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This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – INQOVI® 35/100 (DECITABINE AND CEDAZURIDINE) TABLETS

1 NAME OF THE MEDICINE

Decitabine and cedazuridine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each INQOVI 35/100 tablet contains 35 mg of decitabine and 100 mg of cedazuridine.

INQOVI 35/100 contains lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet

INQOVI 35/100 is a biconvex, oval-shaped, red film-coated tablet, plain-faced on one side and debossed with “H35” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

INQOVI 35/100 is indicated for treatment of adult patients with myelodysplastic syndromes (MDS) intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups, and patients with chronic myelomonocytic leukaemia (CMML).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended dose of INQOVI 35/100 is 1 tablet containing 35 mg of decitabine and 100 mg of cedazuridine taken orally once daily on Days 1 through 5 of each 28-day cycle for

a minimum of 4 cycles. Best response may take longer than 4 cycles. Continue treatment as long as the patient continues to benefit. Repeat cycles every 28 days in the absence of haematologic toxicities not attributed to active disease and blood counts show absolute neutrophil count at least 1,000/µL and platelets at least 50,000/µL, or at least return to pretreatment levels. Delay or reduce the dose per cycle for haematologic toxicity (see Dosage adjustment, Haematological toxicity).

Prior to initiation of INQOVI 35/100, conduct baseline laboratory testing including complete blood cell counts with platelets, serum hepatic panel, and serum creatinine. Obtain complete blood cell counts prior to initiation of INQOVI 35/100 and prior to each cycle (see Dosage adjustment, Haematological toxicity).

Method of administration

INQOVI 35/100 tablets should be taken with water on an empty stomach, at approximately the same time each day. Do not consume food two hours before and two hours after taking INQOVI 35/100.

Agents that increase gastric pH should not be taken within 4 hours of INQOVI 35/100 administration (see INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

INQOVI 35/100 is a cytotoxic drug. INQOVI 35/100 tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

Missed or vomited dose

If the patient misses a dose of INQOVI 35/100 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 a patient misses a dose by more than 12 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day to complete 5 days of treatment per cycle.

If the patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time. Consider pre-medicating with antiemetics for next dose.

Dosage adjustment

Monitor blood counts frequently through resolution of cytopenias. Management of some adverse reactions may require dose delay or dose reduction of INQOVI 35/100 (see also Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects)).

Haematologic toxicity

Obtain complete blood cell counts prior to initiating INQOVI and before each cycle. Dose reduction is not recommended for the first 2 cycles. In case of persistent cytopenias at

4 weeks after start of treatment cycle, delay the next cycle if absolute neutrophil count (ANC) is less than 1,000/µL and platelets are less than 50,000/µL in the absence of active disease. Monitor complete blood cell counts until ANC is 1,000/µL or greater and platelets are 50,000/µL or greater.

- If hematologic recovery occurs (ANC at least 1,000/µL and platelets at least 50,000/µL) within 2 weeks from the delayed cycle, continue INQOVI at the same dose.
- If hematologic recovery does not occur (ANC at least 1,000/µL and platelets at least 50,000/µL) within 2 weeks from the delayed cycle,
    - Delay INQOVI for up to 2 additional weeks AND
    - Resume at a reduced dose by administering INQOVI on Days 1 through 4. Consider further dose reductions in the order listed in Table 1 if myelosuppression persists after a dose reduction. Maintain or increase dose in subsequent cycles as clinically indicated.

Table 1: Recommended INQOVI Dose Reductions for Myelosuppression

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

Manage persistent severe neutropenia and febrile neutropenia with supportive treatment such as growth factors and anti-infective therapy, including anti-fungals (see Section 4.4 Special warnings and precautions for use).

Non-haematologic toxicity

Delay subsequent INQOVI 35/100 cycles for any of the following non-haematologic toxicities, if not present prior to treatment, until toxicities resolve or an alternative cause for the toxicity is clearly established:

- Serum creatinine equal to or greater than 0.2 mg/L
- Serum bilirubin equal to or greater than 2 times upper limit of normal (ULN)
- Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) equal to or greater than 2 times ULN.
- Active or uncontrolled infection

4.3 CONTRAINDICATIONS

Pregnancy.

Hypersensitivity to the active substances, decitabine or cedazuridine, or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Myelosuppression

Fatal and serious myelosuppression may occur with INQOVI 35/100. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anaemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%.

Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of INQOVI 35/100 dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

Fatal and serious infectious complications may occur with INQOVI 35/100. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1% (see Section 4.8 Adverse effects (undesirable effects)).

Obtain complete blood cell counts prior to initiation of INQOVI 35/100, and prior to each cycle, and as clinically indicated to monitor response and toxicity. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose as recommended (see Section 4.2 Dose and method of administration, Haematological toxicity).

Haemorrhage

Serious bleeding-related treatment-emergent adverse events (TEAEs) have been reported with INQOVI 35/100 due to severe thrombocytopenia. Gastrointestinal haemorrhage was reported in 6.7% including Grade ≥ 3 in 2.4%. Intracranial haemorrhage was reported in 1.9% including Grade ≥ 3 in 1.4%. Monitor patients receiving INQOVI 35/100 closely for signs and symptoms of serious bleeding-related adverse reactions.

Embryofoetal toxicity

Based on its mechanism of action and findings in animals, INQOVI 35/100 can cause foetal harm when administered to a pregnant woman. Decitabine alters DNA synthesis and is

expected to result in adverse reproductive effects (see Section 4.6 Fertility, pregnancy and lactation). In studies with decitabine in mice and rats, decitabine was teratogenic, foetotoxic, and embryotoxic at doses less than the recommended human dose.

If INQOVI 35/100 is used during pregnancy, or if a patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus. Advise women of childbearing potential to avoid becoming pregnant while taking INQOVI 35/100 and for 6 months following the last dose. Advise men with female partners of childbearing potential to avoid fathering a child while receiving treatment with INQOVI 35/100, and for 3 months following the last dose. Counsel patients of childbearing potential to use effective contraception during this time (see Section 4.6 Fertility, pregnancy and lactation).

Cardiovascular

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 INQOVI 35/100 in these patients has not been established. Patients with history of severe congestive heart failure or clinically unstable cardiac disease should be closely monitored.

Interstitial Lung Disease

Interstitial lung disease (ILD) (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis) without signs of infectious aetiology were reported in patients receiving intravenous decitabine. Assess patients with acute onset or unexplained worsening of pulmonary symptoms to exclude ILD. If ILD is confirmed, initiate appropriate treatment.

Use in hepatic impairment

A population PK analysis indicated that mild hepatic impairment (total bilirubin > ULN to ≤1.5 × ULN) does not have a clinically meaningful effect on the pharmacokinetics of decitabine or cedazuridine after dosing with INQOVI 35/100. The effects of moderate and severe hepatic impairment (1.5 × ULN) on the pharmacokinetics of decitabine and cedazuridine are unknown. (see Section 5.2 Pharmacokinetic properties).

Use in renal impairment

No modification to the starting dose is recommended in patients with mild or moderate renal impairment (creatinine clearance [CrCL] of 20 to 59 mL/min/1.73 m^2). INQOVI 35/100 has not been studied in patients with severe renal impairment (CrCL < 20 mL/min/1.73 m^2) or end stage renal disease (see Section 5.2 Pharmacokinetic properties).

Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CrCL 20 to 39 mL/min/1.73m^2).

Use in the elderly

Of the 208 patients treated with INQOVI 35/100, 75% were age 65 years and over, while 36% were age 75 years and over. No overall difference in safety was noted between patients age 65 years or older and younger patients.

Paediatric use

The safety and effectiveness of INQOVI 35/100 in paediatric patients have not been established.

Effects on laboratory tests

There was no clinically notable central tendency shifts in liver or renal laboratory values over multiple treatment cycles. In haematology, neutrophils decreased in the first 2 cycles then stabilised or increased, while haemoglobin and platelets tended to increase over multiple cycles as patients responded to treatment.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Cedazuridine is an inhibitor of the cytidine deaminase (CDA) enzyme. Same day concomitant administration of INQOVI 35/100 with drugs metabolised by CDA may result in their increased systemic exposure with potential for increased toxicity of these drugs. Avoid coadministration of INQOVI 35/100 on the same day as other drugs known to be metabolised by CDA.

Drug interaction studies have not been conducted with INQOVI 35/100 *in vivo*. *In vitro* studies show that cedazuridine does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5 at clinically relevant concentrations and does not induce CYP1A, 2B6, 2C9 or 3A4. Cedazuridine is not a substrate of P-glycoprotein, MATE1, MATE2-k, OAT1, OAT3, OATP1B1, OAPT1B3, OATP2B1, OCT1 or OCT2 and does not inhibit P-glycoprotein, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OAPT1B3 or OCT2.

In vitro data show that decitabine is not a substrate or inhibitor of P-glycoprotein, does not inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6 or 3A4/5 at clinically relevant concentrations, and is not an inducer of CYP1A2, 2B6, 2C9 or 3A4/5.

Cedazuridine is converted to its epimer prior absorption and its bioavailability may be affected by gastric PH. However, no effect on cedazuridine or decitabine PK was shown when co-administered with gastric pH modifying drugs as long as they are not administered within 4 hours of Inqovi administration.

Food

INQOVI 35/100 tablets should be taken with water on an empty stomach. The oral bioavailability of decitabine is decreased in the presence of food (see Section 5.2 Pharmacokinetic properties).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on findings with decitabine in animals, male fertility may be compromised by treatment with INQOVI 35/100.

Decitabine impaired fertility in male mice given IP doses ≥0.3mg/m^2 (well below the clinical dose). This was accompanied by reduced testes weights, abnormal histology and marked decreases in sperm count. Pre-implantation loss was significantly increased in females mated with treated males.

No fertility studies have been conducted with cedazuridine.

Females and males of reproductive potential

Conduct pregnancy testing of females of reproductive potential prior to initiating INQOVI 35/100 (see Use in pregnancy).

INQOVI 35/100 may cause severe foetal harm when administered to a pregnant woman (see Use in pregnancy and Section 4.4 Special warnings and precautions for use, Embryofoetal toxicity).

Advise females of reproductive potential to avoid pregnancy and use effective contraception while receiving INQOVI 35/100 and for 6 months following the last dose.

Advise males with female partners of reproductive potential to use effective contraception while receiving treatment with INQOVI 35/100 and for 3 months following the last dose.

Use in pregnancy – Pregnancy Category X

INQOVI 100/35 is contraindicated in pregnancy. Based on findings from human data, animal studies, and the mechanism of action for decitabine, INQOVI 35/100 may cause severe foetal harm when administered to a pregnant woman (see Section 5.1 Pharmacodynamic properties, Mechanism of action).

There are no available data on INQOVI 35100/10035 use in pregnant women. No reproductive or developmental toxicity studies have been conducted with INQOVI 35/100 or cedazuridine.

When administered intravenously decitabine is known to be teratogenic, foetotoxic, and embryotoxic.

Decitabine inhibits proliferation and increases apoptosis of neural progenitor cells of the foetal central nervous system (CNS) in the developing murine foetus.

Decitabine was shown to cause malformations and embryofoetal lethality in pregnant mice and rats following single IP administration at dose levels well below the clinical dose. Foetal abnormalities observed in animals included fused vertebrae and ribs, cleft palate, exophthalmia, exencephaly, and limb and digital defects.

Animal embryofoetal development studies have not been performed with cedazuridine.

In rats given a single IP injection of 2.4, 3.6 or 6 mg/m^2 decitabine (approximately 5, 8, or 13% the daily recommended clinical dose, respectively) on gestation Days 9-12, no maternal toxicity was observed. No live foetuses were seen at any dose when decitabine was injected on gestation Day 9. A significant decrease in fetal survival and reduced foetal weight at doses greater than 3.6 mg/m^2 was seen when decitabine was given on gestation Day 10.

A single published case report of intravenous (IV) decitabine pregnancy exposure in a 39 year old woman with a haematological malignancy described multiple structural abnormalities after 6 cycles of therapy in the 18th week of gestation. These abnormalities included holoprosencephaly, absence of nasal bone, mid-facial deformity, cleft lip and palate, polydactyly, and rocker-bottom feet. The pregnancy was terminated.

Use in lactation

There are no data on the presence of cedazuridine, decitabine, or their metabolites in human milk, the effects on the breastfed child, or on milk production. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from INQOVI 35/100 in a nursing child, advise lactating women to avoid breastfeeding during treatment with INQOVI 35/100 and for at least 2 weeks after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies of the effects on the ability to drive or use machines have been performed. Patients should be advised that they may experience undesirable effects, such as fatigue and dizziness due to anaemia, during treatment. Therefore, caution should be recommended when driving a car or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

The safety of INQOVI 35/100 was evaluated in a pooled safety population that includes patients enrolled in Study ASTX727-01-B and Study ASTX727-02 (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

Patients were randomized to receive INQOVI (35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 in Cycle 1 and decitabine 20 mg/m^2 intravenously on Days 1 through 5 in Cycle 2, or the reverse sequence, and then INQOVI (35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 of each 28-day cycle in

Cycles 3 and beyond. Patients were allowed to have one prior cycle of decitabine or azacitidine and there was no limit for body weight or surface area. Among the patients who received INQOVI 35/100, 61% of patients were exposed for 6 months or longer and 24% were exposed to INQOVI 35/100 for greater than 1 year.

Serious adverse reactions occurred in 68% of patients who received INQOVI 35/100. Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions occurred in 6% of patients. These included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death.

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received INQOVI 35/100. The most frequent adverse reactions resulting in permanent discontinuation were febrile neutropenia (1%) and pneumonia (1%).

Dose interruptions due to an adverse reaction occurred in 41% of patients who received INQOVI 35/100. Adverse reactions requiring dosage interruptions in > 5% of patients who received INQOVI 35/100 included neutropenia (18%), febrile neutropenia (8%), thrombocytopenia (6%), and anemia (5%).

Dose reductions due to an adverse reaction occurred in 19% of patients who received INQOVI 35/100. Adverse reactions requiring dosage reductions in > 2% of patients who received INQOVI 35/100 included neutropenia (12%), anemia (3%), and thrombocytopenia (3%).

The most common adverse reactions (≥ 20%) were fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnoea, diarrhoea, rash, dizziness, febrile neutropenia, oedema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and haemoglobin decreased.
Table 2 summarizes the adverse reactions in the pooled safety population.

Table 2: Adverse Reactions (≥ 10%) in Patients Who Received INQOVI 35/100 in Pooled Safety Population

Adverse Reactions	INQOVI 35/100 Cycle 1 N=107		Intravenous Decitabine Cycle 1 N=106		INQOVI 35/100† All Cycles N=208	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General disorders and administration site conditions						
Fatigue[1]	29	2	25	0	55	5
Haemorrhage[2]	24	2	17	0	43	3
Oedema[3]	10	0	11	0	30	0.5
Pyrexia	7	0	7	0	19	1
Gastrointestinal disorders						
Constipation[4]	20	0	23	0	44	0
Mucositis[5]	18	1	24	2	41	4
Nausea	25	0	16	0	40	0.5
Diarrhoea[6]	16	0	11	0	37	1
Transaminase increased[7]	12	1	3	0	21	3
Abdominal pain[8]	9	0	7	0	19	1
Vomiting	5	0	5	0	15	0
Musculoskeletal and connective tissue disorders						
Myalgia[9]	9	2	16	1	42	3
Arthralgia[10]	9	1	13	1	40	3
Respiratory, thoracic, and mediastinal disorders						
Dyspnoea[11]	17	3	9	3	38	6
Cough[12]	7	0	8	0	28	0
Blood & lymphatic system disorders						
Febrile neutropenia	10	10	13	13	33	32
Skin and subcutaneous tissue disorders						
Rash[13]	12	1	11	1	33	0.5

Adverse Reactions	INQOVI 35/100 Cycle 1 N=107		Intravenous Decitabine Cycle 1 N=106		INQOVI 35/100† All Cycles N=208	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nervous system disorders						
Dizziness[14]	16	1	11	0	33	2
Headache[15]	22	0	13	0	30	0
Neuropathy[16]	4	0	8	0	13	0
Metabolism and nutritional disorders						
Decreased appetite	10	1	6	0	24	2
Infections and infestations						
Upper respiratory tract infection[17]	6	0	3	0	23	1
Pneumonia[18]	7	7	7	5	21	15
Sepsis[19]	6	6	2	1	14	11
Cellulitis[20]	4	1	3	2	12	5
Investigations						
Renal impairment[21]	9	0	8	1	18	0
Weight decreased	5	0	3	0	10	1
Injury, poisoning, and procedural complications						
Fall	4	0	1	0	12	1
Psychiatric disorders						
Insomnia	6	0	2	0	12	0.5
Vascular disorders						
Hypotension[22]	4	0	6	1	11	2
Cardiac Disorders						
Arrhythmia[23]	3	0	2	0	11	1

†Includes adverse reactions that occurred during all cycles, including during treatment with 1 cycle of intravenous decitabine.

1 Includes fatigue, asthenia, and lethargy

2 Includes contusion, epistaxis, petechiae, hematuria, conjunctival hemorrhage, mouth hemorrhage, purpura, angina bullosa hemorrhagica, gingival bleeding, hematoma, hemoptysis, eye contusion, hemorrhagic diathesis, increased tendency to bruise, vaginal hemorrhage, abdominal wall hematoma, blood blister, bone contusion, catheter site bruise, ecchymosis, genital

Adverse Reactions	INQOVI 35/100 Cycle 1 N=107		Intravenous Decitabine Cycle 1 N=106		INQOVI 35/100† All Cycles N=208	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)

hemorrhage, intra-abdominal hematoma, oral mucosa hematoma, periorbital hemorrhage, procedural hemorrhage, pulmonary alveolar hemorrhage, retinal hemorrhage, scleral hemorrhage, thrombotic thrombocytopenic purpura, tongue hemorrhage, and vessel puncture site hemorrhage

3 Includes edema peripheral, peripheral swelling, swelling face, fluid overload, localized edema, face edema, edema, eye swelling, eyelid edema, fluid retention, periorbital swelling, scrotal edema, scrotal swelling, and swelling

4 Includes constipation and feces hard

5 Includes oropharyngeal pain, stomatitis, mouth ulceration, proctalgia, oral pain, gingivitis, oral disorder, gingival pain, colitis, glossodynia, mouth swelling, pharyngitis, proctitis, duodenitis, enteritis, gingival discomfort, gingival swelling, lip disorder, lip ulceration, mucosal ulceration, nasal ulcer, noninfective gingivitis, oral mucosal blistering, oral mucosal erythema, pharyngeal erythema, pharyngeal ulceration, tongue ulceration, and vulvitis

6 Includes diarrhoea and faeces soft

7 Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, liver function test increased, and transaminases increased

8 Includes abdominal pain, abdominal pain upper, abdominal pain lower, epigastric discomfort, and abdominal discomfort

9 Includes myalgia, pain in extremity, muscle spasms, pain, musculoskeletal pain, non-cardiac chest pain, muscular weakness, musculoskeletal chest pain, flank pain, musculoskeletal stiffness, muscle strain, and musculoskeletal discomfort

10 Includes arthralgia, back pain, neck pain, joint stiffness, pain in jaw, joint swelling, bursitis, joint range of motion decreased, and joint injury

11 Includes dyspnoea, dyspnoea exertional, hypoxia, wheezing, chronic obstructive pulmonary disease, and tachypnoea

12 Includes cough and productive cough

13 Includes maculo-papular rash, rash, erythema, skin lesion, folliculitis, dermatitis, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, seborrheic keratosis, skin ulcer, dermatitis allergic, dermatitis contact, eczema nummular, genital erythema, rash papular, rash pruritic, rash pustular, seborrhoeic dermatitis, skin exfoliation, skin irritation, stasis dermatitis, and ulcerative keratitis

14 Includes dizziness, vertigo, postural dizziness, and positional vertigo

15 Includes headache, sinus pain, and sinus headache

16 Includes hypoaesthesia, paresthesia, neuropathy peripheral, gait disturbance, peripheral sensory neuropathy, ataxia, balance disorder, brachial plexopathy, carpal tunnel syndrome, and radicular pain

17 Includes upper respiratory tract infection, nasopharyngitis, sinusitis, and viral upper respiratory tract infection

18 Includes pneumonia, pneumonitis, atypical pneumonia, and lung infection

19 Includes sepsis, bacteremia, septic shock, endocarditis, pseudomonal bacteremia, and staphylococcal bacteraemia

20 Includes cellulitis, catheter site cellulitis, and infected bite

21 Includes blood creatinine increased, acute kidney injury, blood urea increased, blood creatine increased, and renal failure

22 Includes hypotension, blood pressure decreased, and cardiogenic shock

23 Includes sinus tachycardia, atrial fibrillation, bradycardia, tachycardia, atrial flutter, sinus bradycardia, and conduction disorder

Clinically relevant adverse reactions in < 10% of patients who received INQOVI 35/100 included:

- Acute febrile neutrophilic dermatosis (Sweet's syndrome) (1%)
- Tumor lysis syndrome (0.5%)

Table 3: Select Laboratory Abnormalities (> 20%) Worsening from Baseline in Patients Who Received INQOVI 35/100 in Pooled Safety Population

Lab Abnormality*	INQOVI 35/100 Cycle 1†		Intravenous Decitabine Cycle 1†		INQOVI 35/100 All Cycles†	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology						
Leukocytes decreased	79	65	77	59	87	81
Platelet count decreased	79	65	77	67	82	76
Neutrophil count decreased	70	65	62	59	73	71
Haemoglobin decreased	58	41	59	36	71	55
Chemistry						
Glucose increased	19	0	11	0	54	7
Albumin decreased	22	1	20	0	45	2
Alkaline phosphatase increased	22	1	12	0	42	0.5
Glucose decreased	14	0	17	0	40	1
Alanine aminotransferase increased	13	1	7	0	37	2
Sodium decreased	9	2	8	0	30	4
Calcium decreased	16	0	12	0	30	2
Aspartate aminotransferase increased	6	1	2	0	30	2
Creatinine increased	7	0	8	0	29	0.5

* Includes any lab abnormalities that worsened by one or more grades. Grade 3-4 includes any lab abnormalities that worsened to Grade 3 or Grade 4.

† The denominator used to calculate the rate varied from 103 to 107 for INQOVI Cycle 1, from 102 to 106 for Intravenous Decitabine Cycle and from 203 to 208 for INQOVI All Cycles based on the number of patients with a baseline value and at least one post-treatment value.

Post-marketing experience

The following adverse reactions have been identified during post-approval use of decitabine administered intravenously. Because these reactions are 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.

Blood and Lymphatic System Disorders: Differentiation syndrome

Respiratory Disorders: Interstitial lung disease.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no known antidote for overdosage with INQOVI 35/100. Overdosage could cause increased myelosuppression, and neutropenia-related infections such as pneumonia and sepsis. For patients who experience overdose, closely monitor, and provide appropriate supportive treatment.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Decitabine

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 inhibits DNA methylation *in vitro*, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation, proliferation, and the immune system. 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. Non-proliferating cells are relatively insensitive to decitabine.

Decitabine has been shown to induce hypomethylation both *in vitro* and *in vivo*. At the recommended INQOVI 35/100 dose, maximal or near maximal pharmacodynamic effect of long interspersed nucleotide elements-1 (LINE-1) demethylation was observed over the range of decitabine systemic exposures based on modeling.

Cedazuridine

Cedazuridine inhibits cytidine deaminase (CDA). CDA is an enzyme that is responsible for the degradation of nucleosides, including decitabine. High levels of CDA in the gastrointestinal tract and liver rapidly degrade these nucleosides and prohibit or limit their oral bioavailability.

Oral administration of cedazuridine with decitabine enhances the oral bioavailability of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA.

Clinical trials

Study ASTX727-01-B (Phase 2)

The efficacy of INQOVI 35/100 was evaluated in an open-label, randomised, 2-cycle, 2-sequence crossover study with IV decitabine followed by a single-arm INQOVI 35/100 treatment study. The study was conducted in 80 patients with MDS (International Prognostic Scoring System intermediate [IPSS] Intermediate-1, Intermediate-2, or high-risk) and CMML, who were candidates for treatment with a hypomethylating (HMA) agent. Patients were randomised to receive INQOVI 35/100 in Cycle 1 and IV decitabine (20 mg/m^2) in Cycle 2 or the reverse sequence. Both INQOVI 35/100 and IV decitabine were dosed once daily for 5 days in 28-day cycles. All patients received INQOVI 35/100 after Cycle 2 and treatment continued until disease progression, death, or unacceptable toxicity.

The major efficacy outcome measure was response rate. Additional efficacy outcome measures included duration of response, rate of transfusion independence (no transfusions for at least 56-day consecutive period), time to acute myeloid leukaemia (AML), and overall survival (OS).

The efficacy results are shown in Table 1. The median duration of treatment was 7 cycles (range: 1 to 29) and the median follow-up time was 24 months (range: 12 to 29 months).

Table 1: Efficacy Results from Study ASTX727-01-B (Phase 2)

Efficacy Endpoint	**Phase 2 Overall (N=80)**	
	n (%)	**95%CI**
Complete Response (CR)	17 (21.3)	(12.9, 31.8)
Median Duration of CR (months)[*]	13.3	(6.5, 13.8)
Marrow CR with Haematologic Improvement[†]	6 (7.5)	(2.8, 15.6)
Overall Response (OR)[‡]	48 (60.0)	(48.4, 70.8)
Median time to AML or death (months)	12.1	(10.2, 21.5)
Median Overall Survival (OS) (months)	18.3	(13.1, not estimable)
Post-treatment RBC transfusion independence[§]	19/38 (50)	(33.4, 66.6)
Post-treatment platelet transfusion independence[§]	6/12 (50)	(21.2, 78.9)

[*] From start of CR until relapse, [†] Patients with Marrow CR who also achieved Haematologic Improvement, [‡] OR included patients with a best response of CR, Partial Response (PR), Marrow CR, or Haematologic Improvement, [§] No transfusion for at least 56 consecutive days post-treatment in patients who were transfusion-dependent at baseline. RBC = Red blood cell

Study ASTX727-02 (Phase 3)

INQOVI 35/100 was evaluated in an open-label, randomised, 2-cycle, 2-sequence crossover with IV decitabine study followed by a single-arm INQOVI 35/100 treatment study. The study was conducted in 133 patients with MDS (IPSS Intermediate-1, Intermediate-2, or high-risk), and CMML. Patients were randomised 1:1 to receive INQOVI 35/100 in Cycle 1 and IV decitabine (20 mg/m^2) in Cycle 2 or the reverse sequence. Both INQOVI 35/100 and IV decitabine were dosed once daily for 5 days in each 28-day cycle. All patients received INQOVI 35/100 after Cycle 2 and treatment continued until disease progression, death, or unacceptable toxicity.

The primary outcome measure of this study was decitabine 5-day AUC between INQOVI 35/100 and IV decitabine. INQOVI 35/100 achieved decitabine AUC exposures equivalent to IV infusion of decitabine at 20 mg/m^2 (Table 2).

Table 2: 5-Day Decitabine AUC$_{0\text{-}24}$ Equivalence Assessment

5-day AUC$_{0\text{-}24}$ (h*ng/mL) (N=123)	**IV Decitabine Geo. LSM**	**Oral INQOVI 35/100 Geo. LSM**	**Ratio as Oral/IV (%) of Geo. LSM (90% CI)**	**Intra-Subject (CV%)**
	864.9	855.7	98.9 (92.7, 105.6)	31.7

CI = confidence interval; CV = coefficient of variation; Geo. LSM=Geometric Least Squares Means; IV = intravenous

The median duration of treatment for all treated subjects was 8.2 months (range 0.2 to 19.7) with a median follow-up time of 12.6 months (range: 9.3 to 20.5). Twenty-seven (20%) of the 133 treated patients went on to transplant. Clinical response data from all 133 treated patients are presented in Table 3.

Table 3: Efficacy Results in Patients with MDS or CMML from Study ASTX727-02 (Phase 3)

Efficacy Endpoints	**INQOVI (N= 133)**	
Complete Response (CR) (%) (95% CI)	21 (15, 29)	
Median duration of CR – months (range) *	7.5 (1.6, 17.5)	
Median Time to CR – months (range)	4.3 (2.1, 15.2)	

* From start of CR until relapse or death

Among the 57 patients who were dependent on RBC and/or platelet transfusions at baseline, 30 (53%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 76 patients who were independent of both of both RBC and platelet transfusions at baseline, 48 (63%) remained transfusion-independent during any 56-day post-baseline period.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After oral administration of INQOVI 35/100, the median T_{max} was 3 hours (range: 0.52 to 7.9) for cedazuridine and 1 hour (range: 0.3 to 3) for decitabine. When co-administered with cedazuridine, decitabine oral relative bioavailability is enhanced to achieve systemic AUC exposures seen with IV decitabine. In a ^{14}C-ADME study, approximately 47.5% of oral cedazuridine dose was absorbed and bioavailability was 20.7%.

Administration of INQOVI 35/100 with a high-fat, high-calorie meal (comprised of approximately 800-1000 kilocalories (kcal), including approximately 500-600 kcal from fat) decreased the mean maximum decitabine concentration (C_{max}) by 54% and AUC by approximately 40%. Administration with food delayed cedazuridine time to maximum concentration (T_{max}) slightly but had little effect on systemic exposures.

Distribution

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%).

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%).

Metabolism

The primary metabolic pathway for cedazuridine is conversion to its epimer. This occurs non-enzymatically. The epimer of cedazuridine is a major circulating metabolite but possesses much weaker pharmacological activity than its parent.

Decitabine is mainly metabolised via deamination by cytidine deaminase (CDA) Decitabine is also subject to chemical degradation, involving oxidation, ring opening and deformylation.

Excretion

Following a single oral dose of INQOVI 35/100, the mean (CV%) terminal elimination half-life ($T_{1/2}$) of cedazuridine was 6.3 (18%) hours. The apparent clearance was 30.6 L/hr at Day 1 and 30.3 L/hr at steady state. Following a single oral dose of 100 mg radiolabeled cedazuridine, 46% (17.1% unchanged) of the administered dose was recovered in urine and 51% (mostly unabsorbed drug) was recovered in the feces. Predominant elimination pathway of cedazuridine is renal, as parent and epimer.

Following a single oral dose of INQOVI 35/100, the mean (CV%) terminal elimination half-life ($T_{1/2}$) of decitabine was 1.2 (23%) hours. The apparent clearance was 342 L/hr at Day 1 and 197 L/hr at steady state. The primary elimination pathway for decitabine is metabolic, by cytidine deaminase and also physicochemical degradation at physiological conditions.

Special populations

Age (32-90 years), sex, body weight (41-158 kg), or mild to moderate hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or > 1.5 to ≤ 3 × ULN) do not have a clinically meaningful effect on the pharmacokinetics of decitabine or cedazuridine after dosing with INQOVI 35/100.

Mild or moderate renal impairment (CrCL ≥ 20 up to 59 mL/min/1.73 m^2) had an effect on cedazuridine exposures, but not considered to be clinically meaningful. The effects of severe hepatic impairment (total bilirubin > 3 × ULN) or severe renal impairment (CrCL <20 mL/min/1.73 m^2) on the pharmacokinetics of decitabine and cedazuridine is unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cedazuridine and decitabine are genotoxic.

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 also caused chromosomal rearrangements in larvae of fruit flies.

Cedazuridine was genotoxic in a reverse bacterial mutation assay (Ames test) and in an *in vitro* chromosomal aberration assay in human lymphocytes. Negative results were obtained for cedazuridine in an *in vivo* mouse bone marrow micronucleus test.

Carcinogenicity

Carcinogenicity studies with decitabine, cedazuridine or the two medicines in combination have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of INQOVI 35/100 contains the following inactive ingredients: lactose monohydrate, hypromellose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate. The film coating material contains OPADRY II complete film coating system 85F15458 RED (PI 110931).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

High-density polyethylene (HDPE) bottles with child resistant closure containing a silica gel desiccant. Pack size: 5 film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

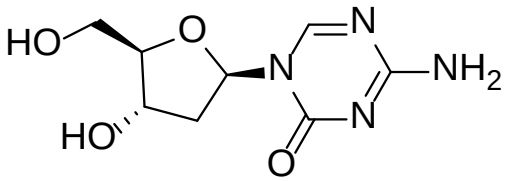
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

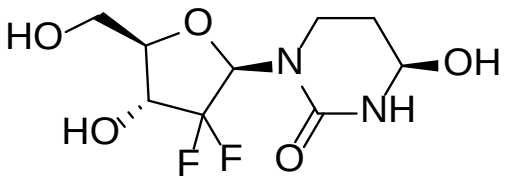
Decitabine

Decitabine is a nucleoside metabolic inhibitor. Decitabine is white to off-white solid with the molecular formula of $C_8H_{12}N_4O_4$ and a molecular weight of 228.21 daltons. Its IUPAC chemical name is 4-amino-1-[(2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2(1*H*)-one and it has the following structural formula:



Cedazuridine

Cedazuridine is a cytidine deaminase inhibitor. Cedazuridine is white to off-white solid with molecular formula of $C_9H_{14}F_2N_2O_5$ and a molecular weight of 268.21 daltons. Its international union of pure and applied chemistry (IUPAC) chemical name is (4*R*)-1-[(2*R*,4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-4-hydroxy-1,3-diazinan-2-one and has the following structural formula:



CAS numbers

Decitabine: 2353-33-5

Cedazuridine: 1141397-80-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – PRESCRIPTION ONLY MEDICINE

8 SPONSOR

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INQOVI® is a registered trademark of Otsuka Pharmaceutical Co., Ltd.

9 DATE OF FIRST APPROVAL

29 October 2020

10 DATE OF REVISION