Revumenib (REVUFORJ) Tablets
National Drug Mini-Monograph
February 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CO, crossover; CR, complete remission; CRc, composite complete remission (defined as CR + CRh + CRi + CRp); CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HSCT, hematopoietic stem cell transplant; ICER, Institute for Clinical and Economic Review; *KMT2A*r, lysine methyltransferase 2A rearranged; MC, multicenter; MN, multinational; OL, open-label; MPAL, mixed phenotype acute leukemia; ORR, overall response rate; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial; R/R, relapsed or refractory

FDA APPROVAL INFORMATION	
Description|MOA	First-in-class, small molecule, menin inhibitor that blocks the interaction of menin with both wild-type lysine methyltransferase 2A (*KMT2A*) and *KMT2A* fusion proteins. *KMT2A* is also known as the mixed lineage leukemia [MLL] gene. Menin is a tumor promoter in *KMT2A* rearranged (*KMT2A*r) acute leukemia. Menin–*KMT2A* complexes prevent hematopoietic differentiation and upregulate homeobox (HOX)/myeloid ecotropic virus insertion site 1 (MEIS1) genes, leading to uncontrolled cell proliferation with expansion and persistence of leukemic blasts and development of leukemia. While needed for leukemogenesis, the menin-*KMT2A* interaction is not necessary for normal hematopoiesis.[1] By selectively inhibiting the binding of menin to *KMT2A*, revumenib inhibits leukemogenesis, allowing apoptosis and differentiation of immature leukemic cells. Revumenib is designated an orphan drug by the FDA.
Indication Under Review[2]	Treatment of adults with relapsed/refractory (R/R) acute leukemia with a *KMT2A* rearrangement. Treatment of relapsed or refractory acute myeloid leukemia (AML) with a susceptible nucleophosmin 1 (NPM1) mutation in patients who have no satisfactory alternative treatment options.
Dosage Regimen	Initial dosage depends on the patient's weight and CYP3A4 drug-interactions. The dosage shown below is for body weights ≥ 40 kg. See prescribing information for patients weighing < 40 kg. Revumenib may be given till disease progression or unacceptable toxicity. Administer doses in a fasted state or with a low-fat meal (e.g., meals with about 400 calories, ≤ 25% fat). <u>Weight ≥ 40 kg</u> • *Without Strong CYP3A4 Inhibitors*: 270 mg PO twice daily • *With Strong CYP3A4 Inhibitors*: 160 mg PO twice daily Tablets should be swallowed whole and not cut or chewed. If patients are unable to swallow tablets, they may be crushed and dispersed in water and taken within 2 hours of preparation.
Dosage Modifications for Adverse Reactions	Refer to prescribing information. Includes dosage modifications for differentiation syndrome and QTc interval prolongation.
Dosage Forms Under Review	110- and 160-mg tablets (For patients < 40 kg, 25-mg tablets are also available and an oral solution will be available via an expanded access program.)

EFFICACY CONSIDERATIONS	
Trial	**Menin Inhibition With Revumenib for *KMT2A*-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101)[3] [NCT04065399]**
Design	First-in-human, multinational, phase I/II, open-label, dose-escalation and expansion, observational study. The protocol originally allowed all patients with R/R acute leukemia. However, after no clinical activity was seen in patients without a *KMT2A* rearrangement or *NPM1* mutation, the protocol was amended to include only either *KMT2A* rearrangement or *NPM1* mutation and extend patient age to as young as 1 month.[1] Dosages were also amended to account for impaired revumenib metabolism when the drug was administered with strong CYP3A4 inhibitors. Results of the phase II, registration-enabling phase in the *KMT2A*–rearrangement patients are reviewed here. *Primary End Points*: Complete remission (CR), CR with partial hematologic recovery (CR + CRh), safety. The per-protocol null hypothesis set the CR + CRh response at 10%. The study included a Simon 2-stage design to target a 25% CR/CRh rate and exclude a 10% rate.
Population	94 patients (safety population) aged ≥ 30 days; Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, and relapsed/refractory *KMT2A* rearranged (*KMT2A*r) acute leukemia, including those with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or mixed-phenotype acute leukemia (MPAL). Patients with 11q23 partial tandem duplication (PTD) were excluded. Patients with CNS disease at the most recent relapse were allowed if no active CNS disease remained present at study entry. *Baseline Characteristics (N = 94, Safety Population)*: Median age 37 (range, 1.3–75 years); 71 adults (76%; median age 44 years); 13.8% age ≥ 65 years; 40% male; 72.3% White; 19.1% primary refractory (persistent leukemia following intensive induction chemotherapy); 57.4% relapsed refractory (unresponsive to most recent salvage treatment); 83% AML; 14.9% ALL; 2.1% acute leukemia of ambiguous lineage; 43.6% with ≥ 3 prior lines of therapy (median 2 lines; range 1–11 lines [i.e., heavily pretreated]); 65% had prior venetoclax; and 50% had prior hematopoietic stem cell transplantation (HSCT). 5 patients (8.8%) in the Efficacy Population (N = 57) had CNS disease at the most recent relapse.
Intervention	Revumenib (capsules or liquid) 163 mg (95 mg/m^2 if weight < 40 kg) every 12 hours in 28-day cycles for up to 4 cycles. (The 163-mg dose was used because apparently all patients were taking an unidentified, strong CYP3A4 inhibitor.)[4] Maintenance revumenib therapy post-HCT was allowed until disease progression or unacceptable toxicity.
Comparator	None
Allowed Concomitant Medications	Use of azole antifungals (strong CYP3A4 inhibitors) was not reported. Use of azoles are common in AML, and the 163-mg dose per protocol suggests all patients were on a strong CYP3A4 inhibitor.[4]

Results

Study enrollment was stopped early for efficacy.

Phase II Interim Results for Up to 12 Months, Efficacy-Evaluable Subpopulation

End Point	Revumenib, All Patients
CR + CRh, n/N (%; 95% CI)	13/57 (22.8; 12.7, 35.8)
Median time to first response, months	1.87
Median duration of CR + CRh, months	6.4
Median overall survival in adults, months (95% CI)	8.0 (4.1, 10.9)
Overall response rate (ORR; 95% CI)	36/57 (63.2; 49.3, 75.6)
Median time to first response, months	0.95
Median duration of response, months	4.3
Received allogeneic HCT, n/N (%)	14/36 (38.9)
Best response: Morphological leukemia-free state, n/N (%)	10/57 (17.5)
Negative for Measurable Residual Disease†	
Within CR + CRh, n/N (%)	7/10 (70.0)
Within CRc, n/N (%)	15/22 (68.2)

CR, complete remission; CRc, composite complete remission (defined as CR + CRh + CRi + CRp); CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery
† Assessed locally by flow cytometry

One (20%) of five patients with CNS disease at the most recent relapse responded, with a best response of morphological leukemia-free state.

Among patients who were transfusion-dependent at baseline, transfusion independence for at least 56 days (TI-56, defined as any transfusion-free period of ≥ 56 consecutive days during revumenib therapy or after discontinuation of revumenib but before start of new therapy) was achieved in 18.9% of patients for RBCs and 18.2% of patients for PLTs (see table below).

Transfusion Status

Transfusion Status, Baseline | Postbaseline	RBCs	PLTs	RBCs and PLTs
Dependent | Independent, n/N (%)	7/37 (18.9)	8/44 (18.2)	8/46 (17.4)
Dependent | Dependent, n/N (%)	30/37 (81.1)	36/44 (81.8)	38/46 (82.6)
Independent | Dependent, n/N (%)	8/20 (40)	4/13 (30.8)	5/11 (45.5)
Independent | Independent, n/N (%)	11/20 (55)	8/13 (61.5)	5/11 (45.5)

Authors' Conclusions

Revumenib provided clinical benefit with low rates of discontinuations due to adverse events (and thus a predictable safety profile) in patients with refractory acute leukemia who would typically receive palliative therapy. Almost 25% of revumenib-treated patients with resistant leukemia proceeded to potentially curative HCT.

Other Notable Trials

SAVE, a phase I/II trial.[5] Preliminary results of this study suggested that revumenib in combination with venetoclax and a hypomethylating agent has acceptable tolerability and favorable remission efficacy.

Studies evaluating the combination of revumenib with standard induction and consolidation chemotherapy are ongoing or planned.

Trial

Menin Inhibition With Revumenib for NPM1 mutation Relapsed or Refractory Acute Leukemia (AUGMENT-101)[6] [NCT04065399]

Design

Results of the phase II, registration-enabling phase in the NPM1 mutation cohort are reviewed here.

Single-arm cohort, open-label, multicenter trial (AUGMENT-101 described above)

Patients with NPM1 mutation, confirmed via NGS or PCR

Population

N=65 patients; median Age 65 years (range, 11-84); 50% with age ≥ 65 years; 48% age 17-64 years;

60% female; 58% white; 20% unknown; 10% black

NPM1 mutation type: 66% type A

Median prior regimens 2 (range 1-7); Prior SCT 23%

Results	Primary endpoints: CR + CRh, duration of response, conversion to transfusion independence At median follow-up 3.8 months CR + CRh 23%; median DoR 4.5 months (95% CI, 1.2 – 8.1) CR 18%; median DoR 3.7 months CRh 4.6% 17% became independent of RBC and platelet transfusions during any 56-day period 68% remained transfusion independent

SAFETY CONSIDERATIONS	
Boxed Warnings	***Differentiation syndrome*.** Differentiation syndrome, a potentially fatal condition, occurs when cancer treatment (oftentimes menin inhibitors) removes the block on cell maturation, causing differentiation of malignant blasts and triggering a rapid release of cytokines from leukemia cells that can lead to inflammation and organ failure. Symptoms include fever, dyspnea, hypoxia, peripheral edema, pleuropericardial effusion, acute renal failure, and/or hypotension. In clinical trials, differentiation syndrome occurred in 29% (39/135) of patients and was rated Grade 3 or 4 in 13%, with one fatality. Onset occurred at a median of 10 days (range, 3–41 days). Treatment interruption or withdrawal was required in 7% or 1% of patients, respectively. Prompt initiation of corticosteroid therapy and hemodynamic monitoring is required. ***QTc Interval prolongation and Torsades de Points.*** QTc interval prolongation reported in 36%; grade 3 in 15%; grade 4 in 2%; Dose reduction was required for 7%; impacted 46% of patients aged ≥ 65 years; one cardiac arrest event; one with nonsustained Torsades. Correct electrolyte abnormalities (hypokalemia, hypomagnesemia) prior to and throughout treatment. Check ECG prior to start; do not start therapy with QTcF > 450 msec; refer to prescribing information for ECG monitoring details and frequency.
Contraindications	None
Other Warnings	*Embryofetal Toxicity*: Can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of the risk to a fetus and to use effective contraception.
Top 5 AEs (≥20%)	Hemorrhage, nausea, increased phosphate, musculoskeletal pain, infection
Fatal AEs	4 patients (3%): 2 with differentiation syndrome, 1 with hemorrhage, and 1 with sudden death.
Serious AEs (SAEs)	SAEs occurred in 99 patients (73%). The most frequent SAEs (≥ 5%) were infection (24%), febrile neutropenia (19%), bacterial infection (17%), differentiation syndrome (12%), hemorrhage (9%), and thrombosis (5%).
AUGMENT-101 Safety Results	*Treatment-emergent adverse events (TEAEs)*: 93/94 (98.9%) *Discontinuation due to TEAE*: 12/94 (12.8%) *Grade ≥ 3 AEs*: 86/94 (91.5%); included febrile neutropenia, neutropenia, thrombocytopenia, anemia, differentiation syndrome (15/94 [16.0%], QTc prolongation (13/94 [13.8%]), sepsis, hypokalemia
Drug Interactions	*Strong CYP3A4 Inhibitors*: Reduce revumenib dose. *Strong or Moderate CYP3A4 Inducers*: Avoid concomitant use. *QTc Prolonging Drugs*: Avoid concomitant use. If concomitant use is unavoidable, monitor patients more frequently.
Pregnancy	Based on animal studies and mechanism of action, revumenib can cause fetal harm in pregnant women. There is insufficient data in pregnant women to evaluate for a drug-associated risk.
Lactation	Insufficient data. Advise not to breastfeed during treatment and for 1 week after the last dose.
Females and Males of Reproductive Potential	Can cause fetal harm when given to pregnant women. *Pregnancy Testing*: Verify pregnancy status in females of reproductive potential within 7 days prior to initiating revumenib. *Contraception*: Advise females and males of reproductive potential to use effective contraception during treatment and for 4 months after the last dose. *Infertility*: Based on animal studies, revumenib may cause reversible impairment of fertility.

Geriatric Use	In clinical trials, 16 patients (12%) were ≥ 65 years of age and 3 patients (2%) were ≥ 75 years of age. Patients ≥ 65 years of age had higher incidences of QTc prolongation and edema than younger patients.

OTHER CONSIDERATIONS	
Resistance to Revumenib	In patients who relapsed in the phase I part of AUGMENT-101, clonal expansion of menin mutations were seen in 38.7% of patients who received > 2 cycles of treatment.[1] Menin inhibitors less susceptible to development of resistance and use of combination therapies to overcome revumenib resistance are active areas of research.
Effect of Food on Absorption	No clinically significant effects on the pharmacokinetics (C_{max} and AUC) were observed when taken with a low-fat meal. No information available on the effects of higher-fat meals.
FDA Review[7]	The recommendation to approve revumenib was based on the study showing a CR/CRh rate of 21% (95% CI 11%, 34%) in the 57-patient Pivotal Cohort; a median duration of CR/CRh of 6.4 months (2.7, not estimable [NE]); and a 14% (8, 24) rate of conversion to 56-day transfusion independence (TI-56). The results were considered positive because the lower bound of the 95% CI exceeded the prespecified lower bound of 10%. The median duration of treatment was short (71 days; range, 3–619 days), with the possibility that remission could not have occurred during this period, and thereby could have led to low point estimates for CR/CRh and TI-56 and not very robust consistencies between CR/CRh and other measures of benefit (such as severe infection or bleeding). However, remissions occurred in patients with refractory disease and were durable, and subgroup analyses showed results consistent with the overall analysis. Secondary malignancy was an adverse event of special interest because menin-mediated signaling can be involved in tumor suppression. Follow-up in clinical trials was too short to adequately assess this risk.
Uncertainties	The effect size in R/R AML is uncertain because AUGMENT-101 lacked a control group and included a small number of patients. Effects of treatment in each subtype of acute leukemia (AML, ALL, or ambiguous lineage) and by primary refractory or relapsed refractory subgroup is uncertain. Efficacy of revumenib in non–R/R AML was not evaluated and is uncertain. Effects in newly diagnosed acute leukemia Safety and efficacy of revumenib used in combination therapy Long-term safety Dosages in liver or kidney impairment Applicability of results to the typical VHA patient population (solely adult, mostly elderly with comorbidities)

GUIDELINE/GUIDANCE PLACE IN THERAPY AND TREATMENT ALTERNATIVES	
NCCN Guidelines for R/R AML (After Completion of Consolidation Therapy)[4]	Enrollment in a **clinical trial** is recommended as a strongly preferred option. Treatment alternatives other than best supportive care include **targeted therapy or chemotherapy, each followed by allogeneic HCT (alloHCT)** if the patient is physically fit and there is an available donor. Revumenib is a targeted therapy for R/R AML with • *KMT2A* rearrangement (category 2A) • *NPM1* mutation (category 2A) Intensive chemotherapy regimens for appropriate patients with R/R AML include regimens that contain purine analogs (e.g., fludarabine, cladribine, clofarabine). These treatments have been associated with remission rates of 30%–45%.[4] Less intensive chemotherapy regimens include hypomethylating agents (HMAs; azacitidine or decitabine) and low-dose cytarabine (LDAC). Treatment alternatives for *KMT2A* rearranged AML: Venetoclax with either HMA or LDAC is another treatment option. A retrospective report in R/R AML (n=30) with KMT2A rearrangement treated with venetoclax + HMA showed a response rate of 40-50%, but median duration with median OS 6-8 months.
NCCN Guidelines for R/R Acute Lymphoblastic Leukemia[4]	Revumenib is an Other Recommended regimen (category 2A) in adults for R/R Ph-negative B-cell acute lymphoblastic leukemia (B-ALL) or T-cell acute lymphoblastic leukemia (T-ALL) with *KMT2A* rearrangement.
VA AML – Relapsed pathway	Revumenib is not included in November 2025 - V2.2025

POTENTIAL PLACE IN THERAPY	
Treatment Gaps Filled	Acute leukemia includes acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and mixed-phenotype acute leukemia (MPAL, aka acute leukemia of ambiguous lineage). AML is an uncommon cancer (representing 1% of all cancers) but constitutes about 30% of leukemias in adults, with the average age of first diagnosis being 69 years. In the US, the incidence of AML is 4.3 per 100,000 individuals or 20,000 new cases per year.[8] ALL tends to occur mostly in children, with 40% of cases affecting adults. The *KMT2A* rearrangement is the key disease driver in 5% to 10%, 10%, and 8% of patients with newly diagnosed AML, ALL, and MPAL, respectively.[1] In AML, the *KMT2A* rearrangement commonly occurs in patients after cytotoxic chemotherapy. In ALL, it frequently occurs in infants. The *KMT2A* rearrangement is associated with drug resistance and an intermediate or poor/adverse risk in AML and a poor risk in B-cell ALL Patients with R/R *KMT2A*r acute leukemia have a median survival of less than 1 year and a 5-year OS of less than 10%.[7] Published outcome data for R/R *KMT2A*r ALL or MPAL are not available. CR after relapse in *KMT2A*r AML has occurred in 66% after first-line (1L) therapy, 34% after 2L therapy, and only 5% of patients after ≥ 3 lines of therapy.[5] Second salvage therapy is associated with an overall survival lasting only 2.4 months.[7] Intensive salvage chemotherapy followed by alloHCT provides the best chance of cure for R/R AML. Given substantial toxicities, this treatment approach is considered more suitable for younger patients and less suitable for adverse-risk patient subgroups. Venetoclax-based regimens have also been used off-label to treat R/R *KMT2A*r acute leukemia. Revumenib is the first treatment evaluated in a prospective study for R/R *KMT2A*r acute leukemia and first targeted therapy approved for this indication.
Option for R/R *KMT2A*r Acute Leukemia and NPM1m AML	Revumenib clinical benefit has been demonstrated in terms of median OS, CR and transfusion independence. Current treatment alternatives, primarily venetoclax-based regimens provide a similar CR rate with limited duration of response. Responses to revumenib were noted in pretreated patients that included prior venetoclax and/or prior HSCT. Revumenib is a targeted therapy for the treatment of relapsed or refractory acute leukemia associated with a *KMT2A* rearrangement and *NPM1*-mutated AML. That is, for treatment of persistent acute leukemia despite at least 2 lines of therapy or relapse of disease following the most recent salvage therapy.

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