Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

decitabine / cedazuridine

COMMON TRADE NAME(S): Inqovi®

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B - Mechanism of Action and Pharmacokinetics

Decitabine / cedazuridine is a combination of a nucleoside metabolic inhibitor and a cytidine deaminase inhibitor. Decitabine exerts its effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Hypomethylation in cancer cells may restore normal function to genes that are necessary for control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity 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 catalyzes the degradation of cytidine, including the cytidine analog decitabine. Cedazuridine increases the systemic exposure of decitabine by inhibiting CDA in the gastrointestinal tract and liver that degrade decitabine and limit its oral bioavailability.

Absorption	Bioavailability	Decitabine: Increased with cedazuridine Cedazuridine: 21% (range: 13% - 26%)
	Effects with food	Decitabine: Administration with a high-fat, high calorie meal reduced the overall decitabine exposure (AUC_{0-8hr}) and C_{max} significantly.

		Cedazuridine: Administration with a high-fat, high calorie meal slightly delayed T_{max} but systemic exposure was not affected.
	Peak plasma levels	Decitabine: 1 hour (range: 0.3 to 3 hours) Cedazuridine: 3 hours (range: 1 to 8 hours)
	Time to reach steady state	Steady state is achieved in 2 days. Decitabine AUC (from decitabine-cedazuridine) at steady state is equivalent to levels achieved with decitabine 20 mg/m^2 IV infusion.
Distribution	PPB	Decitabine: 5% Cedazuridine: 35%
Metabolism	Main enzymes involved	Decitabine: Primarily via cytidine deaminase (CDA) and by physiochemical degradation Cedazuridine: Conversion to epimer by physiochemical degradation
Elimination	Feces	Cedazuridine: 51% (27% unchanged)
	Urine	Cedazuridine: 46% (17% unchanged)
	Half-life	Decitabine: 1.2 hours Cedazuridine: 6.3 hours

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C - Indications and Status

Health Canada Approvals:

- Myelodysplastic syndromes (MDS)
- Chronic myelomonocytic leukemia (CMML)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in > 10% of patients in all cycles in the pooled safety population. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (11%)	E
	Hypotension (11%)	E
Dermatological	Other - acute febrile neutrophilic dermatosis (1%)	E
	Rash (33%)	E
Gastrointestinal	Abdominal pain (19%)	E
	Anorexia, weight loss (24%)	E
	Constipation (44%)	E
	Diarrhea (37%)	E
	Enterocolitis (may be severe)	E
	Mucositis (41%)	E
	Nausea, vomiting (40%)	E
General	Edema (30%) (<1% severe)	E
	Fall (12%)	E
	Fatigue (55%) (5% severe)	E

Hematological	Myelosuppression ± infection, bleeding (62%) (54% severe; including CNS, GI bleeding up to 7%)	E
	Other - Differentiation syndrome (rare)	E
Hepatobiliary	Other - ↑ serum transaminase (21%)	E
Hypersensitivity	Anaphylaxis (rare)	E
Metabolic / Endocrine	Tumor lysis syndrome (<1%)	E
Musculoskeletal	Musculoskeletal pain (42%)	E
Nervous System	Dizziness (33%)	E
	Headache (30%)	E
	Insomnia (12%)	E
	Neuropathy (13%)	E
Renal	Creatinine increased (18%)	E
Respiratory	Cough, dyspnea (38%)	E
	Interstitial lung disease (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for decitabine / cedazuridine include myelosuppression ± infection, bleeding, fatigue, constipation, musculoskeletal pain, mucositis, nausea, vomiting, cough, dyspnea, diarrhea, dizziness and rash.

Fatal and serious **myelosuppression** can occur with decitabine / cedazuridine. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients.

Fatal and serious **infectious** complications can occur with decitabine / cedazuridine. Fungal infections, severe **pneumonia** and **sepsis** have been observed. Rare fatalities due to pneumonia, sepsis, and septic shock were also reported.

Serious **anaphylactic reactions** have been reported with decitabine. **Hypersensitivity reactions** have been reported with intravenous decitabine and decitabine / cedazuridine. Rash is reported in early cycles of decitabine / cedazuridine and diminishes with later cycles.

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E - Dosing

Refer to protocol by which patient is being treated.

Do not substitute decitabine / cedazuridine for an IV decitabine product within a cycle.

Adults:

Oral: 35/100* mg Daily on days 1 to 5 of each 28-day treatment cycle

*1 tablet contains 35 mg of decitabine and 100 mg of cedazuridine

Dosage with Toxicity:

Do not modify the recommended dose for the first 2 cycles.

Hematologic Toxicity

Dosage Reduction for Myelosuppression:

Dose Level	Decitabine / Cedazuridine Dose
0	1 tablet once daily on days 1 through 5
-1	1 tablet once daily on days 1 through 4
-2	1 tablet once daily on days 1 through 3
-3	1 tablet once daily on days 1, 3, and 5

Dose modifications in the absence of active disease:

Toxicity	Decitabine / Cedazuridine Dose
ANC < 1 x 10^9/L and/or Platelets < 50 x 10^9/L	Hold, and: • If hematologic recovery* occurs within 2 weeks of the last treatment cycle, resume at same dose. • If hematological recovery* does not occur within 2 weeks of the last treatment cycle: ◦ Delay treatment for up to 2 additional weeks. Resume at 1 dose level ↓. ◦ Consider further dose level ↓ if myelosuppression persists after a dose reduction. ◦ Maintain or ↑ dose in subsequent cycles as clinically indicated.

*ANC ≥ 1 x 10^9/L and Platelets ≥ 50 x 10^9/L

Non-hematologic Toxicity

Toxicity	Decitabine / Cedazuridine Dose
Serum creatinine ≥ 176.8 µmol /L	Delay treatment until resolved; manage patient appropriately. Resume at same dose level or at 1 dose level ↓ (e.g., administer fewer days per cycle).
Bilirubin ≥ 2 x ULN	
ALT or AST ≥ 2 x ULN	
Active or uncontrolled infection	
Severe hypersensitivity	Discontinue; manage patient appropriately.

Dosage with Hepatic Impairment:

Hepatic Impairment	Decitabine / Cedazuridine Starting Dose
Mild (bilirubin > 1 to ≤ 1.5 × ULN)	No dosage adjustment necessary.
Moderate (bilirubin > 1.5 to 3 x ULN)	No data available.
Severe (bilirubin > 3 × ULN)	

Dosage with Renal Impairment:

Creatinine Clearance (mL / min)	Decitabine / Cedazuridine Starting Dose
≥ 60	No dosage adjustment necessary.
≥ 30 to 59	No dosage adjustment necessary; monitor for increased incidence of adverse reactions.
15 to 29	Use with caution; No data available.
< 15 (ESRD)	

Dosage in the elderly:

No adjustment required. Overall, no differences in efficacy and safety were observed between patients ≥ 65 years and younger patients.

Children:

Safety and efficacy in children have not been established.

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F - Administration Guidelines

- Administer at approximately the same time each day for 5 days in each cycle.
- Tablets should be swallowed whole with water; do not cut, crush, or chew.
- Decitabine / cedazuridine should be taken on an empty stomach; do not consume food 2 hours before and 2 hours after each dose.
- Missed dose:
  - If the missed dose is within 12 hours of the time it is usually taken, administer the missed dose as soon as possible and then resume the normal daily dosing schedule.
  - If dose is missed by more than 12 hours of the time it is usually taken, the patient should wait and take the missed dose the following day at the usual time and extend the dosing period by 1 day for every missed dose to complete 5 daily doses for each cycle.

- If a dose is vomited, do not administer an additional dose, continue with the next scheduled dose.
- Store tablets in original packaging at room temperature (15 to 30°C).

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Caution with driving or using machinery as fatigue or dizziness may occur with treatment due to anemia.
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Other Drug Properties:

- Carcinogenicity: No information available

Pregnancy and Lactation:

- Mutagenicity: Yes
- Genotoxicity: Yes
- Fetotoxicity: Yes
  Decitabine / cedazuridine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment and for at least **6 months** following the last dose in women and at least **3 months** following the last dose in men.
- Excretion into breast milk: Likely
  Breastfeeding is not recommended during decitabine / cedazuridine treatment and for at least **2 weeks** after the last dose.
- Fertility effects: Yes
  Prior to treatment, male patients should seek advice on conservation of sperm and female patients of childbearing potential should seek consultation regarding oocyte cryopreservation.

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H - Interactions

Drug-drug interaction studies were not conducted with decitabine or cedazuridine.

Decitabine is not a substrate for P450 and did not inhibit or induce cytochrome P450 enzymes in vitro. Cedazuridine is not a substrate or modulators of CYP enzymes or major transporters, therefore, CYP450-mediated drug-drug interactions are unlikely.

Decitabine / cedazuridine is not expected to affect P-glycoprotein (P-gp) mediated transport of co-administered medicinal products as decitabine is a weak inhibitor of P-gp, and cedazuridine is neither a substrate nor an inhibitor of transporters including P-gp, MDR1, BCRP, MATE and OAT.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CDA substrates (i.e. cytarabine, gemcitabine, azacitadine, zidovudine, lamivudine, abacavir, emtricitabine, tenofovir, adefovir, entecavir, trifluridine)	↑ substrates concentration and/or toxicity	Cedazuridine is an inhibitor of the CDA enzyme.	Avoid co-administration with drugs metabolized by CDA
Gastric pH Modifying Agents (i.e. proton pump inhibitors, H2 antagonists)	↑ decitabine / cedazuridine concentration and/or toxicity	↑ dissolution with increased pH	Avoid gastric acid reducing agents within 4 hours of decitabine / cedazuridine administration

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, prior to each cycle, and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated

Clinical toxicity assessment for infection, bleeding, fatigue, rash, hypersensitivity, tumour lysis syndrome, differentiation syndrome, GI and respiratory effects.	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- decitabine / cedazuridine - For the treatment of adult patients with myelodysplastic syndromes (MDS), according to clinical criteria

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K - References

Inqovi (decitabine/cedazuridine). Prescribing Information. Princeton, NJ: Taiho Oncology, Inc., July 2020.

Inqovi (decitabine/cedazuridine) Product Monograph. Oakville, Ontario: Taiho Pharma Canada Inc., July 2020.

January 2023 Added EAP funding info

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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