# *An update on Myelodysplastic Syndromes – Patient Management*

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Austin Health | Olivia Newton-John Cancer & Wellness Centre

# Decisions, decisions

- **Watch & wait?**
- **Best supportive care?**
- **Allogeneic bone marrow transplant?**

  Royal Melbourne Hospital 25 of 336 allografts 2007 to mid 2013.
- **Azacitidine?**
- **Clinical trial?**

# How do patients make these crucial decisions?

- Do they understand what MDS actually is?
  - Melanoma, bone cancer, problem with my blood
  - Or those with internet medical degrees
- Kinetics of disease evolution
  - Individualised
- Treatment timeframes?
  - Individualised
- Potential for transformation?
- Where am I in my life right now?

# They need information

- At The Austin Hospital we are ***very*** fortunate to have a Haematology Clinical Nurse Consultant working closely with other disciplines and acting as patient liaison & advocate.

- Role is not funded by the hospital or health department

- Nurse led clinic at all Haematology Outpatient Clinics

- Patients & families can have as much time as they need to understand options fully.  Not just at treatment decision time.

# Best Supportive Care

- Not just Transfusions, EPO, G-CSF, chelation, antibiotics, antifungals
- Emotional support; taking an interest in the patient and being proactive in identifying issues & pursuing interventions throughout disease course
- Transport assistance, home pathology visits, support groups, co-ordinating hospital appointments
- Home visit injection programme

# Improving patient & caregiver satisfaction and care

- We are a long way to achieving our goal if we
  - improve understanding of disease & disease evolution
  - clarify goals of treatment approaches
  - foster a realistic appreciation of expected outcomes

  But still we have patients that “just don’t want to know.”

Smith B D, American J Med 2012 125, 7a 526 - 530

# Outcomes

- We have seen fantastic outcomes in dire situations
- We also see failure to respond, refractory disease, treatment related morbidity & mortality
- But we don’t have a crystal ball, and we have to be honest whilst always being encouraging

# Fatigue

- Symptomatic anaemia with fatigue typically seen in 60 – 80%[1] or up to 95%[2] of MDS patients – depending on your reference
- Packed cell infusions may improve QOL but generally not dramatically
- Contribution of abnormally high cytokine levels [2]
  - Interleukins, interferon, TNF
- Encourage people to stay active physically & exercise.


- 1 NHS Regional Drug & Therapeutic Centre 2009
- 2 Steensma D P, 2008 Leukemia Res 32 (5) 691 – 698

# Iron loading

- Ferritin is a protein which serves to bind, store and transport iron in a safe form
- Free iron is highly toxic to cells
- Average human contains 3 – 4 grams of iron
- *Every 4 units of packed red cells results in equivalent of 1 gram of extra iron.*
- The body has no mechanism to excrete excess iron in any quantity.
- Can impact marrow function, heart failure, renal failure, liver cirrhosis/fibrosis, diabetes, arthritis, depression, impotence etc.

# MDS: Iron Chelation Therapy

- No prospective, randomised controlled trials of ICT in MDS
- Potential toxicity, expense and time required, make role of ICT in MDS controversial
- Deferasirox (exjade)– oral,
- Potential side effects include gastrointestinal, cramps, bloating, diarrhoea, headache, liver & kidney impairment, hearing loss, cataracts
- May require several months to several years to have impact
- Expensive
- Reasonable to use in chronically transfused, low risk patients expected to live for years:

Stone R M, Blood 2009 113, 25, 6296 - 6303

# MDS: Growth Factors

- Erythropoietin etc
- 25% of patients reduce transfusion requirement by >50% or Hb increase by 10g/l
- Response can take >8 weeks, with dose titration
  - Addition of G-CSF increases response rate to 40%
- Increased response rate if:
  - Patients are not transfusion dependent
  - Relatively low intrinsic levels of serum erythropoietin
- Response duration usually 1-2 years
- Survival benefit suggested for responding low risk patients

Stone R M, Blood 2009 113, 25, 6296 - 6303

# MDS: Growth Factors

- Neutrophils increase in most patients treated with G-CSF
  - Our practice to use titrated dosing in selected patients
  - Need to be mindful of proximity to BMAT's
- No currently available cytokines for thrombocytopenic MDS pts
  - Phase I/II studies suggest that romiplostim will improve platelet counts in approximately 50% of MDS pts
  - Eltrombopag used in some small studies
  - Issues: Availability, cost, potential for marrow fibrosis, falling platelet count if ceased, and the potential to stimulate myeloblasts in higher risk pts
- ?Flogging an intrinsically deranged and therefore potentially unresponsive marrow stem cell.

Stone R M, Blood 2009 113, 25, 6296 - 6303

# Infection risk

- Educate your patients
  - Neutropenia, neutrophil dysfunction persists
  - Bacterial infections predominate
  - posaconazole
- Early presentation in event of symptoms
- G.P. Liaison

# Vidaza Indication[1]

Vidaza is indicated for the treatment of patients with:

- Intermediate-2 High risk Myelodysplastic Syndrome (MDS) according to the International Prognostic Scoring System (IPSS),
- Chronic Myelomonocytic Leukemia (CMMoL (10%–29% marrow blasts without Myeloproliferative Disorder)),
- Acute Myeloid Leukemia (AML) with 20%–30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO),

in whom allogeneic stem cell transplantation is not indicated.

Vidaza is a funded medicine, special authority criteria apply.
Vidaza is a Prescription Medicine. Before prescribing Vidaza please refer to the data sheet, which is available on the Medsafe website.

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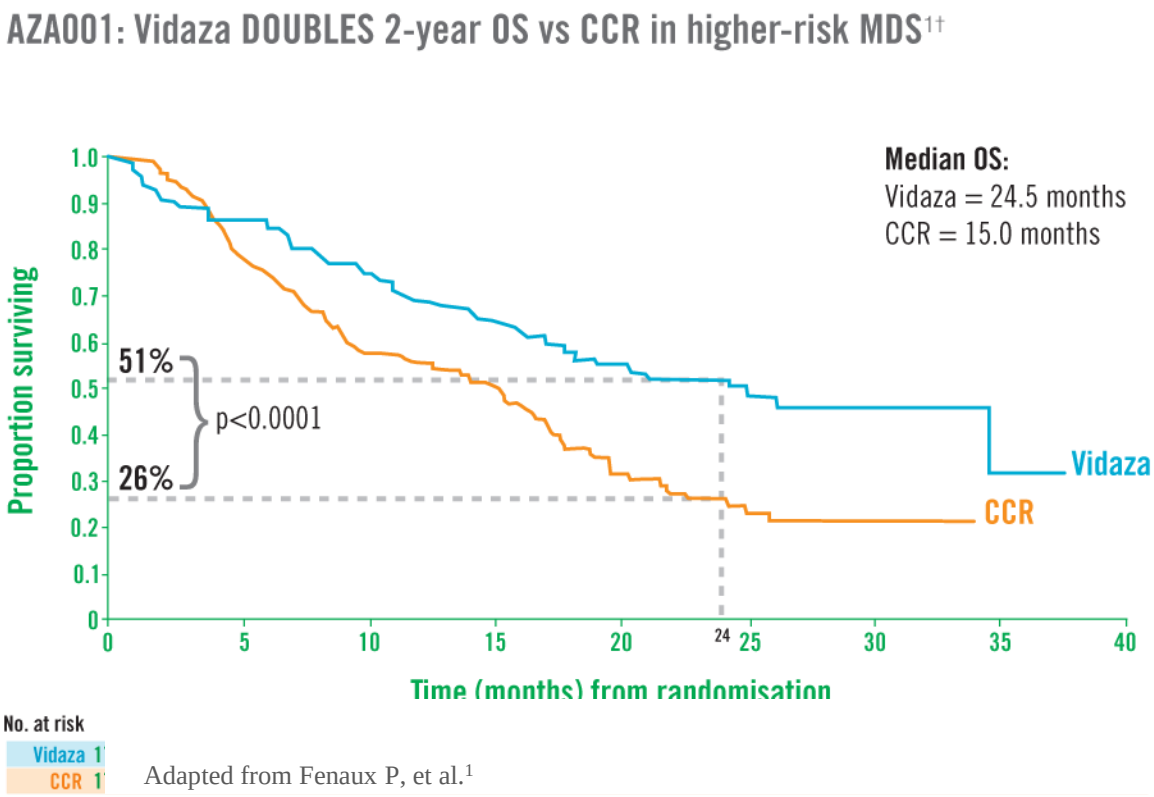
1. Vidaza data sheet, 15 Oct 2013

# Vidaza doubles 2 year OS vs CCR in higher risk MDS Patients[1]




Adapted from Fenaux P, et al.[1]

OS: overall survival. CCR: conventional care regimens: best supportive care only, n=105; low dose Ara-C (LDAC, 20mg/m$^2$ per day x 14 d q28 d), n=49; intensive chemotherapy (Ara-C, 100-200mg/m$^2$ per day by continuous IV infusion x 7d + 3d either IV daunorubicin 45-60mg/m$^2$ per day, idarubicin 9-12mg/m$^2$ per day, or mitoxantrone 8-12mg/m$^2$ per day), n=25[1]

1. Fenaux P, et al. Lancet Oncol 2009;10:223-32

# Safe handling of Vidaza[1,2]

- Vidaza is a cytotoxic drug
- Caution should be exercised when handling and preparing Vidaza
- Procedure for proper handling and disposal of anti-cancer medicinal products should be applied
- If reconstituted Vidaza comes into contact with the skin, immediately and thoroughly wash with soap and water
- If it comes into contact with mucous membranes, flush thoroughly with water

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1. Vidaza Product Information, 25 October 2011. 2. Vidaza Material Safety Data Sheet.

# Suggested management of adverse events in Vidaza recipients[1,2]

| AE | Suggested action | Suggested medication |
|---|---|---|
| Haematological[1] | • Monitoring<br>• Delay of next cycle<br>• Dose adjustment | • Prophylactic antibiotics<br>• Growth factor support<br>• Transfusions |
| Infections[1] | | • Anti-infectives and/or growth factor support |
| Injection site reactions[2] | • Injection technique<br>• Supporting technique | • Antihistamines<br>• Corticosteroids<br>• Analgesics |
| Nausea, vomiting[2] | • Premedication | • Anti-emetics |
| Diarrhoea[2] | • Manage symptomatically | • Anti-diarrhoeals |
| Constipation[2] | • Manage symptomatically | • Laxatives, stool softeners |

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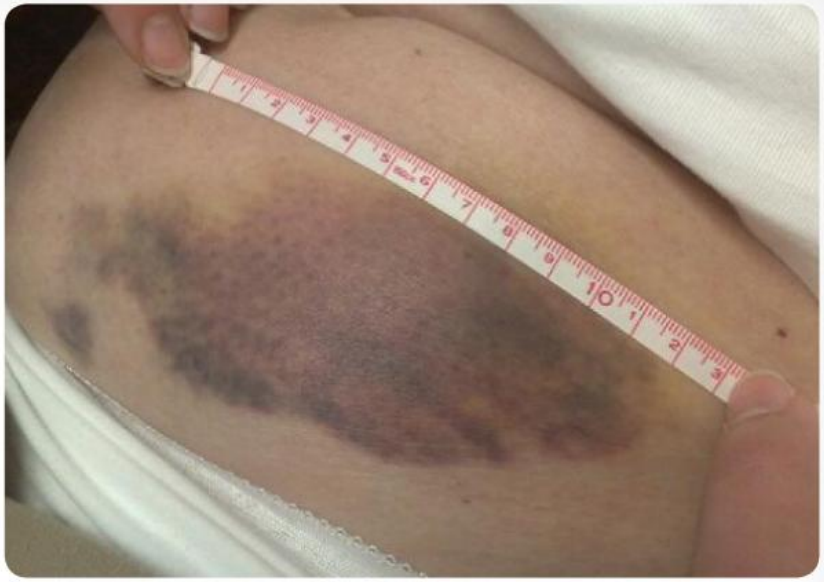
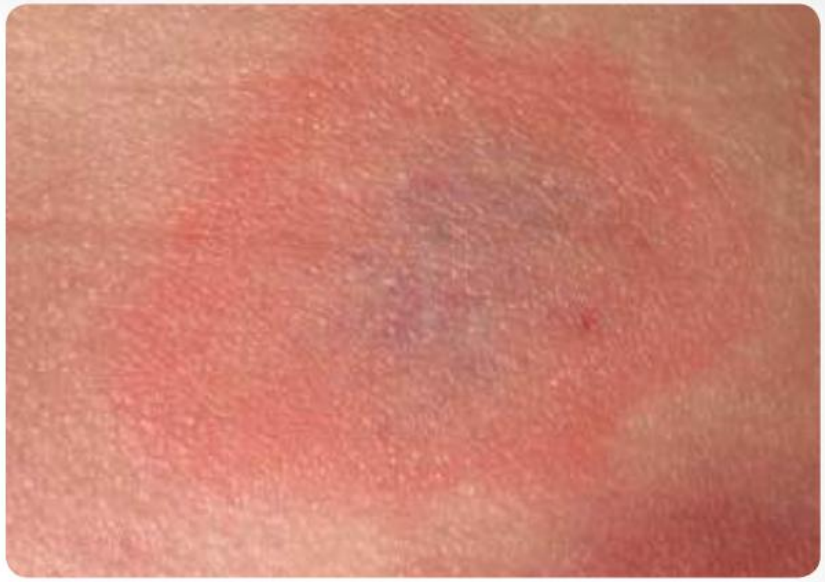
1. Vidaza Product Information, 25 October 2011. 2. Demakos E, Linebaugh JA. *Clin J Oncol Nurs 2005;9:417-23.*

# The majority of skin and subcutaneous AEs are local injection site reactions[1]





1. Vidaza Product Information, 25 October 2011.

# Re-suspension[1]

- Vidaza is a cloudy suspension
- Vidaza should be administered at room temperature
- If required, warm the syringe to room temperature in your hands BEFORE attaching a needle
  - Ensuring the Vidaza is at room temperature allows more Vidaza to dissolve (it will still be a cloudy suspension)
- The contents of the dosing syringe must be re-suspended immediately prior to administration
- To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved
- There should be no large particles

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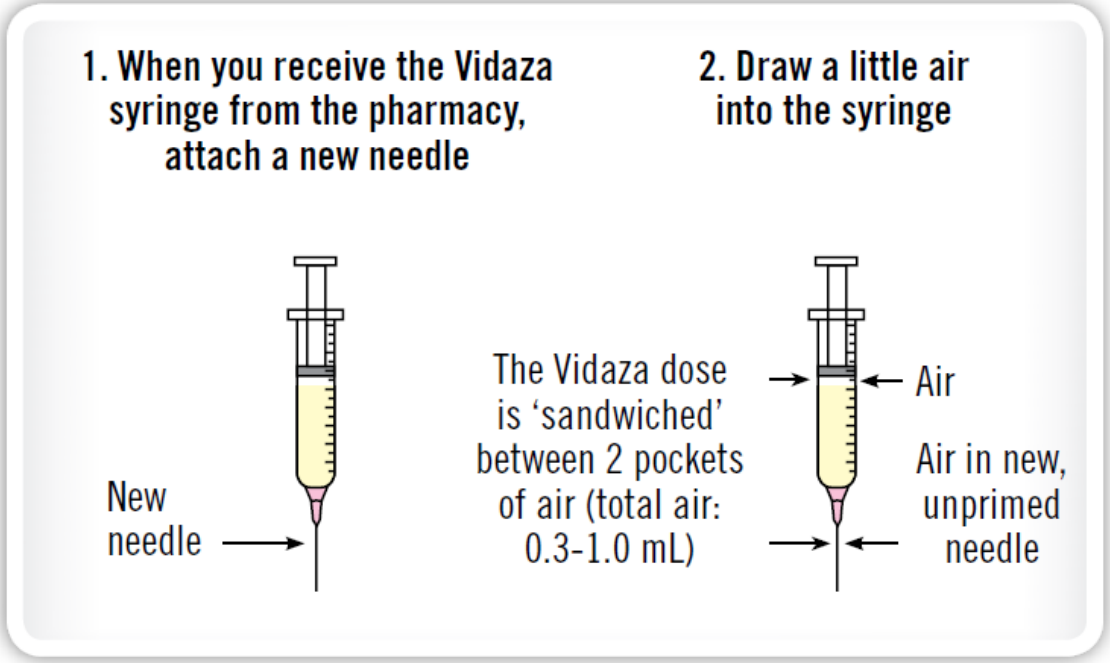
1. Vidaza Product Information, 25 October 2011.

# The ‘air sandwich’: Air-Vidaza-Air

- Attach a fresh 25-gauge s.c. needle to the syringe and do not prime[1]
- Make an ‘air sandwich’ in the syringe to ensure the full volume is delivered
  - i.e. a small pocket of air above the Vidaza suspension (approx. 0.5 mL) and air below the suspension (contained in the new unprimed needle)
- The Vidaza suspension and air pocket will be injected into the subcutaneous tissue

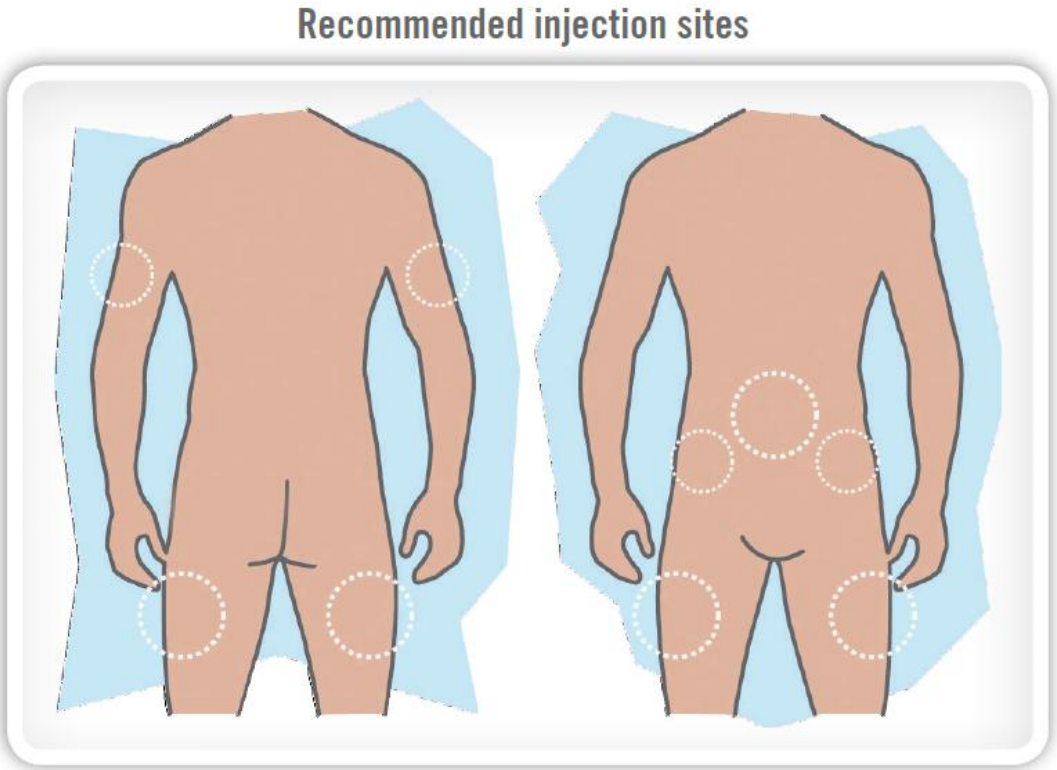





1. Demakos E, Linebaugh JA. *Clin J Oncol Nurs 2005;9:417-23.*

# Choose an injection site

- **Ask the patient what their preferences are**
- The risk and severity of injection site reactions **may** be reduced by using:
  - Appropriate injection sites
  - Small (≤4 mL per site) injection volumes
- Reconstituted Vidaza should be injected subcutaneously into the upper arm, thigh or abdomen[1]

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1. Vidaza Product Information, 25 October 2011.

# Choose an injection site

- Give new injections ≥2.5 cm from the previous site[1]
- Never inject into tender, bruised, red or hardened areas[1]
- Avoid lean areas or easily-irritated areas[2] (e.g. belt line, elasticised waistbands, inner thigh, seat belt line)
- Vidaza should be administered as soon as practicable after reconstitution or stored for up to:[1]
  - 1 hour at 25°C or
  - 8 hours between 2°C and 8°C or
  - 22 hours between 2°C and 8°C when reconstituted with refrigerated (2°C–8°C) water for injections

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1. Vidaza Product Information, 25 October 2011. 2. Demakos E, Linebaugh JA. *Clin J Oncol Nurs 2005;9:417-23.*

# Management of injection site reactions

- Injection site reactions (eg. rash, inflammation, pruritus, erythema or skin lesions) may require management with concomitant medicinal products, such as:[1,2]
  - Antihistamines
  - Corticosteroids

- Be careful about temperature extremes at injection site
  - May use local *warm or cool soaks to soothe the injection site (NOT hot or cold packs)*



1. Demakos E, Linebaugh JA. *Clin J Oncol Nurs 2005;9:417-23. 2. Vidaza Product Information, 25 October 2011.*

# The “other” EPO

Reduction of severity of 5-azacitidine-induced skin reactions in MDS patients with topical evening primrose oil (**preliminary data from a non-randomised trial, n=10**)[1]

6 of the 10 demonstrated, “impressive reductions in site reactions compared to previous cycles. Might be a safe and inexpensive local therapy which could improve patient compliance and adherence to scheduled treatment.”

Costs about $10 per 100 capsules

1. Platzbecker, Ann Hematol. 2010 Apr;89(4):427-8.

# Case study 1

- D G  69 year old male: ESRF on 3 x wk dialysis, IHD with stent, NIDDM, CVA, prostate Ca, AAA repair, hypertension, on EPO.
- Recent trip to Norway for son's wedding!
- Increasing red cell requirements, falling platelets, neutrophils
  - BMAT June 2014:  RAEB-1 with 7% blasts
  - Very poor cytogenetics

# Case study 1

- Frank discussion – not suitable for high dose chemotherapy/BMT approaches – ongoing Haem CNC input, dialysis unit liaison
- Pre azacitidine baseline marrow 7 wks later
  - blast cells 15%: RAEB-2

- **Azacitidine cycle 1: August 2014 at full dose**
- Weekly PRBC Tx Hb 80's, platelets 40, neutrophils 0.5, initial issues with nausea

# Case study 1

- **Start cycle 2**: neutrophils 0.1, platelets 14
  - Intermittent G-CSF, posaconazole prophylaxis
- **Start cycle 3**: no G-CSF mainly in view of planned BMAT, but ? recovering neutrophils
- **End cycle 3**: normal neutrophil/platelet counts, ceased red cell support
  - BMAT:  Blast count 3% with continuing dysplasia

# Case study 1

- Currently: coming up to cycle 8 on home injection programme
- Continuing lethargy and latterly troublesome diarrhoea
- Issues along way with dental infection, and SCC removal

# Case study 2

- S C 64 year old male previously well, admitted late 2009 with staph septicaemia and noted to be cytopenic. BMAT RAEB-1
- At that time, azacitidine not available.
  - Regular monitoring.  Discussion of future therapy
- March 2011 admitted with URTI with worsening pancytopenia.  BMAT low blast count AML
- April 2011: MIDAC induction (elderly AML protocol) – achieved complete remission

# Case study 2

- May 2011, commenced azacitidine

- March 2015, cycle 49
  - Normal counts, local site reactions first week
  - Maintains a normal life
  - Last BMAT March 2012

# Discussion

- Pushing through pancytopenia in early cycles
- Counts often lowest in week 4

- Holidays?
- Extending out cycles or reducing treatment days? i.e. maintenance regimes.
- Dose reduction?
- Ceasing therapy at maximal response?

# Vidaza is a funded medicine, special authority criteria apply. Vidaza is a Prescription Medicine. Before prescribing Vidaza (azacitidine) please refer to the full Data Sheet which is available on the Medsafe website.

**Vidaza® (azacitidine) 100 mg Powder for Injection Data Sheet:** For reconstitution as a suspension for subcutaneous injection or as a solution with further dilution for intravenous infusion. **Indications:** Vidaza is indicated for the treatment of patients with – Intermediate-2 and High-risk Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS); Chronic Myelomonocytic Leukemia (CMMoL [10%-29% marrow blasts without Myeloproliferative Disorder]); Acute Myeloid Leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO) – in whom allogenic stem cell transplantation is not indicated. **Contraindications:** Hypersensitivity to azacitidine or mannitol. Advanced malignant hepatic tumours. Pregnancy. Severe renal impairment. **Precautions:** Adverse effects on male fertility; men should be advised not to father a child whilst receiving Vidaza. Vidaza must not be used during pregnancy or lactation. Men and women of childbearing potential must use effective contraception during and up to 3 months after treatment. Anaemia, neutropenia, thrombocytopenia; perform complete blood counts and reduce or delay dosing based on nadir counts and haematological response. Hepatic Impairment; safety in patients with hepatic impairment not established. Renal toxicity; dose should be delayed or reduced. Advise patients to immediately report oliguria/anuria. Safety in patients with severe congestive heart failure, clinically unstable cardiac disease, or pulmonary disease not established. Vidaza is carcinogenic and genotoxic. No specific dose adjustments are recommended for the elderly. Safety of Vidaza in children has not been established. **Interactions:** No interaction studies have been conducted. Concurrent administration with drugs known to be strong metabolising inducers or inhibitors should be avoided. **Adverse Drug Reactions.** VERY COMMON: pneumonia, nasopharyngitis, febrile neutropenia, neutropenia, leukopenia, thrombocytopenia, anaemia, anorexia, dizziness, headache, dyspnoea, diarrhoea, vomiting, constipation, nausea, abdominal pain, petechiae, pruritus, rash, ecchymosis, arthralgia, fatigue, pyrexia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified). COMMON: neutropenic sepsis, upper respiratory tract infection, urinary tract infection, sinusitis, pharyngitis, rhinitis, herpes simplex, bone marrow failure, pancytopenia, hypokalemia, confusional state, anxiety, insomnia, intracranial haemorrhage, lethargy, eye haemorrhage, conjunctival haemorrhage, hypertension, hypotension, haematoma, dyspnoea exertional, pharyngolaryngeal pain, gastrointestinal haemorrhage, haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia, purpura, alopecia, erythema, rash macular, myalgia, musculoskeletal pain, haematuria, injection site: bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage, malaise, weight decreased. UNCOMMON: hypersensitivity reactions. Adverse effects associated with intravenously administered Vidaza were similar in frequency and severity compared with subcutaneously administered Vidaza. **Dosage and administration:** Administer under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Premedicate for nausea and vomiting. Recommended starting dose for the first treatment cycle is 75 mg/m$^2$ of body surface area given subcutaneously or by intravenous infusion/day for seven days. Cycles should be repeated every 28 days for a minimum of 6 cycles. Patients should be monitored for haematological response and renal toxicities, with dose delay or reduction as indicated in the full Data Sheet. With subcutaneous administration, rotate injection sites. Refer to full Data Sheet for detailed dosage and administration recommendations. **Presentation:** Each vial contains 100 mg azacitidine and 100 mg mannitol. (Minimum Data Sheet V1.5.1)

Celgene Ltd, Level 7, 607 St Kilda Rd, Melbourne Vic 3004, Australia. www.celgene.com.au. NZ Registered Office, Celgene Ltd, PO Box 3035. Wellington, NZ, 6011, New Zealand. Tel 0800 526 529.

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