Iowa PDL New Drug Review

Proprietary Name: Revuforj®
Common Name: revumenib
PDL Category: Antineoplastic Agents

Pharmacology/Usage: Revumenib, the active ingredient of Revuforj®, is a menin inhibitor and blocks the interaction of both wild-type lysine methyltransferase 2A (KMT2A) and KMT2A fusion proteins with menin. The binding of KMT2A fusion proteins with menin is involved in KMT2A-rearranged (KMT2Ar) acute leukemias through activation of a leukemogenic transcriptional pathway. In nonclinical studies using cells that express KMT2A fusions, inhibition of the menin-KMT2A interaction with revumenib altered the transcription of multiple genes including differentiation markers. In nonclinical in vitro and in vivo studies, revumenib demonstrated antiproliferative and antitumor activity in leukemia cells harboring KMT2A fusion proteins.

Indication: For the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animals and its mechanism of action, Revuforj® can cause fetal harm when administered to a pregnant women. There are no available data on use in pregnant women to assess for a drug-associated risk. Advise pregnant women of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential within 7 days prior to starting treatment. Advise females of reproductive potential and males of reproductive potential to use effective contraception during treatment with Revuforj® and for 4 months after the last dose. The safety and efficacy of use in the pediatric population less than 1 year old have not been established. Based on the findings in animals, monitor bone growth and development in pediatric patients.

Dosage Form: Film-Coated Tablets: 25mg, 110mg, 160mg.

Recommended Dosage: Select patients for the treatment of acute leukemia with Revuforj® based on the presence of a KMT2A translocation in bone marrow cells. An FDA-approved companion diagnostic for the detection of a KMT2A translocation is not currently available.

The recommended dosage varies by patient weight and concomitant use of strong CYP3A4 inhibitors. Refer to the table below, which was adapted from the prescribing information, for the recommended dosage for patients 1 year and older. Do not start Revuforj® until the white blood cell (WBC) is reduced to less than 25Gi/L. Continue Revuforj® until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

Patient weight	Without Strong CYP3A4 Inhibitors	With Strong CYP3A4 inhibitors
40kg or more	270mg PO BID	160mg PO BID
Less than 40mg	160mg/m^2 PO BID *	95mg/m^2 PO BID *

* See Table 2 in the prescribing information for the total tablet dosage by body surface area (BSA) if weigh less than 40kg.

If the strong CYP3A4 inhibitor is discontinued, increase the Revuforj® dose after at least 5 half-lives of the strong CYP3A4 inhibitor to the recommended dosage without strong CYP3A4 inhibitors (see table above).

Concurrent use of standard intrathecal chemotherapy prophylaxis is recommended for patients with risk of CNS relapse.

Advise patients to swallow tablets whole and to not cut or chew. If patients are not able to swallow tablets, they may be crushed and dispersed in water and taken within 2 hours of preparation. Administer about the same time each day and administer twice-daily fasted or with a low-fat meal (e.g., meals with about 400 calories, 25% or less fat).

If a dose is missed or not taken at the usual time, administer the dose as soon as possible on the same day and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

Regarding dosage modifications for adverse reactions, assess blood counts, electrolytes, and liver enzymes prior to the start of Revuforj® and monthly thereafter. Perform an electrocardiogram (ECG) prior to the start of Revuforj®, at least once a week for the first 4 weeks, and at least monthly thereafter. Monitor for QTc interval prolongation and manage any abnormalities immediately. Refer to the prescribing information for additional information on recommended management and dosage modifications for adverse reactions, including differentiation syndrome, non-infectious leukocytosis, QTc interval prolongation, potassium abnormalities, other nonhematological adverse reactions, neutropenia/thrombocytopenia, or allergic reactions.

Drug Interactions: Revumenib is primarily metabolized by CYP3A4. If concomitant use of strong CYP3A4 inhibitors is required, reduce the Revuforj® dosage.

Avoid concomitant use with strong or moderate CYP3A4 inducers.

Revuforj® causes QTc interval prolongation. Concomitant use of Revuforj® with other drugs that prolong QTc interval may result in an increase in the QTc interval and adverse reactions associated with QTc interval prolongation. Avoid concomitant use of Revuforj® with other drugs with a known potential to prolong QTc interval. If concomitant use cannot be avoided, obtain ECGs when starting, during concomitant use, and as clinically indicated. Withold Revuforj® if the QTc interval is greater than 480msec. Restart Revuforj® after the QTc interval returns to less than or equal to 480msec.

Box Warning: Revuforj® has a box warning regarding differentiation syndrome. Differentiation syndrome, which can be fatal, has occurred with Revuforj®. Signs and symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and renal dysfunction. If differentiation syndrome is suspected, immediately start corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Revuforj®) with adverse reactions reported in ≥20% for all grades. There was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included hemorrhage (53%), thrombosis (10%), nausea (51%), diarrhea (30%), constipation (23%), musculoskeletal pain (42%), infection (41%), bacterial infection (31%), viral infection (23%), febrile neutropenia (35%), leukocytosis (8%), differentiation syndrome (29%), electrocardiogram QT prolonged (29%), decreased appetite (24%), edema (23%), and fatigue (22%).

Laboratory abnormalities for grades 1-4 included phosphate increased (50%), aspartate aminotransferase increased (37%), alanine aminotransferase increased (33%), parathyroid hormone, intact increased (33%), phosphate decreased (25%), triglycerides increased (25%), potassium decreased (24%), alkaline phosphatase increased (21%), cholesterol increased (19%), creatinine increased (19%), and calcium corrected increased (15%).

Revuforj® can cause QT (QTc) interval prolongation. Correct electrolyte abnormalities, including hypokalemia and hypomagnesemia, prior to treatment with Revuforj®. Perform an ECG prior to initiation of treatment with Revuforj®,

and do not start Revuforj® in patients with QTcF >450msec. Perform an ECG at least once a week for the first 4 weeks on treatment, and at least monthly thereafter. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring may be necessary. Concomitant use of Revuforj® with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Interrupt Revuforj® if QTcF increases to greater than 480msec and less than 500msec, and restart Revuforj® at the same dose twice daily after the QTcF interval returns to less than or equal to 480msec. Interrupt Revuforj® if QTcF increases to greater than 500msec or by >60 msec from baseline, and restart Revuforj® twice daily at the lower dose level after the QTcF interval returns to less than or equal to 480msec. Permanently discontinue Revuforj® in patients with ventricular arrhythmias and in those who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmias.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Syndax Pharmaceuticals

Analysis: The efficacy of Revuforj® was assessed in a single-arm cohort of an open-label, multicenter trial (AUGMENT-101) that included adult and pediatric patients at least 30 days old with relapsed or refractory (R/R) acute leukemia with a KMT2A translocation. Eligibility required a QTcF <450msec at study baseline. Treatment included Revuforj® at a dose equivalent to 160mg in adults PO BID with a strong CYP3A4 inhibitor until disease progression, unacceptable toxicity, failure to achieve morphological leukemia-free state by 4 cycles of treatment, or hematopoietic stem cell transplantation (HSCT).

Baseline characteristics of the included patients (N=104) included a median age of 37 years, including 76% aged ≥17 years of age, as well as 64% who were female, 72% white, 83% with acute myeloid leukemia (AML), 15% with acute lymphoblastic leukemia (ALL), and 2% mixed phenotype acute leukemia (MPAL). In addition, the number of prior regimens was 2 (median).

Efficacy was established on the basis of the rate of complete remission (CR) plus CR with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up was 5.73 months. Efficacy results are presented in the table below, which was adapted from the prescribing information. In addition, on subgroup analysis, CR+CRh was achieved by 18/86 (21%) of patients with AML, 3/16 (19%) of patients with ALL, and 1 of 2 (50%) of patients with MPAL.

Endpoint	Revuforj® (N=104)
CR+CRh, n (%)	22 (21.2%)
Median duration of CR+CRh, months	6.4 months
CR, n (%)	13 (12.5%)
Median duration of CR, months	4.3 months
CRh, n (%)	9 (8.7%)
Median duration of CRh, months	6.4 months

Of the 22 patients who achieved a CR or CRh, the median time to CR or CRh was 1.9 months (range 0.9, 5.6 months).

Among the 83 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 12 (14%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 21

patients who were independent of both RBC and platelet transfusions at baseline, 10 (48%) remained transfusion independent during any 56-day post-baseline period.

Place in Therapy: Revuforj® is a menin inhibitor indicated for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older. Select patients for the treatment of acute leukemia with Revuforj® based on the presence of a KMT2A translocation in bone marrow cells. An FDA-approved companion diagnostic for the detection of a KMT2A translocation is not currently available. Revuforj® has a box warning regarding differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. The efficacy of Revuforj® was assessed in a single-arm cohort of an open-label, multicenter trial that included adult and pediatric patients at least 30 days old with relapsed or refractory acute leukemia with a KMT2A translocation. Efficacy was established on the basis of the rate of complete remission (CR) plus CR with partial hematologic recovery (CRh), which was achieved by 22 patients (21.2%) taking Revuforj®.

Summary

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

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

References

[1] Revuforj [package insert]. Waltham, MA: Syndax Pharmaceuticals Inc; 2025.