Decitabine and cedazuridine (INQOVI)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Inqovi is an oral tablet that contains two different molecular entities, decitabine and cedazuridine. Decitabine is a nucleoside metabolic inhibitor and cedazuridine is cytidine deaminase inhibitor. Decitabine is therapeutic and cedazuridine blocks first pass metabolism of decitabine.

Indication(s) Under Review in This Document

- Treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtype (refractory anemia (RA), RA with ringed sideroblasts, RA with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2 and high-risk International Prognostic Scoring System Groups.

Dosage Form(s) Under Review

- Tablet: 35mg decitabine and 100mg cedazuridine. Package insert dosing is one tablet taken orally once daily on Day 1 through 5 of each 28-day cycle.

Clinical Evidence Summary

Efficacy Considerations

- The clinical trial that established the utility of oral cedazuridine/decitabine (C-DEC) was a phase II trial with pharmacokinetic, pharmacodynamic, and safety endpoints that were meant to establish to a degree of equivalence between C-DEC 100mg/35mg for 5 days and IV decitabine 20mg/m2/day for 5 days (each repeated every 28 days).
- Patients enrolled in this clinical trial received either C-DEC or IV decitabine (IV-D) for cycle 1 then received the other route of administration for cycle 2. From cycle 3 on all patients received C-DEC.
- There was no head-to-head comparison of clinical outcomes comparing C-DEC and IV-D for the entirety of treatment in this trial.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Study Design	ECOG PS	Treatment	Results
Garcia-Manero et al[1]	• Phase 2 • Intermediate and high risk MDS & CMML • Open-label • Multicenter • Randomized • Crossover • N=80 • 1:1 randomization • Compare systemic exposure, demethylation activity and safety in the first 2 cycles	0-2	1 cycle of C-DEC or IV-D with crossover to other treatment for cycle 2 then oral therapy from cycle 3 onwards until disease progression, unacceptable toxicity, or patient withdrawal	Primary end points: mean decitabine systemic exposure of oral/IV 5-day AUC, percent long interspersed nuclear element 1 (LINE-1) DNA methylation for oral vs IV-D, and safety Secondary end points: efficacy Median number of cycles: 7 Results: PK – AUC assessments deemed bioequivalent (see citation for specifics) PD – LINE-1 demethylation assessment showed no clinically or statistically significant difference between oral and IV after cycle 2 Efficacy – ORR (CR+PR+mCR+HI) 60% [CR 21%,PR 0%, mCR 22%, HI 16% (HI-E 10%, HI-N 2%, HI-P 14)]; no response 40%

PK, pharmacokinetic; PD, pharmacodynamic; ORR, overall response rate; CR, complete response; mCR, marrow complete response; HI, hematologic improvement; HI-E, erythroid response; HI-N, neutrophil response; HI-P, platelet response

Safety Considerations

Safety Results from Clinical Trials:

Table 2: Safety results from clinical trials

Study	Results
Garcia-Manero et al[1]	**Any AE:** 92% **Grade 3-4:** 59 to 83% (primarily hematologic toxicities) **Serious adverse events:** 12 to 29% febrile neutropenia; pneumonia/sepsis 8% to 23% **AEs leading to discontinuation:** 5 patients (total n = 80) **AEs leading to dose interruption/modification:** not reported **Deaths due to AE:** 11 patients (total n = 80)

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings / precautions**: Fatal and serious myelosuppression and embryo-fetal toxicity

- **Adverse reactions**
    - **Common (>20%):** neutropenia, thrombocytopenia, fatigue, febrile neutropenia, nausea, diarrhea, leukopenia, dizziness, anemia, constipation, dyspnea
    - **Serious Adverse events / Deaths / Discontinuation:** neutropenia, thrombocytopenia, febrile neutropenia, anemia, pneumonia and sepsis
    - **No difference in GI side effects were noted between PO or IV during cycles 1 and 2**

Other Considerations

Pregnancy: can cause fetal harm when administered to a pregnant woman (see PI for further details)
Lactation: advise to not breastfeed (see PI for further details)
Infertility: can impair fertility (see PI for further details)
Geriatrics: median age of patients enrolled in Garcia-Manero et al was 70 years old

- C-DEC 100/35mg tablets once daily for 5 days was deemed to be equivalent to IV-D 20mg/m2/day x 5 days. C-DEC at currently recommended dosing is not equivalent with other dosing schedules of IV-D.

- Hematologic adverse reactions may be more common in the first cycle of C-DEC compared to IV-D. It is important for clinicians to closely monitor patients on therapy for infections, bleeding and transfusion needs.

- Recommended minimum of 4 cycles of C-DEC prior to determining disease response

- Decitabine is metabolized by cytidine deaminase (CDA) enzyme with a $t_{1/2}$ of 0.5 hours and the cytochrome P450 system does not appear to be involved in drug metabolism. Decitabine and cedazuridine are not P-glycoprotein substrates. Avoid coadministration of C-DEC with other drugs that are metabolized by CDA. Coadministration of proton pump inhibitors had no clinically meaningful effect on exposure to decitabine or cedazuridine.

- Renal adjustment/hepatic adjustment – no current dose recommendations; clinical trial inclusion criteria – Scr < 1.5 or Crcl> 50ml/min/1.73m^2 and AST/ALT $\leq$ 2.5 x ULN, Bilirubin $\leq$ 2 x ULN. Consider risks versus benefits of initiating therapy in cases of renal or hepatic insufficiency.

- Dose reductions are accomplished by reducing number of days of treatment cycle rather than alternative tablet size.

Risk-Benefit Assessment (for Oncology NMEs only) – Cedazuridine is a NME

- **Outcome in clinically significant area:** ORR 60%
- **Effect Size:** ORR 60%
- **Potential Harms:** high risk (grade III-IV toxicities 59-83%)
- **Net Clinical Benefit:** can not be determined

Other Therapeutic Options

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
C-DEC	TBD	CMML/MDS	Equivalent to IV-D 20mg/m2/day x 5 days. Recommended dosing for C-DEC is not equivalent with other dosing schedules of IV-D. Phase 3 conducted with similar design as study referenced above.[3] Only available as supplement – unpublished as full text.
Erythropoietin	F	MDS	Superior transfusion independence vs. placebo (low risk MDS)
Azacitidine (SQ or IV)	PA-F	CMML/MDS	Superior transfusion independence vs. placebo (low risk MDS)
Decitabine (IV)	NF	CMML/MDS	32% ORR (CR + mCR), overall improvement rate 51%; primarily hematologic toxicities (> grade 75%), febrile neutropenia 14%, 65% of patients were hospitalized at some point during therapy.[2] Variety of dosing schemes have been evaluated
Lenalidomide	PA-F	MDS	Superior transfusion independence vs. placebo (low risk MDS); most effective in chromosome 5q deletion
Luspatercept	NF	MDS	Primary endpoint of transfusion independence for 8 weeks or longer vs. placebo (38% vs 13%) (low risk MDS)
Erythropoietin + lenalidomide	F/PA-F	MDS	Superior major erythroid response vs. lenalidomide monotherapy
Azacitidine + vorinostat	PA-F/NF	CMML/MDS	Not superior to azacitidine
Azacitidine + lenalidomide	PA-F	CMML/MDS	Not superior to azacitidine

Other treatments that may be considered and not routine clinical practice are: low dose ARA-C , clofarabine, temozolomide, ATG +/- cyclosporine, midostaurin and alemtuzumab.

Projected Place in Therapy

- MDS is a heterogeneous group of diseases characterized by ineffective, dysplastic hematopoiesis leading to cytopenias. Clinical presentation of MDS is a manifestation of cytopenias including fatigue, infections, and bleeding and risk of transformation to acute myeloid leukemia (AML). Current prognostic classification is the International Prognostic Scoring System-Revised (IPSS-R). Higher-risk MDS can be treated in the frontline setting with hypomethylating agents (HMAs), azacitidine or decitabine. CMML was previously classified as MDS and is currently classified as myelodysplastic/myeloproliferative neoplasm, and the treatment approach is similar to that for MDS. MDS and CMML are serious diseases with a substantial risk of mortality.
- The incidence and prevalence of MDS and CMML within VA health care system are likely established at this time and major shifts in the patients carrying these diagnoses should not be expected to change significantly year to year. Thus the utilization of therapies to manage these diseases should be rather consistent and predictable year to year.
- NCCN guidelines for the treatment of myelodysplastic syndromes (version 2.2022) acknowledge the potential substitution of C-DEC for IV-D in patients with low risk and high risk disease (as assessed by IPSS-R scoring).
- The current utilization of IV-D and azacitidine within VA would be reflective of the potential utilization of C-DEC. C-DEC is not adding additional indications for use of hypomethylating agents. Any patient diagnosed with MDS or CMML that would be appropriate for azacitidine or IV-D could potentially have C-DEC utilized as a more convenient alternative to IV administration.
- C-DEC offers the advantage of oral home administration and potentially reduces a patient's contact with a healthcare system. This needs to be a consideration during the COVID pandemic and the time period following the pandemic. This is especially important given the fact the typical patient on HMAs is elderly with medical comorbidities, which are associated with poor outcomes from COVID. Patients that are likely to receive C-DEC are potentially transfusion dependent and may already have frequent contact with healthcare systems. In these cases the administration benefits of C-DEC would not be fully realized.
- There will likely be an influx of patients to VA for VA's provision of C-DEC due to it being an oral agent that is dispensed as an outpatient prescription for home administration. Previously those patients likely would have received IV-D in a clinic setting and may have been shielded from high out of pocket expenses that are potentially associated with outpatient prescriptions.
- Use of C-DEC preferentially over IV-D or azacitidine may potentially avoid CITC consults and allow VA to continue to provide care to these patients. Patient specific factors to consider are travel time, reliability, degree of social support, access to emergency services and local VA CBOCs.
- Azacitidine and IV-D have been unavailable for purchase by VA due to supply shortages. Supply issues of these products may increase utilization of C-DEC.

- IV-D and azacitidine are treatment options for AML with elderly or medically unfit patients. IV-D or azacitidine in addition to venetoclax is standard of care for elderly or medically unfit and thus not candidates for more intensive AML therapy. An all oral option of C-DEC and venetoclax is going to be potentially viewed as a viable treatment option. Current NCCN guidelines for treatment of AML (version 1.2022) do not make any reference to use of C-DEC for the treatment of AML. Ongoing clinicals are investigating the follow combinations: C-DEC and venetoclax for higher-risk AML, C-DEC plus venetoclax for relapsed/refractory AML, C-DEC maintenance for AML, C-DEC plus venetoclax for treatment-naïve high-risk MDS or CMML.
- There are ongoing clinical trials utilizing C-DEC plus venetoclax with IDH inhibitors and FLT3 inhibitors in treatment AML. Depending upon the results of these clinical trials there is the potential for C-DEC to be used in combination with other AML active agents.
- There may be interest in C-DEC maintenance after 1st line therapy for AML in patients that are not candidates for allogeneic HSCT, similar to the indication for Onureg (oral azacitidine). The most likely current scenario for maintenance C-DEC is for patients that may have had tolerability issues to Onureg. There is an ongoing clinical trial evaluating the role of C-DEC maintenance therapy for myeloid neoplasms.
- Equivalence of C-DEC has not been established with azacitidine IV, SQ, or PO
- The therapies for MDS and CMML discussed in this document are palliative in intent.
- The only treatment option for MDS and CMML with the possibility of curative intent is allogeneic hematopoietic stem cell transplant (alloHSCT). Currently available therapies discussed in this document may serve as valuable bridge therapies to patients that are deemed candidates for alloHSCT.

References

1. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood. 2020;136(6):674-83.
2. Steensma DP, Baer MR, Slack JL, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol. 2009 Aug 10;27(23):3842-8.
3. Savona MR, McCloskey JK, Griffiths EA, et al. Clinical efficacy and safety of oral decitabine/cedazuridine in 133 patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). Blood. 2020;136(Supplement 1):37-38.
4. Patel AA, Cahill K, Saygin C, et al. Cedazuridine/decitabine: from preclinical to clinical development in myeloid malignancies. Blood. 2021;5(8):2264-71.
5. Inqovi (decitabine and cedazuridine) tablets Product Package Insert. Otsuka Pharmaceutical Co., Ltd. Japan; July 202.

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Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing sources for updated information