 weeks. May increase to 100	CR plus PR= 13.9% to 18.8%. Increase in OS. Reduction in RBC	Cytopenias, hepatic and renal toxicity, gastrointestinal	Approval based on 2 single arm and 2 RCTs

			mg/M^2	transfusion requirement.	symptoms, fatigue	
Lenalidomide (Revlimid®) (NDA21880)	Transfusion dependent low or Int-1 risk MDS with deletion of 5q	2005	10 mg orally daily	Transfusion independence achieved in 99/148 (67%) of subjects	Box warning for embryofetal toxicity, neutropenia, thrombocytopenia and venous/arterial thromboembolism. Cardiac toxicity, development of second malignancies, hepatotoxicity, hypersensitivity, tumor lysis and tumor flare, GI synptoms, pruritis	Patient must enroll on RevAssist REMS program

Source:. Reviewer Table

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The sponsor's Azacitidine for Injection is not approved for marketing anywhere in the world. The sponsor states that Azacytidine for Injection is identical to VIDAZA® except that each vial of Azacitidine for Injection contains 100 mg of azacitidine, 170 mg of sucrose, (b) (4) monosodium phosphate monohydrate and (b) (4) disodium hydrogen phosphate dehydrate but does not contain mannitol whereas each vial of VIDAZA contains 100 mg of azacitidine and 100 mg of mannitol as the only excipient. VIDAZA was approved on May 19, 2004.

3.2. Summary of Presubmission/Submission Regulatory Activity

The sponsor did not communicate with FDA regarding Azacitidine for Injection prior to its

submission of the NDA. Azacitidine for Injection is not approved in any country in the world.

3.3. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations was not involved in the review of this NDA. No clinical studies were submitted.

3.4. Product Quality

Product quality is the critical determinant of the approvability of Azacitidine for Injection. Although the drug substance is identical with that of the RLD, Azacitidine for Injection contains different excipients from those that are present in the VIDAZA drug product. Azacitidine for Injection is a parenteral solution for administration by injection, and it has the same final concentration of active ingredient (azacitidine) when ready for administration (either IV or SC), the same dosage form, the same route of administration, and the same intended indications as the listed drug, Vidaza®. In addition, the same posology with the same dose, the same injection volume, the same injection technique, and the same site of injection is proposed. However, there is a difference in the inactive ingredients (sucrose vs mannitol) (b) (4)

The sponsor states that a drug product's *in vivo* bioavailability or bioequivalence may be considered self-evident if the drug product meets the following criteria: "is a parenteral solution intended solely for administration by injection, and contains the same active and inactive ingredients in the same concentration as the listed drug. However, FDA permits waiver of in vivo evidence of bioequivalence under other circumstances beyond those enumerated in 21 CFR 320.22".

In the NDA submission, the sponsor requests a waiver from the need to perform studies of bioavailability between the two products, maintaining that the excipients are not likely to affect the medicinal characteristics of its product compared to VIDAZA because Azacitidine for Injection will be given parenterally (either intravenously or subcutaneously) and thereby is by definition "bioequivalent".

The sponsor has performed the following studies that it purports demonstrate identity between Azacitidine for injection and its RLD:

- Evidence that changes in the formulation of Azacitidine for Injection vs Listed Drug Vidaza® (sucrose vs mannitol (b) (4)) are not expected to influence the subcutaneous absorption profiles of azacitidine, and do not affect the safety or efficacy of the proposed drug product: Demonstration of Pharmaceutical Equivalence, the excipients are safe for SC use, exposure levels are covered by clinical experience

with other approved SC drug products.

- Evidence that developed drug product Azacitidine for Injection, when reconstituted as a suspension for subcutaneous administration, demonstrates bioequivalence: In vitro package comparative with Listed Drug, Vidaza® (Bioequivalence Study Report: Azacitidine for Injection versus Vidaza® for Injection) demonstrating similar physico-chemical characteristics such as viscosity, (b) (4)
(b) (4)
- An experimental study is provided demonstrating that the suspension dissolves rapidly at (b) (4) thus immediately after the administration no suspension is actually present in the body. Given that shortly after the subcutaneous administration, both test and reference products become aqueous solutions, their bioavailability is expected to be essentially the same.
- Stability studies after reconstitution and dilution, and comparative impurity profile: an improvement in stability was noticed for the Actavis formulation based on the lower degradation of (b) (4) and a decrease of the total impurities level.

Reviewer Comments. The sponsor has performed a number of physicochemical tests on Azacitidine for Injection. These studies are under review by CMC and Biopharmaceutics. Whether or not these studies are sufficient to establish "sameness" and whether a biowaiver will be granted will be determined by the CMC and Biopharmaceutics review of the data.

3.5. Clinical Microbiology

This NDA should be reviewed by Microbiology because it is a parenterally administered product.

3.6. Nonclinical Pharmacology/Toxicology

The sponsor requests that FDA review Non-Clinical studies for VIDAZA to assess the Nonclinical Pharmacology/Toxicology for Azacitidine for Injection. Refer to Pharmacology/Toxicology review.

3.7. Clinical Pharmacology

3.7.1. Mechanism of Action

The sponsor has not submitted any information to elucidate the mechanism of action of Azacitidine for Injection.

According to the VIDAZA label, azacitidine is a pyrimidine nucleoside analog of cytidine. VIDAZA is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

3.7.2 Pharmacodynamics

No clinical pharmacodynamic studies of Azacytidine for Injection have been conducted. There are no pharmacodynamic data provided in the VIDAZA label.

3.7.3 Pharmacokinetics

No clinical pharmacokinetic studies of Azacytidine for Injection have been conducted. As described in the VIDAZA label, the pharmacokinetics of azacitidine were studied in 6 MDS patients following a single 75 mg/m^2 subcutaneous (SC) dose and a single 75 mg/m^2 intravenous (IV) dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes. The AUC and Cmax of SC administration of azacitidine in 21 patients with cancer were approximately dose proportional within the 25 to 100 mg/m^2 dose range. Multiple dosing at the recommended dose regimen does not result in drug accumulation. Of note is that the clinical studies to support the effectiveness and safety of VIDAZA were conducted with drug administration predominantly via the subcutaneous route (> 80% of subjects), and the sponsor provided a study comparing the subcutaneous and intravenous routes allowing an understanding of the PK relationship between the two routes of administration.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of

radioactivity in urine following SC administration of ^{14}C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours.

3.8 Devices and Companion Diagnostic Issues

Not applicable.

3.9 Consumer Study Reviews

Not applicable.

4 Sources of Clinical Data and Review Strategy

Table of Clinical Studies

See Section 5.2. There are no clinical studies of Azacitidine for Injection that were submitted to determine efficacy and safety. Azacitidine for Injection has not been administered to any person. Table 4, below, summarizes the relevant clinical trials from the VIDAZA label.

425 **Table 4. Listing of Clinical Trials Relevant to the efficacy and safety of VIDAZA**

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
Study 1	Open label, multicenter RCT	Azacitidine IV, 75 mg/M^2/d x 7 every 4 weeks vs. Best supportive care	Response rate, duration of response	Indefinite treatment/follow-up at 1 year	191	Patients with any FAB type MDS	Multicenter
Study 2	Single arm	Azacitidine SC, 75 mg/M^2/d x 7 every 4 weeks	Response rate, duration of response	Indefinite treatment	72	Patients with any FAB type MDS	Multicenter
Study 3	Single arm, open label	Azacitidine IV, 75 mg/M^2/d x 7 every 4 weeks	Response rate, duration of response	Indefinite treatment/follow-up at 1 year	48	Patients with any FAB type MDS	Multicenter

Study 4	Open label, international, multicenter RCT	Azacitidine IV, 75 mg/M^2/d x 7 every 4 weeks vs. Best supportive care	Overall survival, transfusion requirement	Indefinite treatment	358	Patients with RAEB, RAEB-T, CMML, IPSS Int-2 and High Risk	International

426 Source: Reviewer table based on VIDAZA Label dated May 17, 201

4.2. Review Strategy

This is a 505(b)(2) NDA submission. The sponsor has not submitted any data from clinical trials to support the efficacy or safety of the use of Azacitidine for Injection for the desired indications. For effectiveness and safety, the sponsor is relying entirely on data submitted for NDA50794 (VIDAZA, the reference listed drug) that led to VIDAZA's approval by FDA. Based on the VIDAZA package insert, azacitidine has been previously evaluated in the trials shown in Table 4, all in patients with MDS. The sponsor has reviewed the literature for azacitidine through March 31, 2015, which did not reveal any new findings pertinent to the efficacy or safety of azacitidine.

5 Review of Relevant Individual Trials Used to Support Efficacy

Not applicable. See Section 4.2. No trials were conducted to evaluate the efficacy of Azacitidine for Injection in patients. Clinical efficacy is dependent on the demonstration of the "sameness" of Azacitidine for Injection to VIDAZA in the submitted studies. Therefore, the subsequent subsections are not applicable for this review and have been deleted.

6 Integrated Review of Effectiveness

Not applicable. See Section 4.2. No trials were conducted to evaluate the efficacy of Azacitidine for Injection in patients. Clinical efficacy is dependent on the demonstration of the "sameness" of Azacitidine for Injection to VIDAZA in the submitted studies. Therefore, the subsequent subsections are not applicable for this review and have been deleted.

7 Review of Safety

See Section 4.2. The sponsor has not submitted data from any clinical trials to support the safety of the use of Azacitidine for Injection for the desired indications. The sponsor is relying entirely on data for VIDAZA that the FDA possesses for those purposes. No persons have received Azacitidine for Injection. Therefore, the subsequent subsections are not applicable for

this review and have been deleted.

In the package insert for VIDAZA dated December, 2015, the Warnings and Precaution section contains the adverse reactions of anemia, neutropenia, and thrombocytopenia, hepatic impairment and renal dysfunction (including renal tubular acidosis). The most commonly occurring adverse reactions were nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. The most common adverse reactions when administered intravenously also included petechiae, rigors, weakness and hypokalemia. Adverse reactions most frequently (>2%) resulting in dose adjustment (SC or IV Route) were leukopenia, thrombocytopenia, neutropenia, pyrexia, pneumonia and febrile neutropenia.

In postmarketing experience with VIDAZA, the following adverse reactions have been reported: interstitial lung disease, tumor lysis syndrome, injection site necrosis, Sweet's syndrome (acute febrile neutrophilic dermatosis) and necrotizing fasciitis (including fatal cases).

In regard to the need for pediatric studies, MDS rarely occurs in the pediatric population. It would be extremely difficult to enroll a sufficient number of subjects in a trial to determine the efficacy and safety of the use of Azacitidine for Injection in the pediatric population, and a waiver for the need for pediatric studies should be granted.

7.1. Additional Safety Issues From Other Disciplines

Non-clinical toxicology, chemistry, biopharmaceutics and clinical pharmacology reviews for this NDA are pending at the time of this review. Because the application relies on a conclusion of sufficient sameness between VIDAZA and Azacitidine for Injection and granting of a bioequivalence waiver, the assessments from these disciplines are crucial to the approvability of Azacitidine for Injection.

On March 2, 2016, an e-mail Information Request was sent to the sponsor in which FDA stated that VIDAZA was originally approved based on efficacy/safety data from studies which used the subcutaneous route of administration only, and that data for the intravenous route of administration were only included in the Clinical Pharmacology section (12.3) of the label and do not provide efficacy/safety data for the intravenous route of administration. FDA requested that the sponsor provide justification that permits the use of efficacy/safety data from studies with subcutaneous use to be extrapolated to intravenous use of azacitidine. An alternative would be to resubmit a biowaiver request for the subcutaneous route with supportive data for review. If the latter course of action is selected, the sponsor should explain why observed differences in PK given intravenously and subcutaneously do not affect

the efficacy/safety of azacitidine. This IR was discussed with the sponsor in a teleconference on March 3, 2016.

In a response dated March 10, 2016, the sponsor provided the following.

1. A review of the Vidaza® efficacy and safety data obtained so far (post-approval) with both SC and IV routes and subsequent determination, based on presented data, that a similarity can be established between SC and IV, to permit their interchangeability during treatment administration.
2. A review of the observed differences in PK of IV use compared with the SC and an evaluation of their impact on efficacy and safety effects, as seen with the subcutaneous route.
3. Submission of a new biowaiver request for both SC/IV routes with additional *in vitro* characterization data to demonstrate bioequivalence, in lieu of a biostudy.

The sponsor indicates that the original approval for VIDAZA was for the subcutaneous route of administration. However, several problems related to local injections led VIDAZA's sponsor to assess the intravenous route based on the data published by Marcucci (2005)[9]. The sponsor then re-iterates the evidence submitted from the various studies[9, 10, 11] referred to in its submission dated February 19, 2016, reviewed above.

The sponsor has also provided efficacy and safety data from the AVIDA study[12]. The AVIDA study is a longitudinal, multicenter patient registry designed to prospectively collect data from US community based hematology clinics on the natural history and management of patients with MDS and other hematologic disorders, including acute myeloid leukemia, who are treated with azacitidine. Data from AVIDA has been reported periodically at scientific meetings and in the literature and includes both IV and SC use of azacitidine in the US within the data collection period. A total of 421 patients with various classifications of MDS are included in the database. Of these, 60% have been treated with IV azacitidine and 40% have been treated with subcutaneous azacitidine. IPSS scores were Low and Int-1 in 68.3%, Int-2 and High in 25.3% and Unknown in 6.4%. Fifty-one percent (51%) of patients received less than 7 days of therapy, 17% received 7 days of therapy, 30% received 7 days of therapy with breaks and 2% received more than 7 days of therapy at each cycle. Baseline parameters were similar between the IV and subcutaneously treated patients. At analysis at 600 days, 15% in the subcutaneous group and 17% in the IV group had died. Hematologic improvement had occurred in 61% of patients, and was not different between the two groups. Transfusion independence for RBCs was achieved in 75% of patients and platelet transfusion independence in 70% of patients. Efficacy results were similar between patients who had received azacitidine either intravenously or subcutaneously.

In an additional study (Martin MG, 2009[13]), 22 evaluable patients with various types of MDS (9 lower risk and 13 higher risk) were treated with IV azacitidine at a dose of 75 mg/m^2 for 5

days every 28 days. There were 5 CRs and 1 PR. The median OS was 14.8 months with a median duration of response of 15.0 months. Except for OS, these results were similar to those achieved in other studies of azacitidine in which the drug was administered for 7 days in each cycle. The sponsor also indicates that a search of ClinicalTrials.gov reveals a number of studies investigating both the intravenous and/or subcutaneous use of azacitidine in different disease states, but that there is no published information reported from these trials. Additionally, the sponsor states that, even though intravenous VIDAZA is commonly used in clinical practice, there have been no post-marketing reports of new or different efficacy/safety concerns that have been noted with its use.

Reviewer Comments. The evidence provided by the sponsor strongly suggests that the efficacy and safety of the administration of azacitidine is similar whether azacitidine is given by the subcutaneous or by the intravenous route despite the fact that there are some differences in the PK which are route specific.

In regard to the differences in PK of azacitidine when administered by the intravenous compared to the subcutaneous route, the sponsor re-iterates published studies[9, 10] in which the C_{max} is considerably higher after IV dosing, but the AUC is reasonably similar.

The sponsor also provided literature about the sucrose excipient and an assessment of the possible influence of mannitol replacement with sucrose on the pK profile of azacitidine, as well as a new *in vitro* dissolution study.

The sponsor stated that it prefers to obtain approval for both the SC and IV routes of administration. The sponsor submitted a revised request for waiver of *in vivo* bioavailability testing in its submission of March 10, 2016, for both the SC/IV routes of administration that provides additional *in-vitro* characterization data to demonstrate bioequivalence, in lieu of a biostudy.

Reviewer Comments. The additional PK data and Biowaiver Request for the subcutaneous route are under review by Biopharmaceutics and CMC.

8 Advisory Committee Meeting and Other External Consultations

No Advisory Committee or other external consultations were held or obtained.

9 Labeling Recommendations

9.1. Prescribing Information

The label content submitted by the sponsor is identical to that currently in use for VIDAZA except for the name of the drug, the differences in the inactive ingredients, and company and product specific information.

9.2. Patient Labeling

Not applicable.

9.3. Non-Prescription Labeling

Not applicable.

10 Risk Evaluation and Mitigation Strategies (REMS)

Given the known safety profile of VIDAZA, there are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

11 Postmarketing Requirements and Commitments

There are no proposed PMCs or PMRs for Azacitidine for Injection. At this time, there are no outstanding PMCs or PMRs for VIDAZA.

12 Appendices

12.1. References

1. http://www.cancer.org/cancer/myelodysplasticsyndrome/detailedguide/myelodysplastic-syndromes-key-statistics
2. Rollison DE, Howlader N, Smith MT, Strom SS, Merritt WD, Ries LA et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001- 2004, using data from the NAACCR and SEER programs. Blood 2008; 112(1):45-52.
3. Germing U, Hildebrandt B, Pfeilstocker M, Nosslinger T, Valent P, Fonatsch C et al. Refinement of the international prognostic scoring system (IPSS) by including LDH as an additional prognostic variable to improve risk assessment in patients with primary myelodysplastic syndromes (MDS). Leukemia 2005; 19(12):2223-2231.
4. Greenberg P, Cox C, Lebeau MM, Fenaux P, Morel P, Sanz G et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; 89(6):2079-2088.
5. Greenberg P, Heinz Tuechler, Julie Schanz, Guillermo Sanz et al: Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood. 2012;120(12): 2454-2465
6. Ades L, Lamarque M, Raynaud S: Revised-IPSS (IPSS-R) Is a Powerful Tool to Evaluate the Outcome of MDS Patient Treated with Azacitidine (AZA): The Groupe Francophone Des Myelodysplasies (GFM) Experience. Blood (ASH Annual Meeting Abstracts) 2012;120: Abstract 422
7. Messa E, Gioia D, Evangelista A et al: High Predictive Value of the Revised International Prognostic Scoring System (IPSS-R): An External Analysis of 646 Patients From a Multiregional Italian MDS Registry. Blood (ASH Annual Meeting Abstracts) 2012 120: Abstract 1702
8. Mishra A, Corrales-Yepez M, Ali NA et al: Validation of the revised International Prognostic Scoring System in treated patients with myelodysplastic syndromes. Am. J.Hematol. 88:566–570, 2013
9. Marcucci G et al, 2005: Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. J Clin Pharmacol 2005; 45(5):597-602
10. Uchida T, Ogawa Y, Kobayashi Y, Ishikawa T, Ohashi H, Hata T et al. Phase I and II study of azacitidine in Japanese patients with myelodysplastic syndromes. Cancer Sci 2011; 102(9):1680-1686
11. Silverman et al, 2006: Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006; 24(24):3895-3903.
12. Grinblatt DL, et al. 2015: Patients with myelodysplastic syndromes treated with azacitidine in clinical practice. Leuk Lymphoma. 2015 Apr; 56(4):887-95.
13. Martin MG et al: A phase II study of 5-day intravenous azacitidine in patients with myelodysplastic syndromes. Am. J. Hematol. 84:560–564, 2009.

12.2. Financial Disclosure

The sponsor did not submit any financial disclosure information under Module 1, Section 1.3.4. There were no clinical studies in this application. The submission does include a statement that SPS Pharma Services certifies that it did not and will not use, in any capacity, the services of any persons identified with the US FDA on the current Debarment List in connection with any work done on products.

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/s/

GEORGE G SHASHATY
04/01/2016

KATHY M ROBIE SUH
04/04/2016