# PROFESSIONAL INFORMATION FOR DITICAZA 100 mg/vial

## SCHEDULING STATUS

**S4**

## 1 NAME OF THE MEDICINE

**DITICAZA 100 mg/vial**

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine. The reconstituted suspension contains 25 mg/mL azacitidine.

Contains sugar: mannitol

Each vial contains 100 mg mannitol

'for full list of excipients, see section 6.1'

## 3 PHARMACEUTICAL FORM

White lyophilized powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DITICAZA is indicated for treatment of adult patients with Myelodysplastic syndromes (MDS) including the following subtypes of the French–American–British classification:

- Refractory anaemia (RA) according to the French-American-British classification (FAB) system, plus neutropenia or thrombocytopenia or requiring transfusions.
- Refractory anaemia with ringed sideroblasts (RARS) according to the FAB system, plus neutropenia or thrombocytopenia or requiring transfusions.
- Refractory anaemia with excess blasts (RAEB) according to the FAB system.
- Refractory anaemia with excess blasts in transformation (RAEB-T) according to the FAB system (or acute myeloid leukaemia with 20- 30 % bone marrow blasts and multilineage

dysplasia according to World Health Organisation (WHO) classification).

- DITICAZA is also indicated for treating adult patients with chronic myelomonocytic leukemia (CMML) according to the FAB system.
- Acute myeloid leukemia (AML) with > 30 % bone marrow blasts according to the WHO classification, in patients who are not eligible for hematopoietic stem cell transplantation (HSCT).

**4.2 Posology and method of administration**

**Posology**

DITICAZA treatment should be initiated and monitored under the supervision of a medical practitioner experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting.

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, 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 haematological response/toxicity and renal toxicities (see section 4.8); a delay in starting the next cycle or a dose reduction as described below may be necessary.

**Dosage Adjustment due to haematological toxicity:**

***Patients with baseline blood counts (i.e. White Blood Cells (WBC) > 3,0 x 10$^9$/L and absolute neutrophil count (ANC) > 1,5 x10$^9$/L, and platelets > 75,0 x 10$^9$/L).***

If haematological toxicity is observed following DITICAZA treatment, the next cycle of DITICAZA 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) | |
| ≤ 1,0 | ≤ 50,0 | 50 % |
| > 1,0 | > 50,0 | 100 % |

*Recovery= counts≥ Nadir count + (0,5 x [ baseline count- Nadir count])

***Patients 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)****:*

Following DITICAZA treatment, if the decrease in WBC or ANC or platelets from baseline is less than 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 be 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 DITICAZA 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 ≤ 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 * ≤ 21 days | Recovery* > 21 days |
| 15-50% | 100% | 50% |
| < 15% | 100% | 33% |

*Recovery= counts≥ Nadir count + (0.5 x [ baseline count- Nadir count])

Following dose modifications, the cycle duration should return to 28 days.

**Special populations**

*Patients with Renal Impairment:*

DITICAZA 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 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 (see section 4.4).

*Patients with Hepatic Impairment:*

No formal studies have been conducted in patients with hepatic impairment (see section 4.4).

DITICAZA is contraindicated in patients with malignant hepatic tumours (see sections 4.3 and 4.4).

*Elderly:*

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.

*Laboratory Tests*

Liver function tests and serum creatinine should be determined prior to initiation of therapy.

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.

**Paediatric population**

DITICAZA is not recommended for use in children below 18 years of age, due to insufficient data on safety and efficacy.

**Method of administration**

DITICAZA should be administered under the supervision of a medical practitioner qualified in the use of anticancer medicines. Reconstituted DITICAZA should be injected subcutaneously. Rotate sites for injection (thigh, abdomen, or upper arm).

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.

For instructions on reconstitution of the medicine (see section 6.6).

**4.3 Contraindications**

DITICAZA is contraindicated in the following:

- Patients with known hypersensitivity to azacitidine or to any of the excipients of DITICAZA listed in section 6.1.
- Patients with advanced malignant hepatic tumours (see section 4.4).
- Pregnancy and breast-feeding (see section 4.6).
- Patients must not receive live vaccines while being treated with DITICAZA.
- DITICAZA is not recommended for use in children and adolescents below the age of 18.

**4.4 Special warnings and precautions for use**

*Haematological toxicity*

Treatment with DITICAZA is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles (see section 4.8). 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 (see section 4.2). Patients should be advised to promptly report febrile episodes. Patients and medical practitioners 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 as in DITICAZA, is contraindicated in patients with advanced malignant hepatic tumours (see section 4.3).

*Renal impairment*

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported in patients treated with intravenous (IV) DITICAZA in combination with other chemotherapeutic medicines for non-MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalaemia (serum potassium < 3 mmol/L) developed in 5 patients with chronic myelogenous leukaemia (CML) treated with azacitidine and etoposide. 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 (see section 4.2).

Patients should be advised to report oliguria and anuria to the health care provider immediately. Although no clinically relevant differences in the frequency of adverse reactions were noted between subjects with normal renal function compared to those with renal impairment, patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney (see section 4.2).

*Laboratory Tests*

Liver function tests, serum creatinine and serum bicarbonate should be obtained 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 (see sections 4.2 and 4.8).

*Cardiac and pulmonary disease*

Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal registration studies and therefore the safety and efficacy of azacitidine in these patients has not been established. Recent data from a clinical study in patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine (see section 4.8).

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 as in DITICAZA 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.

*Differentiation syndrome*

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving injectable azacitidine as contained in DITICAZA. Differentiation syndrome may be fatal and symptoms and clinical findings include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction (see section 4.8). Treatment with high-dose IV corticosteroids and haemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation of injectable azacitidine should be considered until resolution of symptoms and if resumed, caution is advised.

DITICAZA contains mannitol and may have a laxative effect.

**4.5 Interaction with other medicines and other forms of interaction**

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); interactions related to these metabolizing enzymes *in vivo* are therefore considered unlikely. Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely (see section 5.2). No formal clinical medicine interaction studies with azacitidine have been conducted.

**4.6 Fertility, pregnancy and lactation**

**Women of childbearing potential / Contraception in males and females**

Women of childbearing potential should be advised to avoid pregnancy during treatment with DITICAZA and should use effective contraception during and up to 3 months after treatment.

**Pregnancy**

DITICAZA may cause foetal harm when administered to a pregnant woman.

Azacitidine was teratogenic in animals. If DITICAZA is used during pregnancy or if a patient becomes pregnant while taking DITICAZA, the patient should be apprised of the potential hazard to the foetus.

Female partners of male patients receiving DITICAZA should not become pregnant.

**Breastfeeding**

Due to the potential serious adverse reactions in the nursing child, breastfeeding must be discontinued during DITICAZA 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**

DITICAZA has minor or moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported with the use of azacitidine. Therefore, caution is recommended when driving or operating machines.

**4.8 Undesirable effects**

**a. Summary of the safety profile**

*Adult population with MDS, CMML and AML (20-30% marrow blasts)*

The most frequently reported adverse reactions were gastrointestinal events (nausea, vomiting and diarrhoea), haematological reactions (anaemia, thrombocytopenia, leukopenia and neutropenia), and injection site reactions (erythema and pain). Less frequently reported serious adverse reactions were neutropenic sepsis, pneumonia, thrombocytopenia and haemorrhagic events such as cerebral haemorrhage.

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

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

Less frequently reported serious adverse reactions were sepsis, neutropenic sepsis, anaemia, urinary tract infection, thrombocytopenia, neutropenia, cellulitis, dizziness and dyspnoea.

**b. Tabulated list of adverse reactions**

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| **Infections and infestations** | Frequent | 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 |
| | Frequency unknown | Necrotising fasciitis* |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | Frequency unknown | Differentiation syndrome |
| **Blood and lymphatic system disorders** | Frequent | Anaemia, febrile neutropenia*, leukopenia, neutropenia, thrombocytopenia, pancytopenia*, bone marrow failure |
| **Immune system disorders** | Less frequent | Hypersensitivity reactions |
| **Metabolism and nutrition disorders** | Frequent | Anorexia, decreased appetite, hypokalemia, dehydration |
| | Less frequent | Tumour lysis syndrome |
| **Psychiatric disorders** | Frequent | Anxiety, insomnia, confusional state |

| | | |
|---|---|---|
| **Nervous system disorders** | Frequent | Dizziness, headache, intracranial haemorrhage*, syncope, somnolence, lethargy |
| **Eye disorders** | Frequent | Eye haemorrhage, conjunctival haemorrhage |
| **Cardiac disorders** | Frequent | Pericardial effusion |
| | Less frequent | Pericarditis |
| **Vascular disorders** | Frequent | Hypotension*, hypertension, orthostatic hypotension, haematoma, flushing |
| **Respiratory, thoracic and mediastinal disorders** | Frequent | Dyspnoea, epistaxis, pleural effusion, dyspnoea exertional, pharyngolaryngeal pain, nasal congestion, haemoptysis |
| | Less frequent | Interstitial lung disease |
| **Gastrointestinal disorders** | Frequent | Constipation, diarrhoea, nausea, vomiting, gastrointestinal haemorrhage (includes mouth haemorrhage), haemorrhoidal haemorrhage, stomatitis, gingival bleeding, loose stools, oral mucosal petechiae, stomatitis, tongue ulceration, abdominal pain (includes upper and abdominal discomfort), dyspepsia |
| | Less frequent | Perirectal abscess |
| **Hepato-biliary disorders** | Less frequent | Hepatic failure*, progressive hepatic coma |
| **Skin and subcutaneous** | Frequent | Ecchymosis, erythema, increased sweating rash, pruritus (includes generalised), rash, |

| | | |
|---|---|---|
| **tissue disorders** | | urticaria, petechiae, purpura, alopecia |
| | Less frequent | Acute febrile neutrophilic dermatosis, pyoderma gangrenosum |
| **Musculoskeletal and connective tissue disorders** | Frequent | Arthralgia, myalgia, musculoskeletal pain (includes back bone and pain in extremity), muscle spasms |
| **Renal and urinary disorders** | Frequent | Renal failure*, haematuria, elevated serum creatinine, dysuria |
| | Less frequent | Renal tubular acidosis |
| **General disorders and administration site conditions** | Frequent | 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 hemorrhage, granuloma, injection site pigmentation changes, lethargy, rigors |
| | Less frequent | Injection site necrosis (at injection site) |
| **Investigations** | Frequent | Blood creatinine increased; weight decreased |
| **Injury, poisoning and procedural complications** | Frequent | Post procedural haemorrhage |

*= rarely fatal cases have been reported

Description of selected adverse reactions

*Haematologic adverse reactions*

The most frequently reported haematological adverse reactions associated with azacitidine treatment include anaemia, thrombocytopenia, neutropenia, febrile neutropenia and leukopenia. 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 as in DITICAZA. 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 DITICAZA 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 of treatment 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 frequently 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 (see section 4.4).

*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 (see section 4.4).

*Cardiac events*

Data from a clinical study allowing enrolment of patients with known history of cardiovascular or pulmonary disease showed an increase in cardiac events in patients with newly diagnosed AML treated with azacitidine (see section 4.4).

*Elderly population*

There is limited safety information available with azacitidine in patients ≥85 years.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of DITICAZA is important. It allows continued monitoring of the benefit/risk balance of the DITICAZA. Healthcare professionals are asked to report any suspected adverse to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform ( who-ucm.org) found on SAHPRA website or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

**4.9 Overdose**

In the event of overdosage, side effects will be exaggerated (see section 4.8). The patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for DITICAZA overdosage.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

**PHARMACOLOGICAL CLASSIFICATION**: A 26 – Cytostatics

Pharmacotherapeutic group: Antineoplastic agents, pyrimidine analogues; ATC code: L01BC07.

Azacitidine is cytidine nucleoside analogue that incorporates into RNA and DNA. Azacitidine is believed to exert its antineoplastic effects by cytotoxicity to abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may be due to inhibition of protein synthesis and activation of DNA damage pathways, due to incorporation into RNA and DNA, respectively. Incorporation of azacitidine into DNA also results in DNA hypomethylation and may allow the re-expression of genes involved in normal cell cycle regulation and differentiation. Non-proliferating cells are relatively insensitive to azacitidine.

**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 0.25 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 the 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 P450isoenzymes (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 ($t_{½}$) 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 (see section 4.2), gender, age, or race on the pharmacokinetics of azacitidine have not been formally studied.

*Renal impairment*

Severe 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.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

- Azacitidine
- Mannitol
- Acetonitrile
- Water for injection
- Nitrogen

**6.2 Incompatibilities**

- This medicine must not be mixed with other medicinal products except those mentioned in section 6.6.

**6.3 Shelf life**

Powder for injection: 24 months

After reconstitution:

When DITICAZA is reconstituted using water for injections that has not been refrigerated, chemical and physical in-use stability of the reconstituted medicine has been demonstrated at 25 °C for 60 minutes and at 2 °C to 8 °C for 8 hours.

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

From a microbiological point of view, the reconstituted medicine 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**

Powder for injection:

Store at or below 25 °C. Protect from light and moisture.

Keep the vial in the carton until required for use.

**KEEP OUT OF REACH OF CHILDREN**.

After reconstitution:

For storage conditions after reconstitution of the medicine, see section 6.3.

**6.5 Nature and contents of container**

DITICAZA 100 mg/ vial

30 ml clear moulded glass vials, type I with 20 mm neck with 5 ml 20 mm igloo rubber GBB stopper with a white flip off seals 20 mm matte top finish.

Pack size: 1 x 30 mL

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

Recommendations for safe handling

DITICAZA is a cytotoxic medicine and, as with other potentially toxic compounds, caution should be exercised when handling and preparing DITICAZA suspensions. Procedures for proper handling and disposal of anticancer medicines should be applied.

If reconstituted DITICAZA 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

DITICAZA should be reconstituted with water for injections. The shelf life of the reconstituted medicine 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 medicine is a homogeneous, cloudy suspension, free of agglomerates. The medicine should be discarded if it contains large particles or agglomerates. Do not filter the suspension after reconstitution since this could remove the active ingredient. 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 medicine 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 medicine 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. When more than 1 vial is needed all the above steps for preparation of the suspension should be repeated. For doses requiring more than 1 vial, the dose should be equally divided 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 medicine should be discarded if it contains large particles or agglomerates.

Storage of the reconstituted medicine

For storage conditions after reconstitution of the medicine, see section 6.3.

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$^2$ | Number of 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 DITICAZA 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.

Disposal

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

**7 HOLDER OF CERTIFICATE OF REGISTRATION**

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate Campus,

Building No.2, First Floor,

74 Waterfall Drive,

Midrand, 2066

Telephone number: 012 644 1220

e-mail address: nokuthula.n@hetero.com

**8 REGISTRATION NUMBER(S)**

56/26/0956.955.

**9 DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION**

26 MAY 2026.

**10 DATE OF REVISION OF THE TEXT**

N/A.