DRUG NAME: Decitabine-cedazuridine

SYNONYM(S): ASTX727[1]

COMMON TRADE NAME(S): INQOVI®

CLASSIFICATION: antimetabolite

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Decitabine-cedazuridine is an orally administered antimetabolite composed of a nucleoside metabolic inhibitor (decitabine) and a cytidine deaminase inhibitor (cedazuridine). Decitabine is a cytidine-nucleoside analog which exerts its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase. This results in hypomethylation of DNA and cellular differentiation and/or apoptosis. Decitabine-induced hypomethylation in cancer cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. Decitabine is cell cycle phase-specific, inducing hypomethylation within the S-phase of the cell cycle. Cedazuridine enhances the bioavailability of decitabine by inhibiting its rapid degradation/first-pass metabolism in the gastrointestinal tract and liver by cytidine deaminase.[1-4]

PHARMACOKINETICS:

Oral Absorption	decitabine: t_{max} = 1 h; cedazuridine: t_{max} = 3 h, bioavailability = 21%; food effect: administration with a high-fat, high-calorie meal significantly reduces overall decitabine exposure and C_{max} and slightly delays cedazuridine t_{max}	
Distribution	cross blood brain barrier?	no information found
	volume of distribution	decitabine: 417 L; cedazuridine: 296 L
	plasma protein binding	decitabine: 5%; cedazuridine: 35%
Metabolism	decitabine: primarily metabolized via deamination by cytidine deaminases cedazuridine: primarily metabolized via conversion to its epimer	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	decitabine: major elimination pathway via cytidine deaminase cedazuridine: major elimination pathway via physiochemical degradation	
	urine	cedazuridine: 45.7%
	feces	cedazuridine: 51%
	terminal half life	decitabine: 1.2 h; cedazuridine: 6.3 h
	clearance	decitabine: 197 L/h; cedazuridine: 30 L/h
Elderly	in patients aged >75 years: 1.2-1.4 fold increase in 5 day cumulative AUC	
Body Weight	lower or higher baseline body weights may affect drug exposure differently; decitabine: 1.3-fold increase in exposure in patients <70 kg, 24% decrease in exposure in patients >93 kg; cedazuridine: 21% increase in AUC in patients >93 kg	

Adapted from standard reference[2,3] unless specified otherwise.

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USES:

Primary uses:

*Myelodysplastic syndromes

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- severe ***myelosuppression*** and serious ***infection*** may occur and are sometimes fatal; consider prophylactic anti-infective therapies in patients with a history of neutropenic infections or other risk factors[2,3,5]

Carcinogenicity: no information found

Mutagenicity: Decitabine is mutagenic in the *E. coli* bacterial test and one mammalian *in vitro* mutation test, and is clastogenic in a mammalian *in vivo* chromosome test. Cedazuridine is mutagenic in the Ames test and it is clastogenic in a mammalian *in vivo* chromosome test.[2,3]

Fertility: In animal studies, decitabine caused reduced testes weight, abnormal histology, and significantly decreased sperm count in male test subjects at exposures lower than those seen following human clinical exposure. Female subjects mated to treated males experienced reduced pregnancy rates and increased preimplantation loss.[2,3] Cedazuridine, in animal studies, caused abnormal ovarian, testicular, and epididymal histology and reduced sperm count at exposures higher than those seen following human clinical exposure.[2,3] Cedazuridine-related effects on male and female reproductive organs in animals were reversible following a recovery period[3]; however, the reversibility of decitabine-related effects is unknown. Consider sperm conservation in male patients and oocyte cryopreservation in female patients of childbearing potential prior to starting treatment.[2]

Pregnancy: In humans, adverse developmental outcomes (including major birth defects and multiple structural abnormalities) were observed. In animal studies with decitabine, increased embryo-fetal mortality, growth alterations, and structural abnormalities were observed at exposures lower than those seen following human clinical exposure. Female patients of childbearing potential should use effective contraception during treatment and for 6 months following the last dose. Male patients with female partners of childbearing potential should use effective contraception during treatment and for 3 months following the last dose.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should wait at least two weeks after the last dose before breastfeeding.[2,3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[5,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (48%, severe 42%)
	febrile neutropenia (severe 32%)
	neutropenia (57%, severe 54%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	thrombocytopenia (62%, severe 54%)
cardiac	arrhythmia (11%, severe 1%)
gastrointestinal	*emetogenic potential:* low[7]
	abdominal pain (19%, severe 1%)
	constipation (44%)
	diarrhea (37%, severe 1%)
	enterocolitis; fatal events reported
	mucositis (41%, severe 4%)
	nausea (40%, severe <1%)
	vomiting (15%)
general disorders and administration site conditions	edema (30%, severe <1%)
	fatigue (55%, severe 5%)
	pyrexia (19%, severe 1%)
immune system	anaphylactic reaction
infections and infestations	cellulitis (12%, severe 5%)
	pneumonia (21%, severe 15%); fatal events reported
	sepsis, septic shock (14%, severe 11%); fatal events reported
	upper respiratory tract infection (23%, severe 1%)
injury, poisoning, and procedural complications	fall (12%, severe 1%)
investigations	albumin decrease (45%, severe 2%)
	alkaline phosphatase increase (42%, severe <1%)
	ALT increase (37%, severe 2%)
	AST increase (30%, severe 2%)
	calcium decrease (30%, severe 2%)
	creatinine increase (29%, severe <1%)
	glucose decrease (40%, severe 1%)
	glucose increase (54%, severe 7%)
	sodium decrease (30%, severe 4%)
	weight loss (10%, severe 1%)
metabolism and nutrition	***appetite decrease*** (24%, severe 2%)
	tumour lysis syndrome (<1%)
musculoskeletal and connective tissue	***arthralgia*** (40%, severe 3%)
	myalgia (42%, severe 3%)
nervous system	***dizziness*** (33%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	headache (30%)
	neuropathy (13%)
psychiatric	insomnia (12%, severe <1%)
renal and urinary	renal impairment (18%)
respiratory, thoracic and mediastinal	cough (28%)
	differentiation syndrome
	dyspnea (38%, severe 6%)
	interstitial lung disease
skin and subcutaneous tissue	acute febrile neutrophilic dermatosis (Sweet's syndrome) (1%)
	rash (33%, severe <1%)
vascular	***hemorrhage*** (43%, severe 3%); including gastrointestinal hemorrhage (7%, severe 2%) and intracranial hemorrhage (2%, severe 1%)
	hypotension (11%, severe 2%)

Adapted from standard reference[2,3] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
gastric pH modifying drugs[2]	bioavailability of cedazuridine may be altered by changes in gastric pH	gastric pH may affect the conversion of cedazuridine to its epimer prior to absorption	avoid administration of gastric pH modifying drugs, particularly within 4 hours of taking decitabine-cedazuridine

Cedazuridine is an inhibitor of cytidine deaminase (CDA). Concurrent administration of ***drugs metabolized by CDA*** with cedazuridine may result in increased exposure and toxicity of these drugs; avoid concurrent use.[2]

Decitabine is a weak inhibitor of P-glycoprotein; clinical significance is not expected.[2]

SUPPLY AND STORAGE:

Oral: Taiho Pharma Canada Inc. supplies decitabine-cedazuridine as a film-coated tablet containing 35 mg decitabine and 100 mg cedazuridine per tablet. Tablets contain lactose. Store at room temperature in original packaging.[2]

Additional information: Decitabine-cedazuridine is supplied in cartons containing one blister card of five tablets.[8] Dispense in original packaging. When dispensing for dose modifications, blister cards may be cut to separate individual blisters from the card, as long as the blisters themselves are not compromised.[9]

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:[2,3,8-11]

Cycle Length:

4 weeks: ***decitabine 35 mg and cedazuridine 100 mg*** (1 tablet) ***PO once daily for five consecutive days from days 1 to 5****
(total dose per cycle decitabine 105-175 mg and cedazuridine 300-500 mg)

*number of days per cycle is adjusted downward for dose reductions (e.g., days 1 to 4, days 1 to 3, or days 1, 3, 5)

Administer on an empty stomach, 2 hours before or 2 hours after a meal.

Swallow whole to ensure proper distribution of the drugs within the dosage form. Do not chew, crush or cut the tablet.[2]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure:

Creatinine clearance (mL/min)	Dose[2,3]
≥ 60	100%
30-59	100%; monitor for toxicity
< 30	no information found

calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: mild impairment (total bilirubin 1 to 1.5 x ULN): no adjustment required[2]
moderate/severe impairment (total bilirubin >1.5 x ULN): no information found

Dosage in dialysis: no information found

Children: safety and efficacy has not been established[2]

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