SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Inaqovi 35 mg/100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 35 mg decitabine and 100 mg cedazuridine.

Excipient with known effect

Each film-coated tablet contains 306 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Red, oval biconvex shaped tablet, 14 mm diameter, plain on one side and debossed with ‘H35’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the use of anticancer therapies.

Posology

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.

- 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 (see section 4.4).
- A delay or reduction in the dose per cycle is to be considered for patients who experience haematologic and non-haematologic toxicities (see "Dose adjustments").

Missed or vomited dose

- If the patient misses a dose within 12 hours of the time it is usually taken, the patient must take the missed dose as soon as possible and resume the normal daily dosing schedule.
- If the patient misses a dose 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 the 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 adjustments

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 have to be considered in the order listed in Table 1 if myelosuppression persists after a dose reduction.

- Dose has to be maintained or increased in subsequent cycles as clinically indicated.

Patients are to be treated with a minimum of 4 cycles of treatments with active disease.

Table 1: Recommended dose reductions for myelosuppression

Dose reduction	Dose
First	1 tablet once daily on Days 1 through 4
Second	1 tablet once daily on Days 1 through 3
Third	1 tablet once daily on Days 1, 3 and 5

Persistent severe neutropaenia and febrile neutropaenia have to be managed with supportive treatment (see section 4.4).

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.

Special populations

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 (see sections 4.4 and 5.2).

Renal impairment

No adjustment of starting dose is recommended for patients with mild or moderate renal impairment (creatinine clearance [CrCl] $\geq$ 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) (see sections 4.4 and 5.2).

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.

Method of administration

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 in order to avoid a risk for lack of efficacy (see section 4.5).

The tablets must not be chewed, crushed, or broken in order to avoid skin contact or release of active substance into the air.

Inaqovi is a cytotoxicmedicinal product. For proper handling and disposal procedures see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Myelosuppression

Fatal and serious myelosuppression can occur with treatment (see section 4.8).

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 sections 4.2 and 4.8). 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. For situations where administration must be delayed, see section 4.2.

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. If ILD is confirmed, appropriate treatment must be initiated (see section 4.8).

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 (see sections 4.2 and 5.2).

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 (see sections 4.2 and 5.2).

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 (see section 4.8). 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 (see section 4.8). Differentiation syndrome may be fatal (see section 4.8). 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’.

4.5 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).

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential/Contraception in men and women

Due to the genotoxic potential of decitabine (see section 5.3), women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant

while being treated with Inaqovi and for 6 months following completion of treatment. Men should use effective contraceptive measures and be advised to not father a child while receiving Inaqovi, and for 3 months following completion of treatment (see section 5.3).

The use of decitabine and cedazuridine with hormonal contraceptives has not been studied.

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 (see section 5.3), Inaqovi may harm the foetus when administered to pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

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 (see section 4.3).

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, consider the above guidance (see section 5.3).

4.7 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.

4.8 Undesirable effects

Summary of safety profile

The safety of Inaqovi was evaluated in one Phase 3 study (ASTX727-02-EU) where 80 AML patients received the medicinal product. The overall safety profile for Inaqovi is described below and also reflects the known safety profile of intravenous decitabine.

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.

Tabulated list of adverse reactions

The safety evaluation of adverse reactions is largely based on experience with Dacogen in patients with AML. The safety of Inaqovi in adult patients was evaluated in a safety population that included AML patients from one Phase 3 study (ASTX727-02-EU, N=80).

Among the 80 patients who received Inaqovi, 38% were exposed for 6 months or longer and 6% were exposed for greater than 1 year.

Table 2 lists adverse drug reactions associated with Inaqovi (N=80), or that have been associated with intravenous decitabine, according to system organ class (SOC) in MedDRA. Within each SOC, the adverse drug reactions are ranked by frequency and then presented in order of decreasing seriousness. The corresponding frequency category for each adverse drug reaction is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from available data).

Table 2: Adverse drug reactions observed with Inaqovi or with intravenous decitabine therapy in AML patients

MedDRA SOC	MedDRA Term [a]	AML (N=80)			
		All CTCAE Grades		CTCAE Grade 3-4	
		%	Frequency	%	Frequency
Infections and infestations	All other infections (viral, bacterial, fungal) [b]	50.0	Very common	25.0	Very common
	Pneumonia [c]	23.8	Very common	18.8	Very common
	Sepsis [d]	10.0	Very common	6.3	Common
	Urinary tract infection [e]	17.5	Very common	2.5	Common
	Sinusitis (including fungal [f] and bacterial [g])	2.5	Common	2.5	Common
Blood and lymphatic system disorders	Leukopenia [h]	81.3	Very common	67.5	Very common
	Thrombocytopaenia [h,i]	73.8	Very common	67.5	Very common
	Anaemia [h]	67.5	Very common	60.0	Very common
	Neutropaenia [h,j]	41.8	Very common	41.8	Very common
	Febrile neutropaenia	28.8	Very common	26.3	Very common
	Pancytopaenia [k]	Not known	Uncommon [k]	Not known	Uncommon [k]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Differentiation syndrome [l]	Not known	Not known	Not known	Not known
Metabolism and nutrition disorders	Hyperglycaemia [h,m]	61.1	Very common	4.2	Common
Nervous system disorders	Headache [n]	2.5	Common	Not known	Common [n]
Cardiac disorders	Cardiomyopathy [o]	Not known	Uncommon	Not known	Uncommon
Respiratory, thoracic and mediastinal disorders	Epistaxis [n]	6.3	Common	Not known	Common [n]
	Interstitial lung disease [l]	Not known	Not known	Not known	Not known
Gastrointestinal disorders	Stomatitis [p]	10.0	Very common	1.3	Common

	Nausea [q]	21.3	Very common	Not known	Uncommon [q]
	Diarrhoea [r]	13.8	Very common	Not known	Common [r]
	Vomiting [r]	12.5	Very common	Not known	Common [r]
	Neutropaenic colitis [s]	1.3	Common	1.3	Common
Hepatobiliary disorders	Aspartate aminotransferase increased [h,t]	30.6	Very common	2.8	Common
	Alanine aminotransferase increased [h,u]	28.8	Very common	2.7	Common
	Alkaline phosphatase increased [h,v]	43.7	Very common	0	Not applicable
	Bilirubin increased [h,w,q]	23.3	Very common	Not known	Uncommon [f]
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis (Sweet's syndrome) [x]	Not known	Uncommon [x]	Not applicable [y]	Not applicable [y]
General disorders and administration site conditions	Pyrexia [z]	23.8	Very common	1.3	Common

[a] The corresponding frequency category for each adverse drug reaction is based on the CIOMS III convention

[b] Grouped terms include anal abscess, anorectal infection, bacteraemia, cellulitis, cellulitis staphylococcal, corona virus infection, coronavirus test positive, enterococcal bacteraemia, enterocolitis viral, erythema, escherichia bacteraemia, folliculitis, furuncle, gingival swelling, herpes virus infection, infection, klebsiella bacteraemia, nasal congestion, nasopharyngitis, oral candidiasis, oral herpes, oropharyngeal candidiasis, otitis externa, periodontitis, pharyngitis, polyserositis, pseudomonal bacteraemia, staphylococcal bacteraemia, staphylococcal infection, streptococcal bacteraemia, respiratory tract infection, skin infection, tooth abscess, tooth infection, upper respiratory tract infection, varicella zoster virus infection

[c] Grouped terms include bronchitis, pneumonia

[d] Grouped terms include sepsis, septic shock, systemic candidiasis, urosepsis

[e] Grouped terms include bacteriuria, cystitis, dysuria, escherichia urinary tract infection, urinary tract infection, urinary tract infection enterococcal

[f] Grouped terms include sinusitis aspergillus, sinusitis fungal

[g] Sinusitis bacterial was not observed in the clinical trial with Inaqovi, however sinusitis (organism not specified) was observed in clinical trials with IV decitabine at a frequency of common (3%, 1%)

[h] Based on laboratory values

[i] Thrombocytopaenia may lead to bleeding and haemorrhagic reactions that may be fatal

[j] Neutrophils decreased (n=79)

[k] Pancytopaenia, including fatal events, was not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine at a frequency of uncommon (< 1%)

[l] Differentiation syndrome and interstitial lung disease were not observed in the clinical trial with Inaqovi, however they were observed in post-market setting with the use of IV decitabine

[m] Hyperglycemia (n=72)

[n] Headache and epistaxis Grade 3-4, were not observed in the clinical trial with Inaqovi, however they were observed in clinical trials with IV decitabine at a frequency of common (1% and 2%)

[o] Cardiomyopathy was not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine at a frequency of uncommon (< 1%)

[p] Grouped terms include aphthous ulcer, glossitis, oral discomfort, oropharyngeal discomfort, oropharyngeal pain, stomatitis, tongue ulceration, toothache
[q] Nausea and bilirubin increased, Grade 3-4, were not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine at a frequency of uncommon (< 1%)
[r] Diarrhoea and vomiting, Grade 3-4, were not observed in the clinical trial with Inaqovi, however they were observed in clinical trials with IV decitabine at a frequency of common (2% and 1%)
[s] Caecitis (including fatal events) was not observed in the clinical trial with Inaqovi, however they were observed in post-market setting with the use of IV decitabine
[t] Aspartate aminotransferase increased (n=72)
[u] Alanine aminotransferase increased (n=73)
[v] Alkaline phosphatase increased (n=71)
[w] Bilirubin increased (n=73)
[x] Acute febrile neutrophilic dermatosis was not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine (all Grades) at a frequency of uncommon (< 1%)
[y] Not applicable (Grade 3-4): Adverse drug reaction has not been observed with either Inaqovi or IV decitabine in both clinical trials and post-market
[z] Grouped terms include chills and pyrexia
CTCAE= Common Terminology Criteria for Adverse Events

Description of selected adverse reactions

Haematologic adverse drug reactions

The most commonly reported haematologic adverse drug reactions associated with treatment included leukopaenia, thrombocytopaenia, anaemia, neutropaenia and febrile neutropaenia. These adverse drug reactions are manifestations of myelosuppression and may present as pancytopenia.

Serious bleeding-related adverse drug reactions, such as gastrointestinal haemorrhage and cerebral haemorrhage in the context of severe thrombocytopaenia, were reported in patients receiving treatment. Bleeding may also occur with the eyes, skin, and mucous membranes (mouth and anorectal).

Haematological adverse drug reactions must be managed by routine monitoring of CBCs 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 treatment must be delayed, see section 4.2.

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 reported in patients receiving treatment.

Gastrointestinal disorders

Occurrences of enterocolitis, including neutropaenic colitis, have been reported during treatment. 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 reported in patients receiving intravenous decitabine.

Differentiation syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving intravenous decitabine. 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. Differentiation syndrome may occur with or without concomitant leucocytosis. Capillary leak syndrome and coagulopathy can also occur (see section 4.4).

Other special populations

Elderly

Of the 80 patients in clinical studies who received Inaqovi, 39% were younger than 75 years, and 61% were 75 years and older. No overall differences in safety or effectiveness were observed between patients aged 75 years and older and younger patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

Overdose could cause increased myelosuppression and neutropaenia-related infections such as pneumonia and sepsis.

Management

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues; cytidine deaminase inhibitor; ATC code: L01BC58.

Mechanism of action

Decitabine is a nucleoside metabolic inhibitor that is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA.

Cytidine deaminase (CDA) is an enzyme that is responsible for the degradation of cytidine nucleosides, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver rapidly degrade these nucleosides and prohibit or limit their oral bioavailability. Cedazuridine inhibits CDA. Oral administration of cedazuridine with decitabine increases the systemic exposure of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA.

Clinical efficacy and safety

Inaqovi was evaluated in a Phase 3 (ASTX727-02-EU, NCT03306264) open-label, randomised, 2-cycle, 2-sequence crossover study that included adult patients with *de novo* or secondary AML as defined by World Health Organisation (WHO) criteria, who were not candidates for standard induction chemotherapy. A total of 89 patients were randomised 1:1 to receive Inaqovi (35 mg decitabine and 100 mg cedazuridine) orally in Cycle 1 and decitabine (20 mg/m2) intravenously in Cycle 2 (n=44) or the reverse sequence (n=45). Both Inaqovi and intravenous decitabine were administered once daily on Days 1 through 5 of the 28-day cycle. Starting with Cycle 3, all patients received Inaqovi orally once daily on Days 1 through 5 of each 28-day cycle until disease progression, death, or unacceptable toxicity. Two of the patients randomised did not receive any study treatment and fifteen were treated in Cycle 1 alone: 8 with Inaqovi, and 7 with intravenous decitabine.

The median treatment duration was 5 months (range 0 to 18 months).

Demographic and baseline disease characteristics are shown in Table 3.

Table 3: Demographic and disease baseline characteristics (Phase 3)

Characteristic	Phase 3 Inaqovi (N=89)
Age (years)	

Characteristic	Phase 3 Inaqovi (N=89)
Median (min, max)	78 (61, 92)
Gender (%)	
Male	54 (60.7)
Female	35 (39.3)
ECOG Performance Score (%)	
0	36 (40.4)
1	53 (59.6)
Disease Category (%)	
de novo AML	57 (64.0)
Secondary AML	32 (36.0)
MDS	18 (20.2)
Other antecedent haematological disorder	7 (7.9)
Therapy-related AML	7 (7.9)
Prior HMA Therapy (%)	
Prior azacitidine	2 (2.2)
Transfusion Dependence[a] (%)	
RBC transfusion dependence	37 (41.6)
Platelet transfusion dependence	14 (15.7)

[a] Defined as documentation of ≥ 2 units of transfusion within 56 days of the first day of study treatment.
AML=acute myeloid leukaemia; ECOG=Eastern Cooperative Oncology Group; HMA=hypomethylating agent; MDS=myelodysplastic syndrome; RBC=red blood cell.

The primary outcome measure of the Phase 3 study was 5-day cumulative decitabine AUC between Inaqovi and intravenous decitabine. Inaqovi achieved $AUC_{0\text{-}24h}$ exposures equivalent to intravenous infusion of decitabine at 20 mg/m^2 (see section 5.2).

Secondary efficacy endpoints included complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence. Descriptive summaries of efficacy are shown in Table 4.

Table 4: Efficacy results in patients with AML study ASTX727-02-EU AML (Phase 3)

Efficacy endpoints	Inaqovi (N=89)
Complete response (%) [95% CI]	21 [13.4, 31.3]
Median duration of CR* - months [95% CI]	5.8 [3.3, NE]
Median time to CR - months [range]	3.0 [1.8, 7.4]
Overall response† (%) [95% CI]	32 [22.0, 42.2]

* From start of CR until relapse or death

† OR included patients with a best response of CR, CRi, and PR
CI=confidence interval; CR=complete response; NE=not evaluable; OR=overall response; PR=partial response.

A patient was considered transfusion independent if the patient was both RBC and platelet transfusion free post-treatment for ≥ 56 consecutive days. Among a total of 41 patients (out of the 87 treated patients) who were dependent on either RBC and/or

platelet transfusions at baseline, 14 (34%) became independent of RBC or platelet transfusions during any 56-day post-baseline period. Of the 46 patients who were independent of both RBC and platelet transfusions at baseline, 12 (26%) remained transfusion-independent during any 56-day post-baseline period.

Paediatric population

The obligation to submit the results of studies with Inaqovi in one or more subsets of the paediatric population in AML has been deferred by the European Medicines Agency. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) parameters of decitabine and cedazuridine were studied following administration of Inaqovi at the recommended dose in patients with myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML), and AML.

Decitabine AUC exposures equivalent to those achieved with intravenous infusion of decitabine at 20 mg/m^2 was achieved with the recommended dose of Inaqovi for 5 consecutive days. The geometric mean ratio (GMR) of 5-day total decitabine AUC_{0-24h} between Inaqovi and intravenous decitabine was 99% for patients with MDS/CMML and 100% for patients with AML (90% confidence interval [CI] 93%, 106% and 91%, 109% for MDS/CMML and AML, respectively).

At steady state (achieved with the second dose), circulating plasma concentrations were typically 1.8 times and 1.1 times the Day 1 plasma concentrations for decitabine and cedazuridine, respectively.

In the MDS population (highest number of subjects available; data from AML were similar), decitabine mean (% coefficient of variation [CV]) AUC_{0-24h} exposure at steady state was 189 (55%) ng×h/mL and C_{max} was 145 (55%) ng/mL, respectively. Cedazuridine mean AUC_{0-24h} exposure at steady state (Day 2) was 3290 (45%) ng×h/mL and C_{max} was 349 (49%) ng/mL.

Absorption

After oral administration of Inaqovi, the median time to peak concentration ($t_{max)}$ at steady state was 3 hours (range: 0.5 to 7.9) for cedazuridine and 1 hour (range: 0.3 to 3) for decitabine. Co-administered with cedazuridine increased decitabine oral relative bioavailability to achieve systemic AUC exposures seen with intravenous decitabine. The bioavailability of cedazuridine was 20.7% (range: 12.7% to 25.6%).

In a crossover food effect study conducted in 16 patients, administration of the medicinal product with a high-fat, high-calorie meal reduced the overall decitabine exposure (AUC) by approximately 40% and C_{max} by 54%. Cedazuridine time to

maximum concentration (t_{max}) was slightly delayed but its systemic exposure was not significantly affected by the meal.

Distribution

Decitabine

Decitabine is approximately 5% bound to human plasma proteins *in vitro*. The geometric mean (CV%) of apparent volume of distribution at steady state is 417 L (54%).

Cedazuridine

Cedazuridine is approximately 35% bound to human plasma proteins *in vitro*. The geometric mean (CV%) of apparent volume of distribution for cedazuridine is 296 L (51%).

Biotransformation

Decitabine

Decitabine is metabolised primarily via deamination by cytidine deaminases and also physiochemical degradation at physiological conditions.

Cedazuridine

The primary metabolic pathway for cedazuridine is conversion to its epimer by physiochemical conversion in GI tract preabsorption.

Elimination

Decitabine

Following a single oral dose of Inaqovi, the mean (CV%) terminal elimination half-life ($t_{1/2}$) of decitabine was 1.2 (23%) hours. The apparent oral clearance (CL/F) was 197 L/h at steady state. The main pathway of elimination for decitabine is metabolic/degradation. Metabolites and degradation products are excreted mainly renally.

Cedazuridine

Following a single oral dose of Inaqovi, the mean (CV%) $t_{1/2}$ of cedazuridine was 6.3 (18%) hours. The mean (CV%) apparent oral clearance (CL/F) was 25.6 (159%) L/h at steady state.

The two major elimination pathways of cedazuridine are renal elimination as parent drug and conversion to its epimer (which is then renally excreted). Following a single oral dose of 100 mg radiolabeled cedazuridine, 46% (17.1% unchanged) of the administered dose was recovered in urine and 51% was recovered in the faeces.

Linearity/non-linearity

An approximately dose-proportional increase in peak concentrations (C_{max}) and AUC over the dosing interval was observed for decitabine over a dose range from 20 mg to 40 mg in combination with 100 mg cedazuridine.

Exposure for cedazuridine over the dose range evaluated from 40 mg to 100 mg once daily were dose proportional.

Special populations

Age, sex, body weight, and body surface area did not have a clinically relevant effect on the PK parameters of decitabine or cedazuridine after dosing with Inaqovi.

Renal impairment

The PK of decitabine and cedazuridine have not been formally studied in patients with impaired renal function. Patients with normal renal function (N=65) as well as mild (N=129) and moderate (N=103) renal impairment were included in the clinical studies. Renal impairment increases the exposure of cedazuridine (as renal elimination of parent drug is a major elimination pathway) and potentially also increases the exposure of decitabine (due to inhibition of decitabine metabolism caused by increased cedazuridine exposure). Decitabine is mainly metabolised and not excreted renally as unchanged drug. Only three patients with severe renal impairment and no patient with end stage renal disease were included in the studies. See also sections 4.2 and 4.4.

Hepatic impairment

The PK of decitabine and cedazuridine have not been formally studied in patients with hepatic impairment. Very few patients with impaired liver function were included in the clinical studies. Large effects of hepatic impairment on decitabine or cedazuridine exposure are not expected as cedazuridine is not hepatically metabolised and decitabine is metabolised by cytidine deaminase, which is present in several tissues.

5.3 Preclinical safety data

Carcinogenicity, mutagenesis, and impairment of fertility

Carcinogenicity studies with decitabine, cedazuridine, or their combination have not been conducted.

Decitabine was mutagenic in *in vitro* and *in vivo* studies. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells and mutations were produced in an *Escherichia coli* lac-I transgene in colonic DNA of decitabine-treated mice. Decitabine caused chromosomal rearrangements in larvae of fruit flies.

Cedazuridine was mutagenic in the reverse bacterial mutation assay (Ames assay) and was genotoxic in the *in vitro* chromosomal aberration study using human lymphocytes. Cedazuridine was negative for the genotoxicity assessment in three *in vivo* studies including the mouse micronucleus, Comet assay, and the Pig-A assay.

Fertility and repeat-dose toxicity studies in animals showed adverse outcomes on reproductive function and fertility.

In male mice given intraperitoneal injections of 0.15, 0.3, or 0.45 mg/m^2 decitabine (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, testes weights were reduced, abnormal histology was observed, and significant decreases in sperm number were found at doses $\geq$ 0.3 mg/m^2. In females mated to males dosed with $\geq$ 0.3 mg/m^2 decitabine, pregnancy rate was reduced, and preimplantation loss was significantly increased.

Decitabine was administered orally to male rats at 0.75, 2.5, or 7.5 mg/kg/day in cycles of 5-days-on/23-days-off for a total of 90 days. Low testes and epididymis weights, abnormal histology, and reduced sperm number were observed at doses $\geq$ 0.75 mg/kg (approximately $\geq$ 3 times the exposure in patients at the recommended clinical dose based on AUC).

Cedazuridine was administered orally to male and female mice at 100, 300, or 1,000 mg/kg/day in cycles of 7-days-on/21-days-off for a total of 91 days. Adverse reactions including abnormal histology in the testes, epididymis, and ovaries, as well as reduced sperm numbers were observed at the 1,000 mg/kg dose (approximately 108 times the exposure in patients at the recommended clinical dose). These findings showed evidence of reversibility following 3 weeks off-dose.

Teratogenic effects

Evidence from the literature indicates that decitabine has carcinogenic potential. The available data from *in vitro* and *in vivo* studies provide sufficient evidence that decitabine has genotoxic potential. Data from the literature also indicate that decitabine has adverse effects on all aspects of the reproductive cycle, including fertility, embryo-foetal development and post-natal development. Multi-cycle repeat-dose toxicity studies in rats and rabbits indicated that the primary toxicity was myelosuppression, including effects on bone marrow, which was reversible on cessation of treatment. Gastrointestinal toxicity was also observed and in males, testicular atrophy that did not reverse over the scheduled recovery periods.

Decitabine administration to neonatal/juvenile rats showed a comparable general toxicity profile as in older rats. Neurobehavioural development and reproductive capacity were unaffected when neonatal/juvenile rats were treated at dose levels inducing myelosuppression.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Hypromellose (E464)
Croscarmellose sodium (E466)
Silica, colloidal anhydrous
Magnesium stearate (E572)

Film-coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Polyethylene glycol (E1521)
Talc (E553b)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

5 film-coated tablets in PVC/Aluminum blisters with laminated desiccant (3-ply cold formable aluminum-plastic).

6.6 Special precautions for disposal

Safe handling of Inaqovi film-coated tablets

The handling of Inaqovi film-coated tablets should follow guidelines for the handling of cytotoxic medicinal products according to prevailing local recommendation and/or regulations.

Provided the outer coating of the tablet is intact, there is no risk in handling Inaqovi film-coated tablets.

Inaqovi film-coated tablets must not be crushed or divided.

Disposal

Any unused medicinal product should be destroyed in accordance with relevant local requirements concerning the disposal of cytotoxic medicinal products.

7 MARKETING AUTHORISATION HOLDER

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1101 CT Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 50697/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

16/04/2025