Prescribing Information (GREAT BRITAIN)

Inaqovi ▼ (decitabine, cedazuridine)

35mg/100mg film coated tablets

Please refer to the full Summary of Product Characteristics (SmPC) before prescribing.

Indication: Inaqovi is indicated as monotherapy for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy.
Dose: The recommended dose of Inaqovi is 1 tablet once daily on Days 1 through 5 of each 28-day cycle. Cycles are to be repeated every 28 days. Treatment is to be continued for a minimum of 4 cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than 4 cycles.
Method of administration: Treatment must be initiated and supervised by a physician experienced in the use of anticancer therapies. Inaqovi is for oral use. The tablets must be swallowed whole with water at approximately the same time each day. Food is not to be consumed 2 hours before and 2 hours after taking treatment. The tablets must not be chewed, crushed, or broken to avoid skin contact or release of active substance into the air. Inaqovi is a cytotoxicmedicinal product. Substitution with an intravenous decitabine product within a cycle is not recommended. Premedication with standard antiemetic therapy prior to each dose to minimise nausea and vomiting is to be considered. A delay or reduction in the dose per cycle is to be considered for patients who experience haematologic and non-haematologic toxicities**.** ***Missed or vomited dose:*** If dose is missed within 12 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If dose is missed by 12 or more hours, the patient must wait and take the missed dose the following day at the usual time and then extend the dosing period by one day for every missed dose to complete 5 daily doses for each cycle. If patient vomits following dosing, no additional dose is to be taken that day. The next dose must be taken at the usual time and resume the normal daily dosing, with no extension of the dosing period. ***Dose adjustment based on haematologic adverse reactions*****:** The next cycle must be delayed if absolute neutrophil count (ANC) is less than 1.0×10^9/L and platelets are less than 50×10^9/L in the absence of active disease. Complete blood cell (CBC) counts must be monitored until ANC is 1.0×10^9/L or greater and platelets are 50×10^9/L or greater. In the absence of active disease: If haematological recovery occurs (ANC at least 1.0×10^9/L and platelets at least 50×10^9/L) within 2 weeks of the last treatment cycle, treatment is to be continued at the same dose. If haematological recovery does not occur (ANC at least 1.0×10^9/L and platelets at least 50×10^9/L) within 2 weeks of the last treatment cycle: Treatment must be delayed for up to 2 additional weeks AND the patient must resume treatment at a reduced dose on Days 1 through 4. Further dose reductions must be considered in order if myelosuppression persists after a dose reduction. First dose reduction is 1 tablet once daily on Days 1 through 4. Second dose reduction is 1 tablet once daily on Days 1 through 3. Third dose reduction is 1 tablet once daily on Days 1, 3 and 5. Persistent severe neutropaenia and febrile neutropaenia must be managed with supportive treatment. ***Dose adjustment based on non-haematologic adverse reactions:*** Subsequent treatment cycles must be delayed for the following non-haematologic adverse reactions and resumed at the same or reduced dose upon resolution: Serum creatinine 2 mg/dL or greater, serum bilirubin 2 times the upper limit of normal (ULN) or greater, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 2 times the ULN or greater, active or uncontrolled infection. Dose adjustments for all other Grade 3 or higher adverse reactions should follow institutional guidelines. ***Hepatic impairment:*** Studies in patients with hepatic impairment have not been conducted. The need for dose adjustment in patients with hepatic impairment has not been evaluated. If worsening hepatic function occurs, patients should be carefully monitored. ***Renal impairment:*** No adjustment of starting dose is recommended for patients with mild or moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min/1.73 m^2). Due to the potential for increased adverse reactions, patients with moderate renal impairment (CrCl 30 to 59 mL/min/1.73 m^2) must be monitored. Inaqovi has not been studied in patients with severe renal impairment (CrCl 15 to 29 mL/min/1.73 m^2) or end stage renal disease (CrCl <15 mL/min/1.73 m^2). ***Paediatric population:*** The safety and efficacy of Inaqovi in the paediatric population (aged less than 18 years) have not been established. No data are available.

Contraindications: Hypersensitivity to the active substance or to any of the excipients; breast-feeding.
Special warnings and precautions: ***Myelosuppression:*** Fatal and serious myelosuppression can occur with treatment. Complete blood cell counts must be obtained prior to the initiation of treatment, prior to each cycle, and as clinically indicated to monitor response and toxicity. Growth factors and anti-infective therapies must be administered for treatment or prophylaxis as appropriate. The next cycle must be delayed and resumed at the same or reduced dose as recommended (see SmPC). Patients must be monitored for signs and symptoms of infection and treated promptly. ***Neutropaenia:*** Supportive treatments include, administration of prophylactic antibiotics and/or growth factor support (e.g., G-CSF) for neutropaenia according to institutional guidelines.
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 intravenous decitabine. Patients with an acute onset or unexplained worsening of pulmonary symptoms must be carefully assessed to exclude ILD.
Hepatic impairment: Use in patients with hepatic impairment has not been established. Caution must be exercised in the administration of medicinal product to patients with hepatic impairment and in patients who develop signs or symptoms of hepatic impairment. Liver function tests must be performed prior to the initiation of therapy, prior to each treatment cycle, and as clinically indicated.
Renal impairment: Use in patients with severe renal impairment has not been studied. Caution must be exercised in the administration of the medicinal product to patients with severe renal impairment (CrCl < 30 mL/min). Renal function tests must be performed prior to the initiation of therapy, 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 the medicinal product 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 with intravenous decitabine. Patients, especially those with a history of cardiac disease, must be monitored for signs and symptoms of heart failure.
Differentiation syndrome: Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported during the post-marketing period with intravenous decitabine. Differentiation syndrome may be fatal. Treatment with high-dose intravenous corticosteroids and haemodynamic monitoring must be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Treatment must be temporarily discontinued until symptoms resolve, and if resumed, caution is advised.
Administration of antiemetics: Nausea and vomiting may occur during treatment. Administration of standard antiemetic therapy prior to each dose should be considered to minimise nausea and vomiting.
Excipients: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.
Interaction with other medicinal products and other forms of interaction:
Effect of other medicinal products on Inaqovi: Decitabine and cedazuridine are not substrates or inhibitors for cytochrome P450 (CYP450); thus interactions with CYP inhibitors or inducers are not expected. ***Cytidine deaminase inhibitors:*** Because decitabine is a substrate for the cytidine deaminase (CDA) enzyme, which metabolises decitabine resulting in an inactive deaminated form, other medicinal products inhibiting CDA should be avoided, as co-administration may result in increased decitabine exposure.
Effect of Inaqovi on other medicinal products:
Medicinal products metabolised by cytidine deaminase:
Cedazuridine is an inhibitor of CDA and thereby increases the exposure of decitabine following oral administration. Concomitant administration of Inaqovi with medicinal products metabolised by CDA (i.e., cytarabine, gemcitabine, azacitidine) may result in increased systemic exposure with a potential for increased toxicity of these medicinal products. Co-administration of Inaqovi with medicinal products metabolised primarily by CDA should be avoided.
Food: Overall decitabine exposure has been shown to be reduced when decitabine is administered with a high-fat, high-calorie meal (see section 4.2).
Pregnancy: There are no or a limited amount of human data from the use of decitabine and cedazuridine in pregnant women. Based on the results

of embryo-foetal toxicity studies conducted in animals, Inaqovi may harm the foetus when administered to pregnant women. Studies in animals have shown reproductive toxicity. Inaqovi is not recommended during pregnancy and in women of childbearing potential not using effective contraception. A pregnancy test should be performed on all women of childbearing potential before treatment is started. If Inaqovi 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 unknown whether decitabine, cedazuridine, or their metabolites are excreted in breast milk. A risk to the newborns/infants cannot be excluded. Inaqovi is contraindicated during breast-feeding.

Fertility: No human data on the effect of decitabine and cedazuridine on fertility are available. Ovarian and testicular toxicity, including mutagenicity, has been observed in repeat-dose toxicity studies in mice. Because of the possibility of infertility as a consequence of therapy, men should seek advice on conservation of sperm and female patients of childbearing potential should seek consultation regarding oocyte cryopreservation prior to initiating treatment. Before starting treatment or planning pregnancy, please consult the SmPC.

Effects on ability to drive and use machines: Inaqovi 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 observed when driving a car or operating machinery.

Summary of the safety profile: Among the 80 patients who received treatment, the most common adverse drug reaction (≥ 20%) including Grade ≥ 3 was thrombocytopaenia. The most common serious adverse reactions (≥ 20%) were febrile neutropaenia and pneumonia. Deaths while on treatment occurred in 24% of patients. The most frequent adverse reactions resulting in death included pneumonia (8%), sepsis (3%) and central nervous system haemorrhage in the setting of thrombocytopaenia (3%). Permanent discontinuation occurred in 14% of patients while on treatment. The most frequent adverse reaction resulting in permanent discontinuation was pneumonia (5%). Treatment interruption and dose reductions occurred in 48% of patients. The most frequent adverse reaction resulting in treatment interruption and dose reduction was myelosuppression occurring in 19% of patients (n=15) (neutropaenia [13%, n=10], febrile neutropaenia [5%, n=4], and thrombocytopaenia [3%, n=2]). The adverse reaction pneumonia led to treatment interruption and dose reduction in 5% of patients. ***Adverse events reported during clinical trials are as follows***, where the frequency is defined as: very common, ≥1/10; common, ≥ 1/100 to <1/10. Side effects listed below were observed at all CTCAE grades, please consult the SmPC for frequencies of these side effects observed specifically at CTCAE grade 3-4. ***Very common adverse reactions:*** all other infections (viral, bacterial, fungal), pneumonia, sepsis, urinary tract infection, leukopenia, thrombocytopaenia, anaemia, neutropaenia, febrile neutropaenia, hyperglycaemia, stomatitis, nausea, diarrhoea, aspartate aminotransferase increased, alanine aminotransferase increased, alkaline phosphatase increased, bilirubin increased, pyrexia. ***Common adverse reactions:*** sinusitis (including fungal and bacterial), headache, epistaxis, neutropaenic colitis. ***Serious adverse reactions*** reported during clinical trials are leukopaenia, thrombocytopaenia, anaemia, neutropaenia and febrile neutropaenia (these are manifestations of myelostomasuppression and may present as pancytopenia); gastrointestinal haemorrhage, cerebral haemorrhage (in the context of severe thrombocytopaenia), bleeding from the eyes, skin, and mucous membranes (mouth and anorectal); septic shock, sepsis, pneumonia, other infections (viral, bacterial and fungal); enterocolitis (including neutropaenic colitis); interstitial lung disease (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis without signs of infectious aetiology); differentiation syndrome; acute febrile neutrophilic dermatosis (Sweet's syndrome); cardiomyopathy. Prescribers should consult the summary of product characteristics in relation to other adverse reactions. **Overdose:** Overdose could cause increased myelosuppression and neutropaenia-related infections such as pneumonia and sepsis. There is no known antidote for overdose with the medicinal product. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted. **Legal Classification:** Prescription Only Medicine (POM) **Basic NHS price:** Inaqovi 35mg/100mg tablets, 5 tablet pack size=£3595. **Marketing Authorisation (MA) number:** PLGB 50697/0033

MA Holder: Otsuka Pharmaceutical Netherlands B.V., Herikerbergweg 292, 1101 CT Amsterdam, Netherlands

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Adverse events should be reported. For the UK, reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search MHRA Yellow card in Google Play or the Apple App Store

Adverse events should also be reported to Otsuka Pharmaceuticals (UK) Ltd. by email to OPUKSafety@otsuka.co.uk or by calling 0808 168 6726