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

**DECITAS**
**(Decitabine 50mg/vial Powder for Concentrate for Solution for Infusion)**

## 1. Name of the medicinal product

DECITAS (Decitabine 50mg/vial Powder for Concentrate for Solution for Infusion)

## 2. Qualitative and quantitative composition

DECITAS (Decitabine 50mg/vial Powder for Concentrate for Solution for Infusion)
Each Vial contains:
Decitabine……50 mg
Excipients……q.s.

## 3. Pharmaceutical form

A white to almost white lyophilized powder in a clear glass vial.
Description after reconstitution: Clear colorless solution
List of compatible diluents: 0.9% Sodium Chloride Injection and 5% Dextrose Injection

## 4. Clinical particulars

### 4.1 Therapeutic indications

DECITAS is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British (FAB) subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and Intermediate-1, Intermediate-2, and High-Risk International Prognostic Scoring System (IPSS) groups.

For the treatment of adult patients aged 65 and above with newly diagnosed de novo or secondary acute myeloid leukemia (AML), according to the World Health Organization (WHO) classification, who are not candidates for standard induction chemotherapy.

### 4.2 Posology and method of administration

*Treatment Regimen in Myelodysplastic Syndromes (MDS)*
There are two regimens for DECITAS administration. With either regimen, it is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles.

Complete blood counts and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be obtained prior to initiation of treatment.

**Treatment Regimen – Option 1**
DECITAS is administered at a dose of 15 mg/m$^2$ by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. This cycle should be repeated every 6 weeks. Patients may be premedicated with standard anti-emetic therapy.

If hematologic recovery (ANC $\geq$ 1,000/μL and platelets $\geq$ 50,000/μL) from a previous DECITAS treatment cycle requires more than 6 weeks, then the next cycle of DECITAS therapy should be delayed and dosing temporarily reduced by following this algorithm:

- Recovery requiring more than 6, but less than 8 weeks − DECITAS dosing to be delayed for up to 2 weeks and the dose temporarily reduced to 11 mg/m$^2$ every 8 hours (33 mg/m$^2$/day, 99 mg/m$^2$/cycle) upon restarting therapy.
- Recovery requiring more than 8, but less than 10 weeks − Patient should be assessed for disease progression (by bone marrow aspirates); in the absence of progression, the DECITAS dose should be delayed up to 2 more weeks and the dose reduced to 11 mg/m2 every 8 hours (33 mg/m$^2$/day, 99 mg/m$^2$/cycle) upon restarting therapy, then maintained or increased in subsequent cycles as clinically indicated.

**Treatment Regimen – Option 2**
DECITAS is administered at a dose of 20 mg/m$^2$ by continuous intravenous infusion over 1 hour repeated daily for 5 days. This cycle should be repeated every 4 weeks. Patients may be premedicated with standard anti-emetic therapy.

If myelosuppression is present, subsequent treatment cycles of DECITAS should be delayed until there is hematologic recovery (ANC ≥ 1,000/μL platelets ≥ 50,000/μL ).

*Patients with Non-hematologic Toxicity*
Following the first cycle of DECITAS treatment, if any of the following non-hematologic toxicities are present, DECITAS treatment should not be restarted until the toxicity is resolved: 1) serum creatinine ≥ 2 mg/dL; 2) SGPT, total bilirubin ≥ 2 times ULN; 3) and active or uncontrolled infection.

*Treatment Regimen in Acute Myeloid Leukemia*
In a treatment cycle, DECITAS is administered at a dose of 20 mg/m$^2$ body surface area by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle). The total daily dose must not exceed 20 mg/m$^2$ and the total dose per treatment cycle must not exceed 100 mg/m$^2$. If a dose is missed, treatment should be resumed as soon as possible. The cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial remission may take longer than 4 cycles to be obtained. Treatment may be continued as long as the patient shows response, continues to benefit or exhibits stable disease, i.e., in the absence of overt progression.

If after 4 cycles, the patient's hematological values (e.g., platelet count or absolute neutrophil count), have not returned to pre-treatment levels or if disease progression occurs (peripheral blast counts are increasing or bone marrow blast counts are worsening), the patient may be considered to be a non-responder and alternative therapeutic options to DECITAS should be considered.

Pre-medication for the prevention of nausea and vomiting is not routinely recommended but may be administered if required.

*Management of Myelosuppression and Associated Complications*
**In AML**

Myelosuppression and adverse events related to myelosuppression (thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common in both treated and untreated patients with AML. Complications of myelosuppression include infections and bleeding. Treatment may be delayed at the discretion of the treating physician, if the patient experiences myelosuppression-associated complications, such as those described below:

- Febrile neutropenia (temperature ≥ 38.5ºC and absolute neutrophil count < 1,000/μL)

- Active viral, bacterial or fungal infection (i.e., requiring intravenous anti-infectives or extensive supportive care)
- Hemorrhage (gastrointestinal, genito-urinary, pulmonary with platelets < 25,000/μL or any central nervous system hemorrhage)
- Treatment with DECITAS may be resumed once these conditions have improved or have been stabilized with adequate treatment (anti-infective therapy, transfusions, or growth factors).

In clinical studies, approximately one-third of patients receiving DECITAS required a dose-delay. Dose reduction is not recommended.

*Special Populations*
*Pediatrics*
The safety and effectiveness in pediatric patients have not been established.

*Hepatic impairment*
Studies in patients with hepatic impairment have not been conducted. The need for dosage adjustment in patients with hepatic impairment has not been evaluated. If worsening hepatic function occurs, patients should be carefully monitored (see Warnings and Precautions, Pharmacokinetic Properties).

*Renal impairment*
Studies in patients with renal impairment have not been conducted; however, data from clinical trials that included patients with mild-moderate impairment indicated no need for dosage adjustment. Patients with severe renal impairment were excluded from these trials (see Pharmacokinetic Properties).

**Administration**
DECITAS is administered by intravenous infusion. A central venous catheter is not required. For instructions on reconstitution and dilution of the medicinal product before administration, see Instructions for Use and Handling and Disposal.

**Instruction of Use**
Reconstituted and diluted solution
Decitabine for Injection should be aseptically reconstituted with 10 mL of Sterile Water for Injection; upon reconstitution, each mL contains approximately 5 mg of decitabine at pH 6.7-7.3. Immediately after reconstitution, the solution should be further diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final drug concentration of 0.15 - 1 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C -8°C) infusion fluids and stored at 2°C - 8°C for up to a maximum of 4 hours until administration. However, from a microbiological point of view, the diluted product should be used immediately.

## 4.3 Contraindications
Hypersensitivity to decitabine or to any of the excipients.
Lactation (see Fertility, pregnancy and lactation)

## 4.4 Special warnings and precautions for use

Myelosuppression
Myelosuppression and complications of myelosuppression, including infections and bleeding that occur in patients with AML may be exacerbated with Decitas treatment. Therefore, patients are at increased risk for severe infections (due to any pathogen such as bacterial, fungal and viral), with potentially fatal outcome. Patients should be monitored for signs and symptoms of infection and treated promptly.

Myelosuppression caused by Decitas is reversible. Complete blood and platelet counts should be performed regularly, as clinically indicated and prior to each treatment cycle. In the presence of myelosuppression or its complications, treatment with Decitas may be interrupted and/or supportive measures instituted.

Respiratory, thoracic and mediastinal disorders
Cases of interstitial lung disease (ILD) (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis) without signs of infectious aetiology have been reported in patients receiving decitabine. Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. If ILD is confirmed, appropriate treatment should be initiated.

Hepatic impairment
Use in patients with hepatic impairment has not been established. Caution should be exercised in the administration of Decitas to patients with hepatic impairment and in patients who develop signs or symptoms of hepatic impairment. Liver function tests should be performed prior to initiation of therapy and prior to each treatment cycle, and as clinically indicated.

Renal impairment
Use in patients with severe renal impairment has not been studied. Caution should be exercised in the administration of Decitas to patients with severe renal impairment (Creatinine Clearance [CrCl] < 30 ml/min). Renal function tests should be performed prior to initiation of therapy and prior to each treatment cycle, and as clinically indicated.

Cardiac disease
Patients with a history of severe congestive heart failure or clinically unstable cardiac disease were excluded from clinical studies and therefore, the safety and efficacy of Decitas in these patients has not been established. Cases of cardiomyopathy with cardiac decompensation, in some cases reversible after treatment discontinuation, dose reduction or corrective treatment, have been reported in the postmarketing setting. Patients, especially those with cardiac disease history, should be monitored for signs and symptoms of heart failure.

Excipients
This medicine contains 0.5 mmol potassium per vial. After reconstitution and dilution of the solution for intravenous infusion, this medicine contains less than 1 mmol (39 mg) of potassium per dose, i.e. essentially 'potassium- free'.

This medicine contains 0.29 mmol (6.67 mg) sodium per vial. After reconstitution and dilution of the solution for intravenous infusion, this medicine contains between 13.8 mg-138 mg (0.6-6 mmol) sodium per dose (depending on the infusion fluid for dilution), equivalent to 0.7-7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical drug interaction studies with decitabine have been conducted.
There is the potential for a drug-drug interaction with other agents which are also activated by sequential phosphorylation (via intracellular phosphokinase activities) and/or metabolised by enzymes implicated in the inactivation of decitabine (e.g., cytidine deaminase). Therefore, caution should be exercised if these active substances are combined with decitabine.

Impact of co-administered medicinal products on decitabine

Cytochrome (CYP) 450-mediated metabolic interactions are not anticipated as decitabine metabolism is not mediated by this system but by oxidative deamination.

Impact of decitabine on co-administered medicinal products
Given its low in vitro plasma protein binding (< 1%), decitabine is unlikely to displace co-administered medicinal products from their plasma protein binding. Decitabine has been shown to be a weak inhibitor of P-gp mediated transport in vitro and is therefore also not expected to affect P-gp mediated transport of co-administered medicinal products.

**4.6 Fertility, pregnancy and lactation**

Women of childbearing potential/Contraception in males and females
Women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant while being treated with Decitabine. The time period following treatment with Decitabine where it is safe to become pregnant is unknown. Men should use effective contraceptive measures and be advised to not father a child while receiving Decitabine, and for 3 months following completion of treatment
The use of decitabine with hormonal contraceptives has not been studied.

Pregnancy
There are no adequate data on the use of Decitabine in pregnant women. The potential risk for humans is unknown. Based on its mechanism of action, Decitabine should not be used during pregnancy and in women of childbearing potential not using effective contraception. If Decitabine is used during pregnancy, or if a patient becomes pregnant while receiving this medicinal product, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding
It is not known whether decitabine or its metabolites are excreted in breast milk. Decitabine is contraindicated during breast-feeding; therefore if treatment with this medicine is required, breast-feeding must be discontinued.

Fertility
No human data on the effect of decitabine on fertility are available. Because of the possibility of infertility as a consequence of Decitabine therapy, men should seek advice on conservation of sperm and female patients of childbearing potential should seek consultation regarding oocyte cryopreservation prior to initiation of treatment.

**4.7 Effects on ability to drive and use machines**

Decitabine has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience undesirable effects such as anaemia during treatment. Therefore, caution should be recommended when driving a car or operating machines.

**4.8 Undesirable effects**

Summary of the safety profile
The most common adverse drug reactions reported are pyrexia, anaemia and thrombocytopaenia.
The most common Grade 3/4 adverse drug reactions included pneumonia, thrombocytopaenia, neutropaenia, febrile neutropaenia and anaemia.

Tabulated list of adverse drug reactions

**Table 1: Adverse drug reactions identified with Decitas**

| System Organ Class | Frequency (all Grades) | Adverse Drug Reaction |
|---|---|---|
| Infections and infestations | Very common | pneumonia* |
| | | urinary tract infection* |
| | | All other infections (viral, bacterial, fungal)*[a, b, c] |
| | Common | septic shock* |
| | | sepsis* |
| | | sinusitis |
| Blood and lymphatic disorders | Very common | febrile neutropaenia* |
| | | neutropaenia* |
| | | thrombocytopaenia*[d] |
| | | anaemia |
| | | leukopaenia |
| | Uncommon | pancytopaenia* |
| Immune system disorders | Common | hypersensitivity including anaphylactic reaction[e] |
| Metabolism and nutrition disorders | Very common | hyperglycaemia |
| Nervous system disorders | Very common | headache |
| Cardiac disorders | Uncommon | Cardiomyopathy |
| Respiratory, thoracic and mediastinal disorders | Very common | epistaxis |
| | Not known | interstitial lung disease |
| Gastrointestinal disorders | Very common | diarrhoea |
| | | vomiting |
| | | nausea |
| | Common | stomatitis |
| | Not known | enterocolitis, including neutropaenic colitis, caecitis* |
| Hepatobiliary disorders | Very common | hepatic function abnormal |
| | Common | hyperbilirubinaemia |
| Skin and subcutaneous tissue disorders | Uncommon | acute febrile neutrophilic dermatosis (Sweet's syndrome) |
| General disorders and administration site conditions | Very common | pyrexia |

[a] Excluding pneumonia, urinary tract infection, sepsis, septic shock and sinusitis.
[b] The most frequently reported "other infections": oral herpes, oral candidiasis, pharyngitis, upper respiratory tract infection, cellulitis, bronchitis, nasopharyngitis.
[c] Including enterocolitis infectious.
[d] Including haemorrhage associated with thrombocytopaenia, including fatal cases.
[e] Including preferred terms hypersensitivity, drug hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock.
* Includes events with a fatal outcome.

NA = Not applicable

Description of selected adverse drug reactions

*Haematologic adverse drug reactions*

The most commonly haematologic adverse drug reactions associated with Decitas treatment included febrile neutropaenia, thrombocytopaenia, neutropaenia, anaemia and leukopaenia.

Serious bleeding-related adverse drug reactions, some of which lead to a fatal outcome, such as central nervous system (CNS) haemorrhage and gastrointestinal (GI) haemorrhage, in the context of severe thrombocytopaenia, were observed in patients receiving Decitabine.

Haematological adverse drug reactions should be managed by routine monitoring of complete blood counts and early administration of supportive treatments as required. Supportive treatments include, administration of prophylactic antibiotics and/or growth factor support (e.g., G-CSF) for neutropaenia and transfusions for anaemia or thrombocytopaenia according to institutional guidelines. For situations where Decitabine administration should be delayed.

*Infections and infestations adverse drug reactions*

Serious infection-related adverse drug reactions, with potentially fatal outcome, such as septic shock, sepsis, pneumonia, and other infections (viral, bacterial and fungal) were observed in patients receiving Decitabine.

*Gastrointestinal disorders*

Occurrences of enterocolitis, including neutropaenic colitis, caecitis have been observed during treatment with Decitabine. Enterocolitis may lead to septic complications and may be associated with fatal outcome.

*Respiratory, thoracic and mediastinal disorders*

Cases of interstitial lung disease (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis) without signs of infectious aetiology have been observed in patients receiving Decitabine.

*Paediatric population*

The safety assessment in paediatric patients is based on the available limited safety data from a Phase I/II study to evaluate pharmacokinetics, safety and efficacy of Decitabine in paediatric patients (aged 1 to 14 years) with relapsed or refractory AML. No new safety signal was observed in this paediatric study.

### 4.9 Overdose

There is no direct experience of human overdose and no specific antidote. However, early clinical study data in published literature at doses greater than 20 times higher than the current therapeutic dose, reported increased myelosuppression including prolonged neutropaenia and thrombocytopaenia. Toxicity is likely to manifest as exacerbations of adverse drug reactions, primarily myelosuppression. Treatment for overdose should be supportive.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues; ATC Code: L01BC08

Mechanism of action

Decitabine (5-aza-2′-deoxycytidine) is a cytidine deoxynucleoside analogue that selectively inhibits DNA methyltransferases at low doses, resulting in gene promoter hypomethylation that can result in reactivation of tumour suppressor genes, induction of cellular differentiation or cellular senescence followed by programmed cell death.

## 5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of decitabine following intravenous administration as a 1-hour infusion were described by a linear two-compartment model, characterised by rapid elimination from the central compartment and by relatively slow distribution from the peripheral compartment. For a typical patient (weight 70 kg/body surface area 1.73 $m^2$) the decitabine pharmacokinetic parameters are listed in the Table 2 below.

**Table 2: Summary of population PK analysis for a typical patient receiving daily 1-hour infusions of Decitabine 20 mg/$m^2$ over 5 days every 4 weeks**

| **Parameter** [a] | **Predicted Value** | **95% CI** |
|---|---|---|
| $C_{max}$ (ng/ml) | 107 | 88.5 - 129 |
| $AUC_{cum}$ (ng.h/ml) | 580 | 480 - 695 |
| $t_{1/2}$ (min) | 68.2 | 54.2 - 79.6 |
| $Vd_{ss}$ (L) | 116 | 84.1 - 153 |
| CL (L/h) | 298 | 249 - 359 |

[a] The total dose per cycle was 100 mg/$m^2$

Decitabine exhibits linear PK and following the intravenous infusion, steady-state concentrations are reached within 0.5 hour. Based on model simulation, PK parameters were independent of time (i.e., did not change from cycle to cycle) and no accumulation was observed with this dosing regimen. Plasma protein binding of decitabine is negligible (< 1%). Decitabine $Vd_{ss}$ in cancer patients is large indicating distribution into peripheral tissues. There was no evidence of dependencies on age, creatinine clearance, total bilirubin, or disease.

Biotransformation

Intracellularly, decitabine is activated through sequential phosphorylation via phosphokinase activities to the corresponding triphosphate, which is then incorporated by the DNA polymerase. *In vitro* metabolism data and the human mass balance study results indicated that the cytochrome P450 system is not involved in the metabolism of decitabine. The primary route of metabolism is likely through deamination by cytidine deaminase in the liver, kidney, intestinal epithelium and blood. Results from the human mass-balance study showed that unchanged decitabine in plasma accounted for approximately 2.4% of total radioactivity in plasma. The major circulating metabolites are not believed to be pharmacologically active. The presence of these metabolites in urine together with the high total body clearance and low urinary excretion of unchanged decitabine in the urine (~4% of the dose) indicate that decitabine is appreciably metabolized *in vivo*. *In vitro* studies show that decitabine does not inhibit nor induce CYP 450 enzymes up to more than 20-fold of the therapeutic maximum observed plasma concentration ($C_{max}$). Thus; CYP-mediated metabolic drug interactions are not anticipated, and decitabine is unlikely to interact with agents metabolized through these pathways. In addition, *in vitro* data show that decitabine is a poor P-gp substrate.

Elimination

Mean plasma clearance following intravenous administration in cancer subjects was > 200 L/h with moderate inter-subject variability (coefficient of variation [CV] is approximately 50%). Excretion of unchanged drug appears to play only a minor role in the elimination of decitabine.

Results from a mass balance study with radioactive $^{14}$C-decitabine in cancer patients showed that 90% of the administered dose of decitabine (4% unchanged drug) is excreted in the urine.

Additional information on special populations

The effects of renal or hepatic impairment, gender, age or race on the pharmacokinetics of decitabine have not been formally studied.

*Elderly*

Population pharmacokinetic analysis showed that decitabine pharmacokinetics are not dependent on age (range studied 40 to 87 years; median 70 years).

*Paediatric population*

Population PK analysis of decitabine showed that after accounting for body size, there is no difference between decitabine PK parameters in paediatric AML patients versus adults with AML or MDS.

*Gender*

Population pharmacokinetic analysis of decitabine did not show any clinically relevant difference between men and women.

*Race*

Most of the patients studied were Caucasian. However, the population pharmacokinetic analysis of decitabine indicated that race had no apparent effect on the exposure to decitabine.

*Hepatic impairment*

The PK of decitabine have not been formally studied in patients with hepatic impairment. CYP enzymes are unlikely to be involved in the metabolism of decitabine. In addition, the limited data from the population PK analysis indicated no significant PK parameter dependencies on total bilirubin concentration despite a wide range of total bilirubin levels. Thus, decitabine exposure is not likely to be affected in patients with impaired hepatic function.

*Renal impairment*

The PK of decitabine have not been formally studied in patients with renal insufficiency. The population PK analysis on the limited decitabine data indicated no significant PK parameter dependencies on normalized creatinine clearance, an indicator of renal function. Thus, decitabine exposure is not likely to be affected in patients with impaired renal function.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Potassium dihydrogen phosphate & Sodium hydroxide

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

3 years

**6.4 Storage condition**

Do not store above 30°C.

*Reconstituted and diluted solution*

Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C -8°C) infusion fluids and stored at 2°C - 8°C for up to a maximum of 4 hours until administration. However, from a microbiological point of view, the diluted product should be used immediately.

**6.5 Nature and contents of container**

DECITAS (Decitabine for Injection 50 mg/vial) is available in 20 ml clear glass vial with rubber stopper and plain royal blue seal.
Pack size: Each carton contains 1 glass vial.

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

Recommendations for safe handling

Skin contact with the solution should be avoided and protective gloves must be worn. Standard procedures for dealing with cytotoxic medicinal products should be adopted.

Disposal

This medicinal product is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. Name and Address of Product Registration Holder**

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

Manufactured by:
Intas Pharmaceuticals Ltd.
Plot no.: 5-6 & 7, Pharmez,
Near Village Matoda, Ta.-Sanand,
Dist.-Ahmedabad, Gujarat – 382213, INDIA.

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

Nov 2020