PDL DRUG REVIEW

Proprietary Name: Inqovi®
Common Name: cedazuridine and decitabine
PDL Category: Antineoplastics Combinations

Comparable Products	Preferred Drug List Status
Decitabine Inj	Medical Coverage

Summary

Pharmacology/Usage: Inqovi® is a combination tablet containing both decitabine (a nucleoside metabolic inhibitor) and cedazuridine (a cytidine deaminase inhibitor). It is believed that 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. Decitabine inhibits DNA methylation in vitro, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in cancer cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation.

Cytidine deaminase (CDA) is an enzyme that catalyzes the degradation of cytidine, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver degrade decitabine and limit its oral bioavailability. Cedazuridine is a CDA inhibitor. Administration of cedazuridine with decitabine increases systemic exposure of decitabine.

Indication: For the treatment of adults with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from human data, animal studies, and its mechanism of action, Inqovi® can cause fetal harm when given to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Verify the pregnancy status in females of reproductive potential prior to starting Inqovi®. Advise females of reproductive potential to use effective contraception during treatment with Inqovi® and for 6 months after the last dose. In addition, advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 35mg decitabine/100mg cedazuridine. Swallow tablets whole; do not cut, crush, or chew tablets.

Inqovi® is a hazardous drug. Follow applicable special handling and disposal procedures.

Recommended Dosage: Do not substitute Inqovi® for an IV decitabine product within a cycle.

Consider administering antiemetics prior to each dose to minimize nausea and vomiting.

Take 1 tablet PO QD on days 1 through 5 of each 28-day cycle for a minimum of 4 cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than 4 cycles. Do not consume food 2 hours

before and 2 hours after each dose. If a dose is missed within 12 hours of the time it is usually taken, take the missed dose as soon as possible and then resume the normal daily dosing schedule. Extend the dosing period by one day for every missed dose to complete 5 daily doses for each cycle. Do not take an additional dose if vomiting occurs after Inqovi® administration but continue with the next schedule dose.

Obtain complete blood cell counts prior to starting treatment and before each cycle. Delay the next cycle if the 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 of achieving remission, continue Inqovi® at the same dose.
- If hematologic recovery (ANC at least 1,000/µL and platelets at least 50,000/µL) does not occur within 2 weeks of achieving remission,
    - 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 (see table below, adapted from the prescribing information) if myelosuppression persists after a dose reduction. Maintain or increase dose in subsequent cycles as clinically indicated.

Dose Reduction	Dosage
First	1 tab PO QD on days 1 through 4
Second	1 tab PO QD on days 1 through 3
Third	1 tab PO QD on days 1, 3, and 5

Manage persistent severe neutropenia and febrile neutropenia with supportive treatment.

For non-hematologic adverse reactions, delay the next cycle for the following non-hematologic adverse reactions and resume at the same or reduced dose upon resolution:

- Serum creatinine 2mg/dl or greater
- Serum bilirubin 2 times upper limit of normal (ULN) or greater
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 2 times ULN or greater
- Active or uncontrolled infection

Dose modifications are not required with mild or moderate renal impairment. However, due to the potential for increased adverse reactions, monitor patients with moderate renal impairment frequently for adverse reactions. Inqovi® has not been studied in patients with severe renal impairment or end-stage renal disease. Dose adjustments are not required with mild hepatic impairment; however, the effects of moderate and severe hepatic impairment on the pharmacokinetics of decitabine and cedazuridine are not known.

Drug Interactions: Cedazuridine is an inhibitor of the cytidine deaminase (CDA) enzyme. Coadministration of Inqovi® with drugs that are metabolized by CDA may result in increased systemic exposure with potential for increased toxicity of these drugs. Avoid coadministration of Inqovi® with drugs that are metabolized by CDA.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Inqovi®) for cycle 1/all cycles for all grades. Please note that there was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included fatigue (29%/55%), hemorrhage (24%/43%), edema (10%/30%), pyrexia (7%/19%), constipation (20%/44%), mucositis (18%/41%), nausea (25%/40%), diarrhea (16%/37%), transaminase increased (12%/21%), abdominal pain (9%/19%), vomiting (5%/15%), myalgia (9%/42%), arthralgia (9%/40%), dyspnea (17%/38%), cough (7%/28%), febrile neutropenia

(10%/33%), rash (12%/33%), dizziness (16%/33%), headache (22%/30%), neuropathy (4%/13%), decreased appetite (10%/24%), upper respiratory tract infection (6%/23%), pneumonia (7%/21%), sepsis (6%/14%), cellulitis (4%/12%), renal impairment (9%/18%), weight decreased (5%/10%), fall (4%/12%), insomnia (6%/12%), hypotension (4%/11%), and arrhythmia (3%/11%).

Laboratory abnormalities included leukocytes decreased (79%/87%), platelet count decreased (79%/82%), neutrophil count decreased (70%/73%), hemoglobin decreased (58%/71%), glucose increased (19%/54%), albumin decreased (22%/45%), alkaline phosphatase increased (22%/42%), glucose decreased (14%/40%), alanine aminotransferase increased (13%/37%), sodium decreased (9%/30%), calcium decreased (16%/30%), aspartate aminotransferase increased (6%/30%), and creatinine increased (7%/29%).

Fatal and serious myelosuppression can occur with Inqovi®. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of Inqovi® dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. In addition, fatal and serious infectious complications can occur with Inqovi®. Obtain complete blood cell counts prior to the start of treatment, 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.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Taiho Pharmaceutical Co.

Analysis: Inqovi® was assessed in an open-label, randomized, 2-cycle, 2-sequence crossover study that included adults with MDS (International Prognostic Scoring System [IPSS] Intermediate-1, Intermediate-2, or high-risk) or chronic myelomonocytic leukemia (CMML). Patients were randomized to receive Inqovi® PO in cycle 1 and decitabine 20mg/m^2 IV in cycle 2 or the reverse sequence. Both Inqovi® and IV decitabine were administered once daily on days 1 through 5 of the 28-day cycle. Starting with cycle 3, all patients received Inqovi® PO QD on days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity. Twelve (15%) of the 80 patients went on to stem cell transplantation after Inqovi® treatment.

The median age of included adults was 71 years, while 76% were male, 93% were white, 44% had an ECOG performance score of 0, 48% had an ECOG performance score of 1, 48% had RBC transfusion dependence, and 15% had platelet transfusion dependence. For the disease category, 44% had MDS INT-1, 24% had MDS INT-2, 11% had MDS high-risk, and 21% had CMML.

Efficacy was established on the basis of complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up time was 24 months (range 12 to 28.8 months) and the median treatment duration was 6.6 months. Results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Endpoint	Inqovi®
Complete Response (CR)	18%
Median Duration of CR, months (range)	8.7 (1.1, 18.2)
Median time to CR, months (range)	4.8 (1.7, 10.0)

Among the 41 patients who were dependent on RBC and/or platelet transfusions at baseline, 20 (49%) became independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period. Of the 39 patients who were independent of both RBC and platelet transfusions at baseline, 25 (64%) remained transfusion-independent during any consecutive 56-day post-baseline period.

Study 2 was an open-label, randomized, 2-cycle, 2-sequence crossover study that included adult patients with MDS or CMML, including all French-American-British (FAB) classification criteria and IPSS Intermediate-1, Intermediate-

2, or high-risk prognostic scores (N=133). Patients were randomized to receive Inqovi® PO in cycle 1 and decitabine 20mg/m^2 IV in cycle 2 or the reverse sequence. Starting with cycle 3, all patients received Inqovi® QD on days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity. Twenty-seven (20%) of the 133 patients went on to stem cell transplantation following Inqovi® treatment.

The median age of included adults was 71 years, while 65% were male, 91% were white, 41% had an ECOG performance status of 0, 59% had an ECOG performance status of 1, 39% had RBC transfusion dependence and 8% had platelet transfusion dependence. For the disease category, 44% had MDS INT-1, 20% had MDS INT-2, 16% had MDS high-risk, 8% had MDS low-risk, and 12% had CMML.

The primary outcome measure was comparison of the 5-day cumulative decitabine AUC between Inqovi® and IV decitabine. Efficacy was established on the basis of complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up time was 12.6 months (range 9.3 to 20.5) and the median treatment duration was 8.2 months (range 0.2 to 19.7). Efficacy can be seen in the table below, which was adapted from the prescribing information.

Efficacy Endpoint	Inqovi®
Complete Response (CR)	21%
Median Duration of CR, months (range)	7.5 (1.6, 17.5)
Median time to CR, months (range)	4.3 (2.1, 15.2)

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 RBC and platelet transfusions at baseline, 48 (63%) remained transfusion-independent during any 56-day post-baseline period.

Place in Therapy: Inqovi®, an oral combination of decitabine and cedazuridine, is indicated for the treatment of adults with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. Treatment with Inqovi® resulted in an 18% complete response in one study and 21% complete response in a second study of patients with myelodysplastic syndromes. In addition, some patients achieved transfusion independence.

It is recommended that Inqovi® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Inqovi [package insert]. Princeton, NJ: Taiho Oncology, Inc; 2020.