QILU DECITABINE LYOPHILISED POWDER FOR INFUSION 50 MG/VIAL

DOSAGE FORMS AND STRENGTHS

White to almost white lyophilized powder in 20ml type 1 glass vial.
Decitabine for Injection is aseptically reconstituted with Sterile Water for Injection. The reconstituted solution is clear and colorless.
The reconstituted solution should be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection. The diluted solution is clear and colorless.

List of diluents: Sterile Water for Injection, 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

CLINICAL INFORMATION

INDICATIONS

Qilu DECITABINE LYOPHILISED POWDER FOR INFUSION 50 MG/VIAL is indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all FrenchAmerican-British 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 groups.

Qilu DECITABINE LYOPHILISED POWDER FOR INFUSION 50 MG/VIAL is indicated 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

DOSAGE AND ADMINISTRATION

Qilu Decitabine administration must be initiated under the supervision of physicians experienced in the use of chemotherapeutic medicinal products.

Treatment Regimen in Myelodysplastic Syndromes (MDS)

Pre-Medications and Baseline Testing

• Consider pre-medicating for nausea with antiemetics.
• Conduct baseline laboratory testing: complete blood count (CBC) with platelets, serum hepatic panel, and serum creatinine.

Qilu Decitabine Regimen Options

Three Day Regimen

Administer Qilu Decitabine at a dose of 15 mg/m^2 by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Repeat cycles every 6 weeks upon hematologic recovery (ANC at least 1,000/μL and platelets at least 50,000//μL) for a minimum of 4 cycles. A complete or partial response may take longer than 4 cycles. Delay and reduce dose for hematologic toxicity [see Dosage Modifications for Adverse Reaction in MDS below].

Five Day Regimen

Administer Qilu Decitabine at a dose of 20 mg/m^2 by continuous infusion over 1 hour daily for 5 days. Delay and reduce dose for hematologic toxicity [see Dosage Modifications for Adverse Reaction in MDS below]. Repeat cycles every 4 weeks upon hematologic recovery (ANC at least 1,000/μL and platelets at least 50,000/μL) for a minimum of 4 cycles. A complete or partial response may take longer than 4 cycles.

Patients with Renal or Severe Hepatic Impairment
Treatment with Qilu Decitabine has not been studied in patients with pre-existing renal or hepatic impairment. For patients with pre-existing renal or hepatic impairment, consider the potential risks and benefits before initiating treatment with Qilu Decitabine.

Dosage Modifications for Adverse Reactions in MDS
Hematologic Toxicity
If hematologiv recovery from a previous Qilu Decitabine treatment cycle requires more than 6 weeks, delay the next cycle of Qilu Decitabine therapy and reduce Qilu Decitabine dose temporarily by following this algorithm:
• Recovery requiring more than 6, but less than 8 weeks: delay Qilu Decitabine dosing for up to 2 weeks and reduce the dose temporarily 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: Perform bone marrow aspirate to assess for disease progression. In the absence of progression, delay Qilu Decitabine dosing for up to 2 more weeks and reduce the dose to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then maintain or increase dose in subsequent cycles as clinically indicated.

Non-hematologic Toxicity
Delay subsequent Qilu Decitabine treatment for any the following nonhematologic toxicities and do not restart until toxicities resolve:
• Serum creatinine greater than or equal to 2 mg/dL
• Alanine transaminase (ALT), total bilirubin greater than or equal to 2 times upper limit of normal (ULN)
• Active or uncontrolled infection

Treatment Regimen in Acute Myeloid Leukemia (AML)
In a treatment cycle, Qilu Decitabine 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 Qilu Decitabine 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 Qilu Decitabine may be resumed once these conditions have improved or have been stabilized with adequate treatment (anti-infective therapy, transfusions, or growth factors).
Approximately one-third of patients receiving Qilu Decitabine required a dose-delay. Dose reduction is not recommended.

Special Populations
Pediatrics
The safety and effectiveness in pediatric patients with MDS have not been studied.
Qilu Decitabine should not be used in children with AML aged < 18 years, because efficacy was not established. Currently available data are described in sections Adverse Reactions and Pharmacokinetic Properties.

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.

Administration
Qilu Decitabine 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.

CONTRAINDICATIONS
Known hypersensitivity to decitabine or any of the excipients.
Lactation (see Pregnancy, Breast-feeding and Fertility)

WARNINGS AND PRECAUTIONS
Myelosuppression
Myelosuppression and complications of myelosuppression, including infections and bleeding that occur in patients with MDS or AML may be exacerbated with Qilu Decitabine treatment. Myelosuppression caused by Qilu Decitabine 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 Qilu Decitabine may be interrupted, the dose reduced or supportive measures instituted as recommended in Dosage and Administration, Adverse Reactions.

Hepatic Impairment
The use of Qilu Decitabine in patients with hepatic impairment has not been established. Caution should be exercised in the administration of Qilu Decitabine to patients with hepatic impairment or in patients who develop signs or symptoms of hepatic impairment. Patients should be monitored closely (see Dosage and Administration, Pharmacokinetic Properties).

Renal Impairment
The use of Qilu Decitabine in patients with severe renal impairment has not been studied. Caution should be exercised in the administration of Qilu Decitabine to patients with severe renal impairment (Creatinine Clearance [CrCl] <30 mL/min) and these patients should be monitored closely (see Dosage and Administration).

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 Qilu Decitabine in these patients has not been established.

INTERACTIONS
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 metabolized by enzymes implicated in the inactivation of decitabine (e.g., cytidine deaminase). Therefore, caution should be exercised if these drugs are combined with Qilu Decitabine.

Impact of Co-administered Drugs on Decitabine
CYP450-mediated metabolic drug interactions are not anticipated as decitabine metabolism is not mediated by this system but by oxidative deamination. Displacement of decitabine from its plasma protein binding by co-administered drugs is unlikely given the negligible in vitro plasma protein binding (<1%) of decitabine. In vitro data indicated that decitabine is a poor P-glycoprotein (P-gp) substrate and is therefore not prone to interaction with P-gp inhibitors.

Impact of Decitabine on Co-administered Drugs
Given its low in vitro plasma protein binding (<1%), decitabine is unlikely to displace co-administered drugs from their plasma protein binding. Decitabine does not inhibit nor induce CYP 450 enzymes up to more than 20-fold of the therapeutic maximum observed plasma concentration (Cmax). Thus, CYP-mediated metabolic drug interactions are not anticipated and is unlikely to interact with agents metabolized through these pathways. 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 drugs (See Pharmacokinetic Properties).

PREGNANCY, BREAST-FEEDING AND FERTILITY
Pregnancy
Women of childbearing potential should be advised to use effective contraceptive measures and avoid becoming pregnant while being treated with Qilu Decitabine. The time period following treatment with Qilu Decitabine where it is safe to become pregnant is unknown. There are no adequate data on the use of Qilu Decitabine in pregnant women. Studies have shown that decitabine is teratogenic in rats and mice (See Non-clinical Information). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, Qilu Decitabine should not be used during pregnancy, unless clearly necessary. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving Qilu Decitabine, the patient should be apprised of the potential hazard to the fetus
Use in Males: Men should be advised to not father a child while receiving Qilu Decitabine, and for 3 months following completion of treatment.

Fertility
Female patients of childbearing potential should be advised to seek consultation regarding oocyte cryopreservation prior to initiation of treatment with Qilu Decitabine. Because of the possibility of infertility as a consequence of Qilu Decitabine therapy, men should be advised to seek advice on conservation of sperm prior to any treatment.

Breast-feeding
It is not known whether decitabine or its metabolites are excreted in breast milk. Qilu Decitabine is contraindicated during lactation; therefore, if treatment with Qilu Decitabine is required, breast-feeding must be discontinued (see Contraindications).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies of the effects on the ability to drive or use machines with Qilu Decitabine have been performed. Patients should be advised that they may experience undesirable effects, such as anemia, during treatment. Therefore, caution should be recommended when driving a car or operating machines.

ADVERSE REACTIONS
Adverse Reactions
Qilu Decitabine was administered with the 5-Day or 3-Day dosing regimen. Adverse reactions reported are summarized below in Table 1. The adverse reactions are listed by frequency category. Frequency categories are defined as follows: Very common, Common and Uncommon.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse Reactions Identified with Qilu Decitabine

System Organ Class	Frequency (All Grades)	Adverse Reaction
Infections and infestations	Very common	pneumonia* urinary tract infection* other infections (all viral, bacterial, fungal infections including fatal)*[b]
	Common	septic shock* sepsis* sinusitis
Blood and lymphatic disorders	Very common	Febrile neutropenia* Neutropenia* Thrombocytopenia*[c] Anemia leucopenia
	Common	pancytopenia*
Immune system disorders	Common	hypersensitivity including anaphylactic reaction[d]
Nervous system disorders	Very Common	Headache
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhea Vomiting Stomatitis Nausea
Skin and subcutaneous tissue disorders	Uncommon	Acute febrile neutrophilic dermatosis (Sweet's syndrome)

General disorders and administration site conditions	Very Common	pyrexia

[b] Excluding pneumonia, urinary tract infection, sepsis, septic shock and sinusitis
[c] Including hemorrhage associated with thrombocytopenia, including fatal cases
[d] Including preferred terms hypersensitivity, drug hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock.
* Includes events with a fatal outcome

Description of selected adverse reactions
Hematologic adverse reactions
The most commonly reported hematologic adverse reactions associated with Qilu Decitabine treatment included febrile neutropenia, thrombocytopenia, neutropenia, anemia and leucopenia.
Serious infection-related adverse reactions such as septic shock, sepsis, and pneumonia were reported in patients receiving Qilu Decitabine.
Serious bleeding-related adverse reactions such as CNS hemorrhage and gastrointestinal hemorrhage ,in the context of severe thrombocytopenia, were reported in patients receiving Qilu Decitabine.
Hematological adverse reactions should be managed by routine monitoring of complete blood counts and supportive treatments as required. Supportive treatments include, administration of prophylactic antibiotics and/or growth factor support (e.g. G-CSF) for neutropenia and transfusions for anaemia or thrombocytopenia according to institutional guidelines. For situations where decitabine administration should be delayed, see Dosage and Administration.

Postmarketing Data
In addition to the adverse reactions reported and listed above, the following adverse reactions have been reported during postmarketing experience. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:
Very common
Uncommon
Rare
Very rare

Table 2: Adverse Reactions Identified During Postmarketing Experience	
System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates**
Cardiac disorders	
Cardiomyopathy (including decreased ejection fraction)	Very rare
Hepatobiliary disorders	
Hepatic function abnormal	Very rare
Hyperbilirubinemia	Very rare
Metabolism and nutrition disorders	
Hyperglycemia	Very rare

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

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 doses, reported increased myelosuppression including prolonged neutropenia and thrombocytopenia. Toxicity is likely to manifest as exacerbations of adverse reactions, primarily myelosuppression (see Adverse Reactions). Treatment for overdose should be supportive.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agent, Pyrimidine Analogues.
ATC Code: L01BC08

Mechanism of Action

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

PHARMACOKINETIC PROPERTIES

In the 5-Day regimen, decitabine PK was evaluated on the fifth day of the first treatment cycle. Total dose per cycle was 100 mg/m2. In the 3-Day regimen, decitabine PK was evaluated after the first dose of each dosing day of the first treatment cycle. Total dose per cycle was 135 mg/m2.

Distribution

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. Decitabine Vdss in cancer patients is large indicating distribution of the drug into peripheral tissues. There was no evidence of dependencies on age, creatinine clearance, total bilirubin, or disease.

Metabolism

Intracellularly, decitabine is activated through sequential phosphorylation via phosphokinase activities to the corresponding triphosphate, which is then incorporated by the DNA polymerase. In light of in vitro metabolism data, 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 drug in the urine (~4% of the dose) indicate that decitabine is appreciably metabolized in vivo. In addition, in vitro data show that decitabine is a poor P-gp substrate.

Elimination

Mean plasma clearance following intravenous administration in cancer patients 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 14C-decitabine in cancer patients showed that 90% of the administered dose of decitabine (4% unchanged drug) is excreted in the urine.

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 PK are not dependent on age (range studied 40 to 87 years; median 70 years).

Pediatric 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.
Hepatic impairment
The PK of decitabine have not been formally studied in patients with hepatic impairment. Results from a human mass-balance study and in vitro experiments mentioned above indicated that the 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.
Other Populations
Gender
Population PK analysis of decitabine did not show any clinically relevant difference between men and women.
Race
The population PK analysis of decitabine indicated that race had no apparent effect on the exposure to decitabine.

PHARMACEUTICAL INFORMATION
Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Qilu Decitabine should not be infused through the same intravenous access /line with other medicinal products

Storage conditions
Unopened vial: Do not store above 25°C.
After reconstitution: Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C to 8°C) infusion fluids and stored at 2°C to 8°C for up to a maximum of 4 hours until administration.

Nature and contents of container
20ml Type I transparent glass vial with 20 mm Coated Ethylene-tetrafluoroethylene Polymers Chlorobutyl Rubber Stopper and a 20mm Aluminium-Plastic Cap containing 50 mg of Decitabine as a white to almost white lyophilized powder.
Available in pack of 1 vial.

Instructions for Use and Handling and Disposal
This medicinal product is for single use only. Skin contact with the solution should be avoided and protective gloves must be worn. Standard procedures for dealing with anticancer agents should be adopted. Qilu Decitabine should be aseptically reconstituted with 10 mL of **Sterile Water for Injection**. Upon reconstitution, each mL contains approximately 5.0 mg of decitabine at pH 6.7 to 7.3. Immediately after reconstitution, the solution should be further diluted with 0.9% S**odium Chloride Injection or 5% Dextrose Injection** to a final drug concentration of 0.15 to 1.0 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C to 8°C) infusion fluids and stored at 2°C to 8°C for up to a maximum of 4 hours until administration. Any unused product or waste material should be disposed of in accordance with local requirements.

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DATE OF REVISION : 2023 March

Times New Roman,11