For the Use of a Registered Medical Practitioner or a Hospital or Laboratory only

# AZADINE

**(Azacitidine Powder for Suspension for Injection 100 mg/vial)**

**1. Name of the medicinal product**
AZADINE (Azacitidine Powder for Suspension for Injection 100 mg/vial)

**2. Qualitative and quantitative composition**
AZADINE (Azacitidine Powder for Suspension for Injection 100 mg/vial)
Each Vial contains:
Azacitidine.....100 mg
Excipients.....Q.S.

**3. Pharmaceutical form**
Powder for suspension for Injection
A white lyophilized powder or cake in a clear glass vial.
When reconstituted with 4mL water for injection, it gives White homogeneous cloudy suspension.

**4. Clinical particulars**

**4.1 Therapeutic indications**
Azacitidine is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:
- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification

**4.2 Posology and method of administration**
Azacitidine treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting.

Posology
The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m$^2$ of body surface area, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle).
It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.
Patients should be monitored for haematologic response/toxicity and renal toxicities; a delay in starting the next cycle or a dose reduction as described below may be necessary.

Laboratory tests
Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

Dose adjustment due to haematological toxicity
Haematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets $\leq$ 50.0 x 10$^9$/l and/or absolute neutrophil count (ANC) $\leq$ 1 x 10$^9$/l.

Recovery is defined as an increase of cell line(s) where haematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (i.e. blood count at recovery $\geq$ nadir count + (0.5 x [baseline count – nadir count]).

*Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) $\geq$ 3.0 x 10$^9$/l and ANC $\geq$ 1.5 x 10$^9$/l, and platelets $\geq$ 75.0 x 10$^9$/l) prior to the first treatment*

If haematological toxicity is observed following Azacitidine treatment, the next cycle of the therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

| Nadir counts | | % Dose in the next cycle, if recovery* is not achieved within 14 days |
|---|---|---|
| ANC (x 10$^9$/l) | Platelets (x 10$^9$/l) | |
| $\leq$ 1.0 | $\leq$ 50.0 | 50 % |
| > 1.0 | > 50.0 | 100 % |

*Recovery = counts $\geq$ nadir count + (0.5 x [baseline count – nadir count])

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10$^9$/l or ANC < 1.5 x 10$^9$/l or platelets < 75.0 x 10$^9$/l) prior to the first treatment

Following Azacitidine treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is $\leq$ 50 %, or greater than 50 % but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC or ANC or platelets is greater than 50 % from that prior to treatment, with no improvement in cell line differentiation, the next cycle of Azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50 %, no dose adjustments should be made. If bone marrow cellularity is $\leq$ 50 %, treatment should be delayed and the dose reduced according to the following table:

| Bone marrow cellularity | % Dose in the next cycle if recovery is not achieved within 14 days | |
|---|---|---|
| | Recovery* $\leq$ 21 days | Recovery* > 21 days |
| 15-50 % | 100 % | 50 % |
| < 15 % | 100 % | 33 % |

*Recovery = counts $\geq$ nadir count + (0.5 x [baseline count – nadir count])
Following dose modifications, the cycle duration should return to 28 days.

Special populations
*Elderly patients*
No specific dose adjustments are recommended for the elderly. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

*Patients with renal impairment*
Azacitidine can be administered to patients with renal impairment without initial dose adjustment. If unexplained reductions in serum bicarbonate levels to less than 20 mmol/l occur, the dose should be reduced by 50 % on the next cycle. If unexplained elevations in serum creatinine or blood urea nitrogen (BUN) to $\geq$ 2-fold above baseline values and above upper limit of normal (ULN) occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50 % on the next treatment cycle.

*Patients with hepatic impairment*
No formal studies have been conducted in patients with hepatic impairment. Patients with severe hepatic organ impairment should be carefully monitored for adverse events. No specific modification to the starting dose is recommended for patients with hepatic impairment prior to starting treatment; subsequent dose modifications should be based on haematology laboratory values. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours.

*Paediatric population*
The safety and efficacy of Azacitidine in children aged 0-17 years have not yet been established. No data are available.

Method of administration
Reconstituted Azacitidine should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.
After reconstitution, the suspension should not be filtered. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

**4.3 Contraindications**
Hypersensitivity to the active substance or to any of the excipients
Advanced malignant hepatic tumours (see section Special warnings and precaution for use).
Breast-feeding (see section Fertility, pregnancy and lactation).

**4.4 Special warnings and precautions for use**

Haematological toxicity
Treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles.Complete blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle. After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and haematological response. Patients should be advised to promptly report febrile episodes. Patients and physicians are also advised to be observant for signs and symptoms of bleeding.

Hepatic impairment
No formal studies have been conducted in patients with hepatic impairment. Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline serum albumin < 30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours.

Renal impairment
Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents.

If unexplained reductions in serum bicarbonate (< 20 mmol/L) or elevations of serum creatinine or BUN occur, the dose should be reduced or administration delayed.
Patients should be advised to report oliguria and anuria to their health care provider immediately.

Patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney.

Laboratory tests
Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

Cardiac and pulmonary disease
Safety and efficacy of azacitidine of Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease has not been established. Recent data from a clinical trial in patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine. It is therefore advised to exercise caution when prescribing azacitidine to these patients. Cardiopulmonary assessment before and during the treatment should be considered.

Necrotising fasciitis
Necrotising fasciitis, including fatal cases, have been reported in patients treated with Azacitidine. Azacitidine therapy should be discontinued in patients who develop necrotising fasciitis and appropriate treatment should be promptly initiated.

Tumour lysis syndrome
The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

**4.5 Interaction with other medicinal products and other forms of interaction**
Azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs); interactions related to these metabolizing enzymes are therefore considered unlikely.
No formal clinical drug interaction studies with azacitidine have been conducted.
Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely.

**4.6 Fertility, pregnancy and lactation**
Women of childbearing potential / Contraception in males and females
Women of childbearing potential and men must use effective contraception during and up to 3 months after treatment.

Pregnancy
Azacitidine should not be used during pregnancy, especially during the first trimester, unless clearly necessary.
The advantages of treatment should be weighed against the possible risk for the foetus in every individual case.

Breast-feeding
It is not known whether azacitidine or its metabolites are excreted in human milk. Due to the potential serious adverse reactions in the nursing child, breast-feeding is contraindicated during azacitidine therapy.

Fertility
Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 3 months after treatment. Before starting treatment, male patients should be advised to seek counselling on sperm storage.

**4.7 Effects on ability to drive and use machines**
Azacitidine has minor or moderate influence on the ability to drive and use machines. Fatigue has been reported with the use of azacitidine. Therefore, caution is recommended when driving or operating machines.

**4.8 Undesirable effects**

Summary of the safety profile
Adult population with MDS, CMML and AML (20-30% marrow blast):
Adverse reactions considered to be possibly or probably related to the administration of Azacitidine have occurred in many patients. The most common serious adverse reactions included febrile neutropenia and anaemia. Other serious adverse reactions include infections such as neutropenic sepsis and pneumonia (some with fatal outcome), thrombocytopenia, hypersensitivity reactions and haemorrhagic events (e.g. cerebral haemorrhage), gastrointestinal haemorrhage and intracranial haemorrhage.

The most commonly reported adverse reactions with azacitidine treatment were haematological reactions including thrombocytopenia, neutropenia and leukopenia, gastrointestinal events including nausea, vomiting or injection site reactions.

Adult population aged 65 years or older with AML with > 30% marrow blasts

The most common serious adverse reactions include febrile neutropenia, pneumonia, and pyrexia. Other less frequently serious adverse reactions include sepsis, anaemia, neutropenic sepsis, urinary tract infection, thrombocytopenia, neutropenia, cellulitis, dizziness and dyspnoea.

The most commonly reported adverse reactions were gastrointestinal events, including constipation, nausea, and diarrhoea, general disorders and administration site conditions including pyrexia and haematological events, including febrile neutropenia and neutropenia.

Tabulated list of adverse reactions
Below Table contains adverse reactions associated with azacitidine treatment obtained from the main clinical studies in MDL and AML and post marketing surveillance.

Frequencies are defined as: very common, common; uncommon; rare; very rare; not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| System Organ Class | Very common | Common | Unco-mmon | Rare | Not Known |
|---|---|---|---|---|---|
| **Infections and infestations** | pneumonia* (including bacterial, viral and fungal), nasopharyngitis | sepsis* (including bacterial, viral and fungal), neutropenic sepsis*, respiratory tract infection (includes upper and bronchitis), urinary tract infection, cellulitis, diverticulitis, oral fungal infection, sinusitis, pharyngitis, rhinitis, herpes simplex, skin infection | | | necrotising fasciitis* |
| **Blood and lymphatic system disorders** | febrile neutropenia*, neutropenia, leukopenia, thrombocyto-penia, anaemia | pancytopenia*, bone marrow failure | | | |
| **Immune system disorders** | | | hyperse-nsitivity reactions | | |
| **Metabolism and nutrition disorders** | Anorexia, decreased appetite, hypokalemia | dehydration | | tumour lysis synd-rome | |
| **Psychiatric disorders** | insomnia | confusional state, anxiety | | | |
| **Nervous system disorders** | dizziness, headache | intracranial haemorrhage*, syncope, somnolence, lethargy | | | |
| **Eye disorders** | | eye haemorrhage, conjunctival haemorrhage | | | |
| **Cardiac disorders** | | pericardial effusion | | | |
| **Vascular disorders** | | hypotension*, hypertension, orthostatic hypotension, haematoma | | | |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnea, epistaxis | pleural effusion, dyspnoea exertional, pharyngolaryngeal pain | | inters-titial lung disease | |
| **Gastrointestinal disorders** | diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper and abdominal discomfort) | gastrointestinal haemorrhage* (includes mouth haemorrhage) , haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia | | | |
| **Hepatobiliary disorders** | | | hepatic failure*, progre-ssive hepatic coma | | |
| **Skin and subcutaneous tissue disorders** | petechiae, pruritus (includes generalized), rash, ecchymosis | purpura, alopecia, urticaria, erythema, rash macular | acute febrile neutrop-hilic dermat-osis, pyoderma gangren-osum | | |
| **Musculoskeletal, and connective tissue disorders** | arthralgia, musculoskeletal pain (includes back, bone and pain in extremity) | Myalgia, muscle spasms, | | | |
| **Renal and urinary disorders** | | renal failure*, haematuria, elevated serum creatinine | renal tubular acidosis | | |
| **General disorders and administration site conditions** | pyrexia*, fatigue, asthenia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified) | bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage (at injection site), malaise, chills, catheter site haemorrhage | | injection site necrosis (at injection site) | |
| **Investigations** | weight decreased | | | | |

* = rarely fatal cases

Description of selected adverse reactions
*Haematologic adverse reactions*
The most commonly reported adverse reactions associated with azacitidine treatment include anaemia, thrombocytopenia, neutropenia, febrile neutropenia and leukopenia, and were usually Grade 3 or 4. There is a greater risk of these events occurring during the first 2 cycles, after which they occur with less frequency in patients with restoration of haematological function. Most haematological adverse reactions were managed by routine monitoring of complete blood counts and delaying azacitidine administration in the next cycle, prophylactic antibiotics and/or growth factor support (e.g. G-CSF) for neutropenia and transfusions for anaemia or thrombocytopenia as required.

*Infections*
Myelosuppression may lead to neutropenia and an increased risk of infection. Serious adverse reactions such as sepsis, including neutropenic sepsis and pneumonia were reported in patients receiving azacitidine, some with a fatal outcome. Infections may be managed with the use of anti-infectives plus growth factor support (e.g. G-CSF) for neutropenia.

*Bleeding*
Bleeding may occur with patients receiving azacitidine. Serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage have been reported. Patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia.

*Hypersensitivity*
Serious hypersensitivity reactions have been reported in patients receiving azacitidine. In case of an anaphylactic-like reaction, treatment with azacitidine should be immediately discontinued and appropriate symptomatic treatment initiated.

*Skin and subcutaneous tissue adverse reactions*
The majority of skin and subcutaneous adverse reactions were associated with the injection site. None of these adverse reactions led to discontinuation of azacitidine, or reduction of azacitidine dose in the pivotal studies. The majority of adverse reactions occurred during the first 2 cycles and tended to decrease with subsequent cycles. Subcutaneous adverse reactions such as injection site rash/inflammation/pruritus, rash, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory medicinal products (NSAIDs).

*Gastrointestinal adverse reactions*
The most commonly reported gastrointestinal adverse reactions associated with azacitidine treatment included constipation, diarrhoea, nausea and vomiting. These adverse reactions were managed symptomatically with anti-emetics for nausea and vomiting; anti-diarrhoeals for diarrhoea, and laxatives and/or stool softeners for constipation.

*Renal adverse reactions*
Renal abnormalities, ranging from elevated serum creatinine and haematuria to renal tubular acidosis, renal failure and death were reported in patients treated with azacitidine

*Hepatic adverse reactions*
Patients with extensive tumour burden due to metastatic disease have been reported to experience hepatic failure, progressive hepatic coma and death during azacitidine treatment

*Cardiac events*
In patients with newly diagnosed AML, a significant increase in cardiac events is possible with azacitidine treatment.

*Elderly population*
There is limited safety information available with azacitidine in patients $\geq$ 85 years.

**4.9 Overdose**
In the event of overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for azacitidine overdose.

**5. Pharmacological properties**
**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Antineoplastic agents, pyrimidine analogues; ATC code: L01BC07

Mechanism of action
Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer-suppressing functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.

**5.2 Pharmacokinetic properties**

Absorption
Following subcutaneous administration of a single 75 mg/m$^2$ dose, azacitidine was rapidly absorbed with peak plasma concentrations of 750 ± 403 ng/mL occurring at 0.5 h after dosing (the first sampling point). The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration (single 75 mg/m$^2$ doses) was approximately 89% based on area under the curve (AUC).

Area under the curve and maximum plasma concentration ($C_{max}$) of subcutaneous administration of azacitidine were approximately proportional within the 25 to 100 mg/m$^2$ dose range.

Distribution
Following intravenous administration, the mean volume of distribution was 76 ± 26 L, and systemic clearance was 147 ± 47 L/h.

Biotransformation
Based on in vitro data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs).

Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. In human liver S9 fractions, formation of metabolites was independent of NADPH implying that azacitidine metabolism was not mediated by cytochrome P450 isoenzymes. An in vitro study of azacitidine with cultured human hepatocytes indicates that at concentrations of 1.0 µM to 100 µM (i.e. up to approximately 30-fold higher than clinically achievable concentrations), azacitidine does not induce CYP 1A2, 2C19, or 3A4 or 3A5. In studies to assess inhibition of a series of P450 isoenzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) azacitidine up to 100 µM did not produce inhibition. Therefore, CYP enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Elimination
Azacitidine is cleared rapidly from plasma with a mean elimination half-life (t½) after subcutaneous administration of 41 ± 8 minutes. No accumulation occurs after subcutaneous administration of 75 mg/m$^2$ azacitidine once daily for 7 days. Urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following intravenous and subcutaneous administration of $^{14}$C-azacitidine, 85 and 50 % of the administered radioactivity was recovered in urine respectively, while < 1 % was recovered in faeces.

Special populations
The effects of hepatic impairment gender, age, or race on the pharmacokinetics of azacitidine have not been formally studied.

Renal impairment
Renal impairment has no major effect on the pharmacokinetic exposure of azacitidine after single and multiple subcutaneous administrations. Following subcutaneous administration of a single 75 mg/m$^2$ dose, mean exposure values (AUC and $C_{max}$) from subjects with mild, moderate and severe renal impairment were increased by 11-21%, 15-27%, and 41-66%, respectively, compared to normal renal function subjects. However, exposure was within the same general range of exposures observed for subjects with normal renal function. Azacitidine can be administered to patients with renal impairment without initial dose adjustment provided these patients are monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney.

Pharmacogenomics
The effect of known cytidine deaminase polymorphisms on azacitidine metabolism has not been formally investigated.

**6. Pharmaceutical particulars**
**6.1 List of excipients**
Mannitol

**6.2 Incompatibilities**
This medicinal product must not be mixed with other medicinal products.

**6.3 Shelf life**
3 years

After reconstitution:
When Azacitidine is reconstituted using water for injections that has not been refrigerated, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 25 °C for 45 minutes and at 2 °C to 8 °C for 8 hours.

The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. When Azacitidine is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than 8 hours at 2 °C to 8 °C when reconstituted using water for injections that has not been refrigerated or not longer than 22 hours when reconstituted using refrigerated (2 °C to 8 °C) water for injections.

**6.4 Special precautions for storage**

Unopened vials
Do not store above 30°C.

Reconstituted suspension
For storage conditions of the reconstituted of the medicinal product, see section shelf life

**6.5 Nature and contents of container**
AZADINE (Azacitidine Powder for Suspension for Injection 100 mg/vial) is available in clear type I glass vial sealed with grey siliconised rubber stopper and aluminium flip off white seal. Pack size: Each carton contains 1 glass vial.

**6.6 Special precautions for disposal and other handling**

Recommendations for safe handling
Azacitidine is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions. Procedures for proper handling and disposal of anticancer medicinal products should be applied.

If reconstituted azacitidine 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.

Reconstitution procedure
Azacitidine should be reconstituted with water for injections. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. Details on storage of the reconstituted product are provided below.

1. The following supplies should be assembled:
   Vial (s) of azacitidine; vial(s) of water for injections; non-sterile surgical gloves; alcohol wipes; 5 mL injection syringe(s) with needle(s).

2. 4 mL of water for injections should be drawn into the syringe, making sure to purge any air trapped within the syringe.

3. The needle of the syringe containing the 4 mL of water for injections should be inserted through the rubber top of the azacitidine vial followed by injection of the water for injections into the vial.

4. Following removal of the syringe and needle, the vial should be vigorously shaken until a uniform cloudy suspension is achieved. After reconstitution each mL of suspension will contain 25 mg of azacitidine (100 mg/4 mL). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates. Do not filter the suspension after reconstitution since this could remove the active substance. It must be taken into account that filters are present in some adaptors, spikes and closed systems; therefore such systems should not be used for administration of the medicinal product after reconstitution.

5. The rubber top should be cleaned and a new syringe with needle inserted into the vial. The vial should then be turned upside down, making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of medicinal product required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.

6. A fresh subcutaneous needle (recommended 25-gauge) should then be firmly attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.

7. If needed (doses over 100 mg) all the above steps for preparation of the suspension should be repeated. For doses greater than 100 mg (4 mL), the dose should be equally divided into 2 syringes (e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial).

8. The contents of the dosing syringe must be re-suspended immediately prior to administration. The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 20 °C-25 °C. If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately, and a new dose prepared. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates.

Storage of the reconstituted product
For storage conditions after reconstitution of the medicinal product, see section shelf life

Calculation of an individual dose
The total dose, according to the body surface area (BSA) can be calculated as follows:
Total dose (mg) = Dose (mg/m$^2$) x BSA (m$^2$)

The following table is provided only as an example of how to calculate individual azacitidine doses based on an average BSA value of 1.8 m$^2$.

| Dose mg/m$^2$ *(% of recommended starting dose)* | Total dose based on BSA value of 1.8 m$^2$ | Numberof vials required | Total volume of reconstituted suspension required |
|---|---|---|---|
| 75 mg/m$^2$ (100 %) | 135 mg | 2 vials | 5.4 mL |
| 37.5 mg/m$^2$ (50 %) | 67.5 mg | 1 vial | 2.7 mL |
| 25 mg/m$^2$ (33 %) | 45 mg | 1 vial | 1.8 mL |

Method of administration
Reconstituted Azacitidine should be injected subcutaneously (insert the needle at a 45-90° angle) using a 25-gauge needle into the upper arm, thigh or abdomen.

Doses greater than 4 mL should be injected into two separate sites.

Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

Any unused product or waste material should be disposed of in accordance with local requirements.

**7. Name and Address of Product Registration Holder :**
Accord Healthcare Sdn. Bhd. (1035160 D)
26-6, Menara 1 MK, Kompleks One Mont Kiara, No. 1 Jalan Kiara,
50480 Kuala Lumpur, Malaysia.

Manufactured by:
Intas Pharmaceuticals Limited
Plot No 5/6/7, Pharmez, Near Village Matoda, Sarkhej/Bavla highway,
NH-8A, Matoda, Ahmedabad, Gujarat – 382213 INDIA

**8. Date of revision of the text**
June 2019

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