Vidaza®

azacitidine for injection

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Introduction

This guide is designed to provide you with basic information about VIDAZA, including efficacy, important treatment considerations, preparation, and safety. It also includes information on VIDAZA administration options and related techniques.

For more information about VIDAZA or to request additional materials, contact your VIDAZA sales representative, contact your Clinical Nurse Specialist, visit **www.VIDAZA.com**, or call **1-866-PHARMION** (1-866-742-7646) Monday through Friday from 8 AM to 8 PM Eastern time.

VIDAZA is FDA-approved for the treatment of all myelodysplastic syndrome (MDS) subtypes[1]*:

- 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)
- Chronic myelomonocytic leukemia (CMMoL)

*According to the FAB (French, American, British) Classification System.

Please see important safety information on pages 26-27 and enclosed full prescribing information.

Initiation of MDS treatment is critical

Up to 50% of MDS patients succumb to complications, such as infection or bleeding, before progressing to AML.[2]

Alleviation of disease-related complications, including transfusion requirements, and hematologic improvement are key treatment goals in lower-risk MDS.[3]

- In contrast, altering the natural history of disease is one of the most important treatment goals in higher-risk MDS.[3]

When to initiate MDS treatment

Treatment strategies for lower-risk and higher-risk MDS differ because there are substantial differences in prognosis and outcomes between these categories.[3]

Survival Rates in MDS[4]		
IPSS Score	**Risk Group**	**Median Survival (Yrs)**
0	Low	5.7
0.5-1.0	Int-1	3.5
1.5-2.0	Int-2	1.2
≥2.5	High	0.4

Higher-risk patients require initiation of treatment with greater immediacy[5] because:

- Older, higher-risk patients are at greater risk of succumbing to infections or bleeding than younger patients.[6]
- Higher-risk MDS patients with a greater risk of earlier mortality have >5% bone marrow blasts, 2 or more cytopenias, and/or unfavorable cytogenetics, according to the IPSS.[4,6]

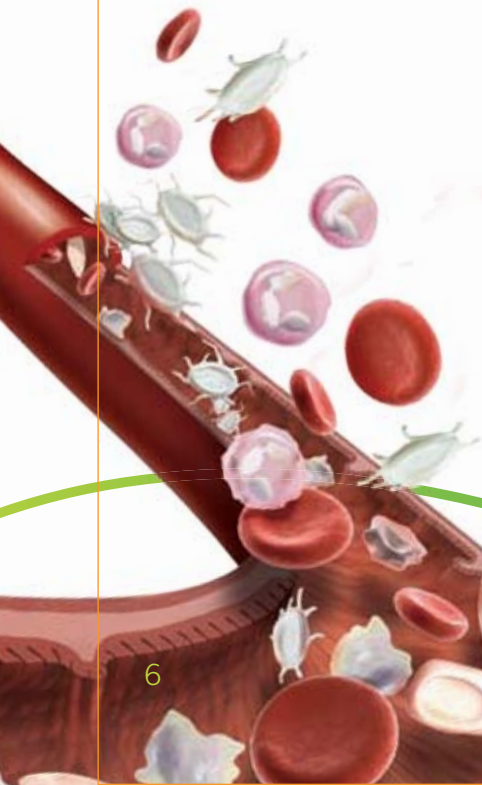
According to the NCCN Guidelines, for patients in the higher-risk group, alteration of the disease natural history is viewed as paramount.[7]

- Initiation of therapy for higher-risk patients is dependent on their candidacy for therapy, including age, performance status, and absence of major comorbid conditions.[7]

Supportive care may not be enough

For many patients, blood transfusions are an important supportive care measure that can help relieve symptoms of MDS and offer patients symptomatic improvement, but they can be inconvenient and time-consuming.[8]

- Transfusions have been associated with additional risks, including iron overload, alloimmunization, transfusion reactions, and infection.[8]
- The more transfusions a patient receives per month, the less likely the patient is to respond to treatment with growth factors.[9]



The use of supportive care to manage cytopenias is a standard practice in patients with lower-risk MDS and in patients with higher-risk MDS who cannot tolerate higher-intensity therapy.[10]

- Treatment with EPO plus growth factors has yet to demonstrate improvement in survival and/or reduced risk of transformation to AML in MDS patients.[11]
- Many patients with lower-risk MDS succumb to the consequences of cytopenias without progressing to AML.[10]
- Patients with lower-risk MDS often become dependent on frequent red blood cell or platelet transfusions, and they may experience repeated infections, bleeding, morbidity, and mortality.[10]

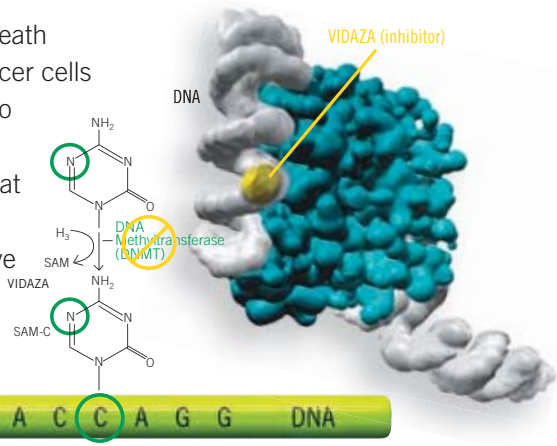
The importance of prolonged treatment with VIDAZA

According to the NCCN Guidelines, VIDAZA and other novel therapeutic agents along with supportive care remain the hallmarks of MDS management.[7]

When VIDAZA is incorporated into DNA in place of a cytidine, DNA methyltransferases may no longer be able to methylate the DNA at this position.[12]

By inhibiting hypermethylation, VIDAZA may restore normal expression to silent genes critical to cell differentiation and proliferation.[1]

VIDAZA also causes death of rapidly dividing cancer cells no longer responsive to normal growth control mechanisms.[1] Cells that do not divide rapidly are relatively insensitive to VIDAZA.[1]



Hypermethylation can reoccur when therapy is discontinued,[12] reversing any positive effects that may have been achieved during treatment.

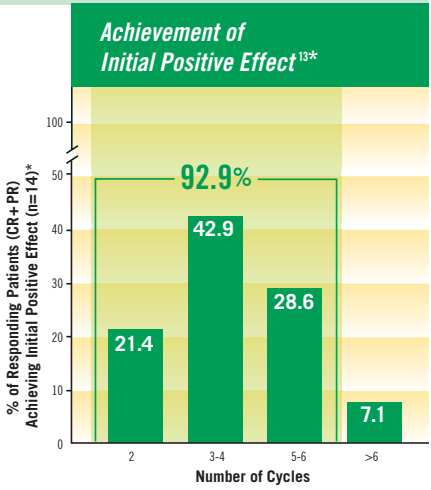
Prolonged treatment with VIDAZA may maintain inhibition of DNA methylation in patients with MDS.[12] VIDAZA may be administered for as long as patients continue to benefit.[1]

Time to response with VIDAZA

It may be necessary to administer VIDAZA for several cycles before a positive result can be achieved.[13]

In the pivotal trial, 92.9% of responding patients achieved initial positive effect* by the end of 6 treatment cycles.[13]

*Initial positive effect was defined as the first day of achievement of target for 4 weeks for at least 1 cell line abnormality.



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Study design

A randomized, open-label phase III study comparing the safety and efficacy of subcutaneous VIDAZA plus supportive care vs supportive care alone.[1]

- 53 US sites.
- Patients with any of the 5 FAB subtypes of MDS were included in the study. Patients with AML were excluded from analysis (n=19).
- For purposes of assessing efficacy, the primary endpoint was overall response rate, defined as complete response + partial response (CR + PR).
- Per protocol, patients achieving CR with VIDAZA therapy were to receive 3 additional treatments before completing the study.

Baseline patient characteristics[1]

Characteristics	VIDAZA (N=99)	Observation (N=92)
Male/Female (n%)	72/27 (72.7/27.3)	60/32 (65.2/34.8)
Mean Age ± SD	67.3 ± 10.39 (N=99)	68.0 ± 10.23 (N=91)
Range	31–92	35–88
MDS diagnosis at study entry (n%)		
RA	21 (21.2)	18 (19.6)
RARS	6 (6.1)	5 (5.4)
RAEB	38 (38.4)	39 (42.4)
RAEB-T	16 (16.2)	14 (15.2)
CMMoL	8 (8.1)	7 (7.6)
AML	10 (10.1)	9 (9.8)

Baseline characteristics were well balanced for both cohorts.

Response criteria

CR and PR were defined as[1]:

		RA	RARS	RAEB	RAEB-T	CMMoL
CR Duration ≥4 weeks	**Marrow**	<5% blasts				
	Peripheral Blood	Normal CBC if abnormal at baseline Absence of blasts in the peripheral circulation				
PR Duration ≥4 weeks	**Marrow**	No marrow requirements	≥50% decrease in blasts Improvement of marrow dyspoiesis			
	Peripheral Blood	≥50% restoration in the deficit from normal levels of baseline white cells, hemoglobin, and platelets if abnormal at baseline No blasts in the peripheral circulation For CMMoL, if WBC is elevated at baseline, a ≥75% reduction in the excess count over the upper limit of normal				

Patients who experienced positive changes in peripheral counts who did not meet the criteria for PR or CR were considered improved.[5]

Supportive care

- Patients receiving VIDAZA and patients randomized to observation could be treated with transfusions, antibiotics, and other treatments as determined by the treating investigator.[13]
- Steroids and the use of hematopoietic growth factors were prohibited.[13]
- If specific criteria were met, the observation period ended and the patient crossed over to azacitidine treatment.[13]

Please see important safety information on pages 26-27 and enclosed full prescribing information.

Proven efficacy

VIDAZA offers significant clinical benefit[1,13]

- 40% of patients treated with VIDAZA experienced clinical benefit: 16% responded* (CR + PR) and 24% improved.[1†]

*Per the 9221 response criteria.

†Patients who had positive changes in peripheral counts but did not meet criteria for CR or PR were considered improved.

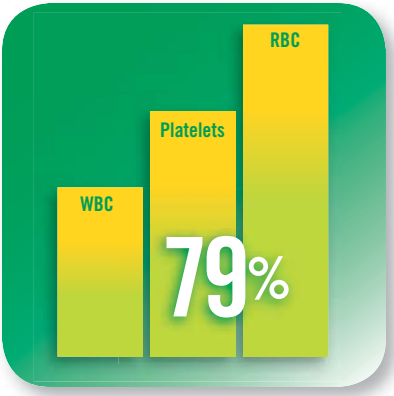
VIDAZA can help patients achieve transfusion independence[1]

- Median duration of transfusion independence was 330 days in VIDAZA patients who achieved PR or better.[1‡]

‡CR + PR per the 9221 response criteria.

VIDAZA helps patients achieve trilineage response

- Of patients who responded‡ to VIDAZA, 79% experienced improvement in not just 1, but 2 or more cell lines.[1]



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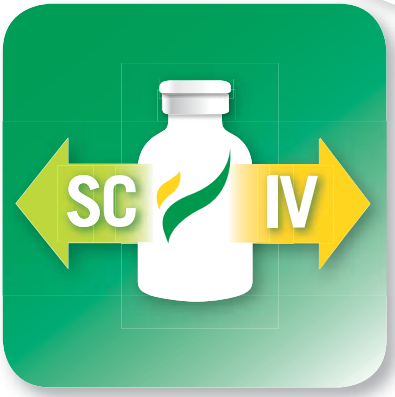
Dosing



A vial of VIDAZA can be used for either SC or IV administration. When using either SC or IV:

- Premedicate patients for nausea and vomiting.[1]
- The recommended starting dose for the first treatment cycle for all patients, regardless of baseline hematology values, is 75 mg/m^2 daily for 7 days.[1]
- VIDAZA is a cytotoxic drug. As with other potentially toxic compounds, caution should be exercised when handling and preparing VIDAZA suspensions or solutions.
- If reconstituted VIDAZA comes into contact with the skin, immediately and thoroughly wash the skin with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.
- Cycles should be repeated every 4 weeks.[1]
  - The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after 2 treatment cycles and if no toxicity other than nausea and vomiting has occurred.[1]

Patients should be monitored for hematologic responses and renal toxicities. Subsequent doses may be adjusted as necessary based on hematology, renal function, or serum electrolytes.[1]

Preparation and administration

IV preparation

1. Reconstitute each vial with 10 mL sterile water. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will be clear.
2. The resulting solution will contain azacitidine 10 mg/mL.
3. Inject desired dose into a 50-100 mL infusion bag of either 0.9% sodium chloride solution or lactated Ringer's solution.[1]
4. VIDAZA is incompatible with 5% Dextrose solutions, Hespan®,* or solutions that contain bicarbonate.

*Hespan® is a registered trademark of B. Braun Medical Inc.

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IV administration

1. Administer dose over a period of 10-40 minutes.
   - **Administration should be completed within 1 hour** of reconstitution of the VIDAZA vial.
2. IV VIDAZA may be administered via a peripheral or central line.

3. It is recommended to flush IV line after administration.

SC preparation

1. VIDAZA should be reconstituted aseptically with 4 mL sterile water for injection.
2. The diluent should be injected slowly into the vial.
3. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy.
4. The resulting suspension will contain azacitidine 25 mg/mL.

SC

Preparation for *immediate* SC administration

- Doses greater than 4 mL should be divided equally between 2 syringes.
- The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for *delayed* SC administration

- The reconstituted product may be kept in the vial or drawn into a syringe.
- Doses greater than 4 mL should be divided equally between 2 syringes.
- The product must be refrigerated immediately, and may be held under refrigerated conditions (2ºC-8ºC, 36ºF-46ºF) for up to 8 hours.
- After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

SC administration

To provide a homogeneous suspension, the contents of the syringe must be resuspended by inverting the syringe 2-3 times and vigorously rolling the syringe between the palms for 30 seconds immediately prior to administration.

Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites.

Institutional internal policy should be followed regarding the maximum volume per subcutaneous injection allowed.

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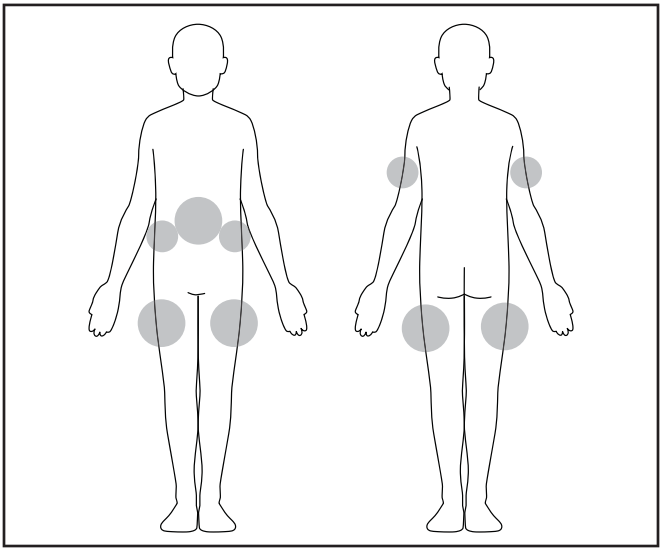
Injection technique

Be sure to rotate the injection site for each injection[1] (fatty tissue of lateral and posterior aspects of upper arm or thigh or abdomen[14]). ***If multiple injection sites are being used each day, separate the injection sites by at least 1 inch.***

Never give injections in areas where the site is tender, bruised, red, or hard.[1]



Follow the steps below once VIDAZA has been properly reconstituted and the appropriate dose has been drawn into the syringe(s):

1. Change the needle for the actual injection. A syringe with a 25-gauge, 5/8" needle is recommended for subcutaneous injection.[14]

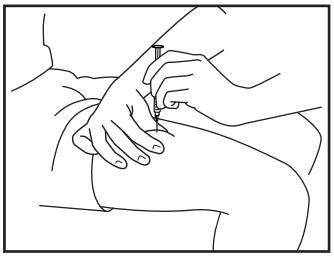
NOTE: Changing the needle and drawing a small amount of air (0.2 cc) into the syringe prior to administration may help to reduce contamination of the outer skin layers during administration, decreasing the potential for irritation at the injection site.

2. Use an antimicrobial wipe to cleanse the injection site and allow the skin to dry.[14] Allowing the skin to dry completely may help to reduce discomfort as the medication is being injected.

IMPORTANT: Icing the site prior to or immediately after the injection is not recommended due to the potential for decreased absorption of the drug.[14]

3. When you are ready to administer VIDAZA, use your thumb and forefinger to gently grasp the loose area of fatty tissue at the injection site ("pinch an inch").[14]

NOTE: Grasping the fatty tissue as described will help ensure that the medication is injected into subcutaneous tissue, not muscle.



A subcutaneous injection into the fatty layer of tissue under the skin.

4. Insert the needle at a 45º-90º angle (depending on the amount of fatty tissue and turgor/elasticity of the skin) to help prevent the injection from going into the muscle layer.[14]

5. Continue to grasp the skin and aspirate by pulling back on the plunger. If no blood appears, administer the injection.[14]

IMPORTANT: Blood indicates that the needle has entered a blood vessel. If blood appears, withdraw the needle, activate the safety feature and discard, prepare a new injection, and begin with step 1.

6. Inject the reconstituted suspension slowly into the tissue.

Side effect management

Nausea and vomiting

Nausea and/or vomiting is one of the most common side effects of treatment with VIDAZA. It can be managed in most patients with antiemetic pretreatment.

Injection site reactions

Injection site reactions are also common and can vary greatly from patient to patient. Regardless of appearance (anything from a small bruise to a large, tender, red welt), injection site reactions usually disappear after several days and normally do not scar.

If a patient develops discomfort or redness at the injection site, a cool or warm compress may be applied for 15 minutes at a time (depending on the patient's tolerance to temperature) to help relieve symptoms.

IMPORTANT: Do not use hot compresses, as these may increase the symptoms or lead to blistering of the skin at the injection site.

Please see important safety information on pages 26-27 and enclosed full prescribing information.

IMPORTANT: Do not ice the injection site, as this may affect absorption of VIDAZA.

Mild injection site reactions can be uncomfortable for the patient, but usually do not require medical attention.

Moderate injection site reactions may appear to be serious, but typically do not require medical attention.

Instruct patients experiencing problematic injection site reactions to contact your office for further treatment.

IV-related reactions

Overall, adverse reactions were qualitatively similar between the IV and SC studies. Adverse reactions that appeared to be specifically associated with the IV route of administration included infusion site reactions (eg, erythema or pain) and catheter site reactions (eg, infection, erythema, or hemorrhage).

Myelosuppression

Although it is generally manageable (and temporary), myelosuppression is a common side effect in patients receiving VIDAZA. Therefore, advise patients that their blood counts may drop before they begin to rise. Also remind patients that myelosuppression can cause any or all of the following side effects:

- Anemia
- Thrombocytopenia
- Leukopenia, neutropenia, or fever

Important
safety information

- VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol and in patients with advanced malignant hepatic tumors.
- In clinical studies, the most commonly occurring adverse reactions by SC route were nausea (70.5%), anemia (69.5%), thrombocytopenia (65.5%), vomiting (54.1%), pyrexia (51.8%), leukopenia (48.2%), diarrhea (36.4%), fatigue (35.9%), injection site erythema (35.0%), constipation (33.6%), neutropenia (32.3%), and ecchymosis (30.5%). Other adverse reactions included dizziness (18.6%), chest pain (16.4%), febrile neutropenia (16.4%), myalgia (15.9%), injection site reaction (13.6%), aggravated fatigue (12.7%), and malaise (10.9%). The most common adverse reactions by IV route also included petechiae (45.8%), weakness (35.4%), rigors (35.4%), and hypokalemia (31.3%).
- Because treatment with VIDAZA is associated with neutropenia and thrombocytopenia, complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle.

- Because azacitidine is potentially hepatotoxic in patients with severe preexisting hepatic impairment, caution is needed in patients with liver disease. In addition, azacitidine and its metabolites are substantially excreted by the kidneys and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.
- VIDAZA may cause fetal harm. While receiving treatment with VIDAZA, women of childbearing potential should avoid becoming pregnant, and men should avoid fathering a child. In addition, women treated with VIDAZA should not nurse.

Additional resources

VIDAZA Patient Assistance Program

Pharmion is committed to providing assistance to patients who have no insurance, have insurance that does not cover VIDAZA, or have been denied access to federal or state-funded assistance programs.

To learn more about the VIDAZA Patient Assistance Program, call **1-866-PHARMION** (1-866-742-7646) Monday through Friday from 8 AM to 8 PM Eastern time or visit us online at **www.VIDAZA.com** (click on *Reimbursement Services*, then *Patient Assistance Program*).

VIDAZA Reimbursement Support Program

Pharmion offers a comprehensive reimbursement support program designed to assist healthcare providers, patients, social workers, and billing personnel with a variety of reimbursement issues related to VIDAZA therapy.

Program staff are available to assist you Monday through Friday from 8 AM to 8 AM (Eastern). You can contact them by

phone at **1-866-PHARMION** (1-866-742-7646) or via fax at 1-866-369-4333. If you prefer, you may also access reimbursement information through our Web site, **www.VIDAZA.com** (click on *Reimbursement Services*, then *Reimbursement Support Program*).

www.VIDAZA.com

An excellent resource for patients, caregivers, and healthcare professionals, **www.VIDAZA.com** features in-depth information about MDS, VIDAZA treatment (including a mechanism of action video and a list of frequently asked questions), and the safety profile of VIDAZA. The site also includes an overview of VIDAZA reimbursement services offered by Pharmion and a link to AllAboutMDS.com (see below).

AllAboutMDS.com

AllAboutMDS.com is a comprehensive Web resource designed to connect people with MDS and their caregivers with the disease-related information they need. The site features links to a variety of MDS overviews (ranging from basic facts to in-depth clinical details), organizations, and local support groups. Visitors can also learn about upcoming clinical trials and MDS centers of excellence and even sign up to receive a free quarterly e-newsletter.

Please see important safety information on pages 26-27 and enclosed full prescribing information.

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Clinical nurse specialist contact information

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