HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REVUFORJ safely and effectively. See full prescribing information for REVUFORJ.

REVUFORJ (revumenib) tablets, for oral use
Initial U.S. Approval: 2024

WARNING: DIFFERENTIATION SYNDROME
See full prescribing information for complete boxed warning.

Differentiation syndrome, which can be fatal, has occurred with REVUFORJ. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution (5.1)

----------INDICATIONS AND USAGE----------
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. (1).

----------DOSAGE AND ADMINISTRATION----------
- Select patients for treatment with REVUFORJ based on the presence of a KMT2A translocation. (2.1)
- Administer REVUFORJ orally twice daily fasted or with a low-fat meal at approximately the same time each day. (2.2)
- See Full Prescribing Information for recommended REVUFORJ dosage regimen, dosage modifications, and administration instructions. (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 25 mg, 110 mg, 160 mg (3)

----------CONTRAINDICATIONS----------
- None. (4)

----------WARNINGS AND PRECAUTIONS----------
- QTc Interval Prolongation: Monitor electrocardiograms and electrolytes. Correct hypokalemia and hypomagnesemia prior to and during treatment. If QTc interval prolongation occurs, interrupt, reduce, or permanently discontinue REVUFORJ. (2.3, 5.2).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 20%) including laboratory abnormalities, are hemorrhage, nausea, phosphate increased, musculoskeletal pain, infection, aspartate aminotransferase increased, febrile neutropenia, alanine aminotransferase increased, parathyroid hormone intact increased, bacterial infection, diarrhea, differentiation syndrome, electrocardiogram QT prolonged, phosphate decreased, triglycerides increased, potassium decreased, decreased appetite, constipation, edema, viral infection, fatigue, and alkaline phosphatase increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Syndax Pharmaceuticals, Inc., at 1-888-539-3REV or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 Inhibitors: Reduce the REVUFORJ dose. (2.2, 7.1)
- Strong or moderate CYP3A4 Inducers: Avoid concomitant use with REVUFORJ. (7.1)
- QTc Prolonging Drugs: Avoid concomitant use with REVUFORJ. If concomitant use is unavoidable, monitor patients more frequently for QTc interval prolongation. (5.2, 7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: DIFFERENTIATION SYNDROME
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
2.2 Recommended Dosage
2.3 Dosage Modifications for Adverse Reactions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Differentiation Syndrome
5.2 QTc Interval Prolongation
5.3 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on REVUFORJ
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Relapsed or Refractory Acute Leukemia with a KMT2A Translocation
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: 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 initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].*

1 INDICATIONS AND USAGE

Relapsed or Refractory Acute Leukemia

REVUFORJ is 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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of acute leukemia with REVUFORJ based on the presence of a KMT2A translocation in bone marrow cells *[see Clinical Studies (14.1)]*. An FDA-approved companion diagnostic for the detection of a KMT2A translocation is not currently available.

2.2 Recommended Dosage

The recommended dosage of REVUFORJ varies by patient weight and concomitant use of strong CYP3A4 inhibitors. See Table 1 for the recommended dosage for patients 1 year and older. Do not start REVUFORJ until the WBC is reduced to less than 25 Gi/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.

Table 1. REVUFORJ Recommended Dosage for Patients 1 Year and Older

Patient Weight	Without Strong CYP3A4 Inhibitors	With Strong CYP3A4 Inhibitors
40 kg or more	270 mg orally twice daily	160 mg orally twice daily
Less than 40 kg	160 mg/m^2 orally twice daily*	95 mg/m^2 orally twice daily*

*See Table 2 for the total tablet dosage by BSA (body surface area) for patients weighing less than 40 kg.

Table 2: Recommended Dosage using Tablets* for Patients Weighing Less than 40 kg

BSA (m^2)	REVUFORJ Dosage for 160 mg/m^2	REVUFORJ Dosage for 95 mg/m^2
1.4	220 mg twice daily	135 mg twice daily
1.3	220 mg twice daily	135 mg twice daily
1.2	185 mg twice daily	110 mg twice daily
1.1	185 mg twice daily	110 mg twice daily
1	160 mg twice daily	100 mg twice daily
0.9	135 mg twice daily	75 mg twice daily
0.8	135 mg twice daily	75 mg twice daily
0.7	110 mg twice daily	50 mg twice daily
0.6	100 mg twice daily	50 mg twice daily
0.5	75 mg twice daily	50 mg twice daily
0.4	50 mg twice daily	25 mg twice daily

* If needed, attain the desired dose by combining different strengths of REVUFORJ tablets.

- 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 (Table 1).

- Concurrent use of standard intrathecal chemotherapy prophylaxis is recommended for patients with risk of central nervous system relapse.

Administration:

- Administer REVUFORJ twice daily fasted or with a low-fat meal (e.g., meals with approximately 400 calories, 25% or less fat).

- Administer REVUFORJ orally around the same time each day.

- Advise patients to swallow tablets whole and to not cut or chew tablets. If patients are unable to swallow tablets, they may be crushed and dispersed in water and taken within 2 hours of preparation *[see Instructions for Use]*.

- If a dose of REVUFORJ 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.

2.3 Dosage Modifications for Adverse Reactions

Assess blood counts, electrolytes, and liver enzymes prior to the initiation of REVUFORJ and monthly thereafter. Perform an electrocardiogram (ECG) prior to the initiation 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 promptly *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Interrupt dosing or reduce dose for adverse reactions as per Table 3. Dose levels for dose reductions are listed in Table 4, Table 5, and Table 6.

Table 3. Recommended Management and Dosage Modifications for Adverse Reactions

Adverse reaction	Recommended action
Differentiation Syndrome *[see Warnings and Precautions (5.1)]*	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days. *[see Warnings and Precautions (5.1)]*. • Interrupt REVUFORJ if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids, or earlier for life-threatening symptoms such as pulmonary symptoms requiring ventilator support *[see Warnings and Precautions (5.1)]*. Resume REVUFORJ at the same dose when signs and symptoms improve to Grade 1* or lower.
Noninfectious leukocytosis	• Initiate treatment with hydroxyurea in patients with an elevated or rapidly rising leukocyte count. Add leukapheresis if clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves.
QTc interval greater than 480 msec to 500 msec *[see Warnings and Precautions (5.2)]*	• Interrupt REVUFORJ. • Check electrolyte levels. Correct hypokalemia and hypomagnesemia *[see Warnings and Precautions (5.2)]*. • Restart REVUFORJ at the same dose level after the QTc interval returns to less than or equal to 480 msec.
QTc interval greater than 500 msec (Grade 3*) *[see Warnings and Precautions (5.2)]*	• Interrupt REVUFORJ. • Check electrolyte levels. Correct hypokalemia and hypomagnesemia *[see Warnings and Precautions (5.2)]*. • Restart REVUFORJ at the reduced dose level** after the QTc interval returns to less than or equal to 480 msec.
QTc interval prolongation with signs/symptoms of life-threatening arrhythmia, Torsades de pointes, polymorphic ventricular tachycardia, signs/ symptoms of life-threatening arrhythmia (Grade 4*) *[see Warnings and Precautions (5.2)]*.	• Permanently discontinue REVUFORJ.

Adverse reaction	Recommended action
Potassium 3.6-3.9 mEq/L, and/or Magnesium 1.7-1.9 mg/dL or 0.66-0.81 mmol/L	• Supplement potassium and/or magnesium. • Continue REVUFORJ.
Potassium ≤ 3.5 mEq/L, and/or Magnesium ≤ 1.6 mg/dL or ≤ 0.65 mmol/L	• Supplement potassium and/or magnesium, and recheck levels within 24 hours. • On recheck of potassium and magnesium labs within 24 hours, if potassium is greater than 3.5 mEq/Land/or magnesium is greater than 1.6 mg/dL, continue REVUFORJ. If potassium is less than 3.5 mEq/L and/or magnesium is less than 1.6 mg/dL, hold REVUFORJ and continue supplementation; resume REVUFORJ at the same dose level when the correction is complete.
Other nonhematological adverse reactions Grade ≥ 3* *[see Adverse Reactions (6.1)]*	• Interrupt REVUFORJ until recovery to Grade 1* or baseline. • If recovered in ≤ 7 days, restart REVUFORJ at the same dose level. If the same Grade ≥ 3* toxicity recurs, interrupt REVUFORJ until recovery to Grade 1* or baseline. Restart REVUFORJ at the reduced dose level.** If recovered in > 7 days, restart REVUFORJ at the reduced dose level.** If the same Grade ≥ 3* toxicity recurs, discontinue REVUFORJ.
Grade 4* neutropenia or thrombocytopenia *[see Adverse Reactions (6.1)]*	• Interrupt REVUFORJ until recovery to Grade ≤ 2* or baseline. • Restart REVUFORJ at the same dose level. • If Grade 4* neutropenia or thrombocytopenia recurs without attributable cause, interrupt REVUFORJ until recovery to Grade ≤ 3*. Restart REVUFORJ at the reduced dose level.**
Grade 3* or higher allergic reactions *[see Adverse Reactions (6.1)]*	• Permanently discontinue REVUFORJ.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening. Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0).
**See Tables 4, 5 and 6 for the reduced dose levels.

Table 4. REVUFORJ Dosage Reduction for Adverse Reactions in Patients NOT on Strong CYP3A4 Inhibitors

	Patients Weighing 40 kg or Greater at Starting Dose 270 mg orally twice daily	Patients Weighing Less Than 40 kg at Starting Dose 160 mg/m^2 orally twice daily
Reduced Dose	160 mg orally twice daily	95 mg/m^2 orally twice daily*

See **Table 6 for BSA-based dosage recommendations for the reduced dosage of 95 mg/m^2 twice daily.

Table 5. REVUFORJ Dosage Reduction for Adverse Reactions in Patients on Strong CYP3A4 Inhibitors

	Patients Weighing 40 kg or Greater at Starting Dose 160 mg orally twice daily	Patients Weighing Less Than 40 kg at Starting Dose 95 mg/m^2 orally twice daily
Reduced Dose	110 mg orally twice daily	65 mg/m^2 orally twice daily*

*See **Table 6** for BSA-based dosage recommendations for the reduced dosage of 65 mg/m^2 twice daily.

Table 6: Recommended Reduced Dosage Using Tablets* for Patients Weighing Less than 40 kg

BSA (m^2)	REVUFORJ Dosage for 95 mg/m^2	REVUFORJ Dosage for 65 mg/m^2
1.4	135 mg twice daily	100 mg twice daily
1.3	135 mg twice daily	75 mg twice daily
1.2	110 mg twice daily	75 mg twice daily
1.1	110 mg twice daily	75 mg twice daily
1	100 mg twice daily	50 mg twice daily
0.9	75 mg twice daily	50 mg twice daily
0.8	75 mg twice daily	50 mg twice daily
0.7	50 mg twice daily	50 mg twice daily
0.6	50 mg twice daily	25 mg twice daily
0.5	50 mg twice daily	25 mg twice daily
0.4	25 mg twice daily	25 mg twice daily

* If needed, attain the desired dose by combining different strengths of REVUFORJ tablets.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 25 mg of revumenib: Pink modified oval film-coated tablet debossed with “S” on one side and “25” on the other side.
- 110 mg of revumenib: Beige modified oval film-coated tablet debossed with “S” on one side and “110” on the other side.
- 160 mg of revumenib: Purple modified oval film-coated tablet debossed with “S” on one side and “160” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome

REVUFORJ can cause fatal or life-threatening differentiation syndrome (DS). Symptoms of differentiation syndrome, including those seen in patients treated with REVUFORJ, include fever, dyspnea, hypoxia, peripheral edema, pleuropericardial effusion, acute renal failure, and/or hypotension.

In clinical trials, DS occurred in 39 (29%) of 135 patients treated with REVUFORJ at the recommended dosage for relapsed or refractory acute leukemia with a KMT2A translocation, including 32% of patients with acute myeloid leukemia (AML), 25% of patients with mixed-phenotype acute leukemia (MPAL), and 14% of patients with acute lymphoblastic leukemia (ALL). DS was Grade 3 or 4 in 13% and fatal in one patient. The median time to onset was 10 days (range 3-41 days). Some patients experienced more than 1 DS event. Treatment interruption was required for 7% of patients, and treatment was withdrawn for 1% *[see Adverse Reactions (6.1)]*.

Reduce the white blood cell count (WBC) to less than 25 Gi/L prior to starting REVUFORJ. If DS is suspected, immediately initiate treatment with systemic corticosteroids (e.g., dexamethasone 10 mg intravenously every 12 hours in adults or dexamethasone 0.25 mg/kg/dose intravenously every 12 hours in pediatric patients weighing less than 40 kg) for a minimum of 3 days and until resolution of signs and symptoms. Institute supportive measures and hemodynamic monitoring until improvement. Interrupt REVUFORJ if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids, or earlier if life-threatening symptoms occur such as pulmonary symptoms requiring ventilator support. Restart steroids promptly if DS recurs after tapering corticosteroids *[see Dosage and Administration (2.3)]*.

5.2 QTc Interval Prolongation

REVUFORJ can cause QT (QTc) interval prolongation *[see Clinical Pharmacology (12.2)]*. In the clinical trials, QTc interval prolongation was reported as an adverse reaction in 39 (29%) of 135 patients treated with REVUFORJ at the recommended dosage for relapsed or refractory acute leukemia with a KMT2A translocation; QTc interval prolongation was Grade 3 in 12%. The heart-rate corrected QT interval (using Fridericia's method) (QTcF) was greater than 500 msec in 8%, and the increase from baseline QTcF was greater than 60 msec in 18%. REVUFORJ dose reduction was required for 5% due to QTc interval prolongation *[see Adverse Reactions (6.1)]*. QTc prolongation occurred in 16% of the 31 patients less than 17 years old, 33% of the 88 patients 17 years to less than 65 years old, and in 50% of the 16 patients 65 years or older.

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 initiate REVUFORJ in patients with QTcF > 450 msec. Perform an ECG at least once a week for the first 4 weeks on treatment, and at least monthly thereafter *[see Dosage and Administration (2.3)]*. 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 *[see Drug Interactions (7.1), Clinical Pharmacology (12.2)]*.

Interrupt REVUFORJ if QTcF increases to greater than 480 msec and less than 500 msec, and restart REVUFORJ at the same dose twice daily after the QTcF interval returns to less than or equal to 480 msec. Interrupt REVUFORJ if QTcF increases to greater than 500 msec 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 480 msec. Permanently discontinue REVUFORJ in patients with ventricular arrhythmias and in those who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.3)]*.

5.3 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, REVUFORJ can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, oral administration of revumenib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, malformations, and altered fetal growth at maternal exposures approximately 0.5 times the human exposure (AUC) at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with REVUFORJ and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome *[see Warnings and Precautions (5.1)]*
- QTc Interval Prolongation *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Relapsed or Refractory Acute Leukemia with KMT2A translocation

The safety of REVUFORJ reflects exposure in 135 patients (104 adult and 31 pediatric patients) with relapsed or refractory (R/R) acute leukemia with KMT2A translocation treated with REVUFORJ at a dose approximately equivalent to 160 mg in adults orally twice daily with a strong CYP3A4 inhibitor *[see Clinical Studies (14.1)]*. The median duration of exposure to REVUFORJ was 2.3 months (range < 1 to 23 months), and 3% of patients were exposed for more than 6 months.

Fatal adverse reactions occurred in 4 (3%) patients who received REVUFORJ, including 2 with differentiation syndrome, 1 with hemorrhage, and 1 with sudden death. Serious adverse reactions were reported in 99 (73%) patients. The most frequent serious adverse reactions (≥ 5%) were infection (24%), febrile neutropenia (19%), bacterial infection (17%), differentiation syndrome (12%), hemorrhage (9%), and thrombosis (5%).

Adverse reactions leading to dose interruption occurred in 42% of patients. The most common adverse reactions (≥ 5%) leading to dose interruption were electrocardiogram QT prolonged, febrile neutropenia, differentiation syndrome, infection, hypokalemia, and nausea. Adverse reactions leading to dose reduction occurred in 10% of patients who received REVUFORJ. Adverse reactions leading to a dose reduction (> 1%) included electrocardiogram QT prolonged. Adverse reactions leading to permanent discontinuation occurred in 12% of patients. Adverse reactions resulting in permanent discontinuation (> 1%) included infection and respiratory failure.

The most common (≥ 20%) adverse reactions were hemorrhage, nausea, phosphate increased, musculoskeletal pain, infection, aspartate aminotransferase increased, febrile neutropenia, alanine aminotransferase increased, parathyroid hormone intact increased, bacterial infection, diarrhea, differentiation syndrome, electrocardiogram QT prolonged, phosphate decreased, triglycerides increased, potassium decreased, decreased appetite, constipation, edema, viral infection, fatigue, and alkaline phosphatase increased.

The common adverse reactions are summarised in Table 7.

Table 7. Adverse Reactions Reported in ≥ 20% (Any Grade) or ≥ 5% (Grade 3 or 4) in Patients with R/R Acute Leukemia with KMT2A Translocation

	REVUFORJ N = 135	
Adverse Reaction	**All Grades %**	**Grade 3 or 4 %**
Vascular disorders		
Hemorrhage[a#]	53	9
Thrombosis[b]	10	5
Gastrointestinal disorders		
Nausea[c]	51	4
Diarrhea[d]	30	4
Constipation	23	1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	42	6
Infections and infestations		
Infection[f]	41	29
Bacterial infection[g]	31	20
Viral infection[h]	23	4
Blood and lymphatic system disorders		
Febrile neutropenia	35	33
Leukocytosis	8	5
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Differentiation syndrome[#]	29	13
Investigations		
Electrocardiogram QT prolonged	29	12
Metabolism and nutrition disorders		
Decreased appetite	24	8
General disorders and administration site conditions		
Edema[i]	23	1
Fatigue[j]	22	5

Includes the following fatal adverse reactions: DS (n=2); hemorrhage (n=1)
a – Includes epistaxis, contusion, petechiae, gingival bleeding, haematuria, mouth hemorrhage, hematoma, hemoptysis, hemorrhoidal hemorrhage, subdural hematoma, vaginal hemorrhage, catheter site hemorrhage, conjunctival hemorrhage, ecchymosis, hemorrhage intracranial, anal hemorrhage, brain stem hemorrhage, eye hematoma, gastrointestinal hemorrhage, genital contusion, hematochezia, injection site hematoma, lower gastrointestinal hemorrhage, melena, mucosal hemorrhage, oral contusion, pulmonary, upper gastrointestinal hemorrhage, vitreous hemorrhage.
b – Includes disseminated intravascular coagulation, pulmonary embolism, cerebrovascular accident, deep vein thrombosis, embolism, hemorrhoids thrombosed, medical device site thrombosis, renal infarct, superficial vein thrombosis, thrombosis, transient ischemic attack.
c – Includes nausea, and vomiting.
d – Includes diarrhea, colitis, neutropenic colitis.
e – Includes back pain, arthralgia, pain in extremity, neck pain, myalgia, musculoskeletal chest pain, myositis, flank pain, musculoskeletal discomfort, musculoskeletal pain.
f – Includes sepsis, pneumonia, urinary tract infection, septic shock, sinusitis, upper respiratory tract infection, device related infection, skin infection, acute sinusitis, enterocolitis infectious, perirectal abscess, rectal abscess, rhinitis, abscess limb, appendicitis, bronchitis, conjunctivitis, endocarditis, epididymitis, eye infection, gastroenteritis, neutropenic sepsis, osteomyelitis, rash pustular, retinitis, shock, sialadenitis, tooth abscess, tooth infection, vascular device infection.
g – Includes bacteremia, cellulitis, clostridium difficile infection, staphylococcal bacteremia, paronychia, clostridium test positive, enterobacter infection, enterobacter sepsis, escherichia bacteremia, alpha haemolytic streptococcal infection, bacteriuria, cellulitis staphylococcal, enterobacter bacteremia, enterococcal bacteremia, enterococcal infection, escherichia urinary tract infection, folliculitis, klebsiella infection, klebsiella sepsis, lactobacillus bacteremia, pseudomonal bacteremia.
h – Includes COVID-19, rhinovirus infection, respiratory syncytial virus infection, cytomegalovirus infection reactivation, herpes simplex, herpes simplex reactivation, herpes zoster, COVID-19 pneumonia, coronavirus infection, cytomegalovirus infection, cytomegalovirus test positive, enterovirus infection, enterovirus test positive, Epstein-Barr virus infection, herpes simplex pharyngitis, herpes virus infection, norovirus infection, oral herpes, pneumonia cytomegaloviral.
i – Includes edema peripheral, generalised edema, edema, localized edema, peripheral swelling.
j – Includes fatigue and malaise.

Clinically relevant adverse reactions in less than 20% of patients who received REVUFORJ include:

Cardiac disorders: Cardiac failure, pericardial effusion, ventricular tachycardia, cardiac arrest

Endocrine disorders: Hyperparathyroidism

Eye disorders: Cataract

Gastrointestinal disorders: Abdominal pain

General disorders and administration site conditions: Sudden death

Immune system disorders: Drug hypersensitivity

Metabolism and nutrition disorders: Hyponatremia, hyperkalemia

Nervous system disorders: Taste disorder, syncope, headache, paresthesia

Renal disorders: Renal impairment

Skin and subcutaneous disorders: Rash

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory acute leukemia with KMT2A translocation are shown in Table 8.

Table 8. Selected New or Worsening Laboratory Abnormalities in Patients with R/R Acute Leukemia with KMT2A translocation

	REVUFORJ	
Laboratory Abnormality	**Grades 1-4* %**	**Grades 3-4 %**
Phosphate increased	50	-
Aspartate aminotransferase increased	37	1
Alanine aminotransferase increased	33	3
Parathyroid hormone, intact increased	33	-
Phosphate decreased	25	-
Triglycerides increased	25	3
Potassium decreased	24	5
Alkaline phosphatase increased	21	0
Cholesterol increased	19	0
Creatinine increased	19	0
Calcium corrected increased	15	0

*The denominator used to calculate the rate varied from 73 to 135 based on the number of patients with a baseline value and at least one post baseline value.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on REVUFORJ

Strong CYP3A4 Inhibitors

If concomitant use of strong CYP3A4 inhibitors is required, reduce the REVUFORJ dosage *[see Recommended Dosage (2.2)]*.

Revumenib is primarily metabolized by CYP3A4 *[see Clinical Pharmacology (12.3)]*. Concomitant use with a strong CYP3A4 inhibitor increases revumenib systemic exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of REVUFORJ adverse reactions.

Strong or Moderate CYP3A4 Inducers

Avoid concomitant use with strong or moderate CYP3A4 inducers.

Revumenib is primarily metabolized by CYP3A4 *[see Clinical Pharmacology (12.3)]*. Concomitant use with a strong or moderate CYP3A4 inducer may decrease revumenib and increase M1 systemic exposure *[see Clinical Pharmacology (12.3)]*, which may reduce REVUFORJ efficacy or increase the risk of QT prolongation associated with the M1 metabolite.

Drugs that Prolong QTc Interval

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 initiating, during concomitant use, and as clinically indicated *[see Warnings and Precautions (5.2)]*. Withhold REVUFORJ if the QTc interval is greater than 480 msec. Restart REVUFORJ after the QTc interval returns to less than or equal to 480 msec *[see Dosage and Administration (2.3)]*.

REVUFORJ causes QTc interval prolongation *[see Clinical Pharmacology (12.2)]*. 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 *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, REVUFORJ can cause fetal harm when administered to a pregnant woman. There are no available data on REVUFORJ use in pregnant women to evaluate for a drug-associated risk.

In an animal reproduction study, oral administration of revumenib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, malformations, and altered fetal growth at maternal exposures approximately 0.5 times the human exposure (AUC) at the recommended dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In an embryo-fetal development study, revumenib was administered once daily via oral gavage at doses of 30, 100, and 300 mg/kg/day to pregnant rats during the period of organogenesis (gestation days 6-17). Decreased maternal body weight gain and adverse embryo-fetal findings including decreases in the number of live fetuses, increases in resorptions and post-implantation loss, and decreases in fetal body weight were observed at all doses. At 300 mg/kg/day, total litter resorption and eye malformations were observed. At the dose of 30 mg/kg/day in rats, the maternal exposures (AUC) were approximately 0.5 times the human exposure at the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of revumenib or its metabolites in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with REVUFORJ and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on findings in animals and its mechanism of action, REVUFORJ can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential within 7 days prior to initiating REVUFORJ.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with REVUFORJ and for 4 months after the last dose.

Males

Advise males of reproductive potential to use effective contraception during treatment with REVUFORJ and for 4 months after the last dose.

Infertility

Females and Males

Based on findings in animals, REVUFORJ may impair fertility. The effects on fertility were reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of REVUFORJ have been established in pediatric patients 1 year and older with relapsed or refractory acute leukemia with a KMT2A translocation. Use of REVUFORJ for this indication is supported by evidence from adequate and well-controlled trials in adults and pediatric patients *[see Clinical Studies (14.1)]* and additional pharmacokinetic and safety data in pediatric patients *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. The patients included 13 infants (age < 2 years), 41 children (age 2 to < 12 years) and 16 adolescents (age 12 to < 17 years). The recommended dosage in patients weighing less than 40 kg is BSA-based.

The safety and efficacy of REVUFORJ in pediatric patients less than 1 year old have not been established**.**

Animal Data

In a repeat dose toxicity study in 6-7 week-old rats treated with revumenib at 75, 150, or 300 mg/kg/day for 13 weeks, an irreversible increase in femur growth plate closure was observed at revumenib exposures approximately 2 times the human exposure (AUC) at the recommended dose.

Based on the findings in animals, monitor bone growth and development in pediatric patients.

8.5 Geriatric Use

Of the 135 patients with relapsed or refractory acute leukemia with a KMT2A translocation in clinical studies of REVUFORJ, 16 (12%) patients were 65 years of age and older and 3 (2%) patients were 75 years of age and older *[see Clinical Studies (14.1)]*.

No overall differences were observed in the effectiveness of REVUFORJ between patients who were 65 years and older and younger patients *[see Clinical Studies (14.1) and Clinical Pharmacology (12.3)]*. Compared to younger patients, the incidences of QTc prolongation and edema were higher in patients 65 years and older *[see Warnings and Precautions (5.2)]*.

11 DESCRIPTION

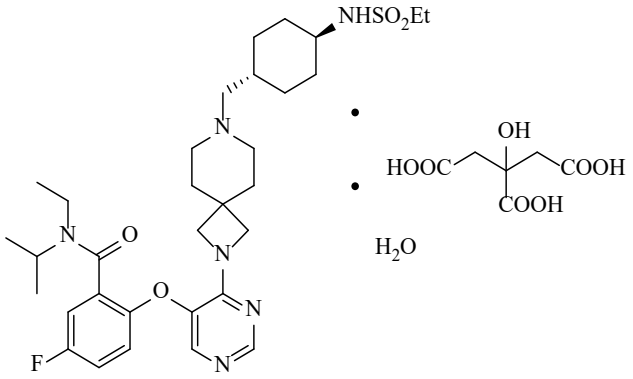
REVUFORJ contains revumenib, a menin inhibitor. Revumenib is present as revumenib citrate hydrate with a chemical name of benzamide, *N*-ethyl-2-[[4-[7-[[trans-4-[(ethylsulfonyl)amino]cyclohexyl]methyl]-2,7-diazaspiro[3.5]non-2-yl]-5-pyrimidinyl]oxy]-5-fluoro-*N*-[1-

methylethyl]-, 2-hydroxypropane-1,2,3-tricarboxylic acid, hydrate (1:1:1). The molecular formula is $C_{32}H_{47}FN_6O_4S \bullet C_6H_8O_7 \bullet H_2O$ with a molecular weight 840.96 g/mol.

Revumenib citrate hydrate is a white to faint pink solid. Revumenib citrate hydrate is soluble at pH 1.2 and 6.8, and sparingly soluble at pH 4.5.

The chemical structure is shown in Figure 1.

Figure 1: Chemical structure of Revumenib Citrate hydrate



REVUFORJ is available as tablets for oral use.

Each 25 mg strength tablet contains 25 mg revumenib, equivalent to 33.4 mg revumenib citrate, and the following inactive ingredients: microcrystalline cellulose, dicalcium phosphate, crospovidone, hypromellose, sodium bicarbonate, hydrophobic colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and red iron oxide.

Each 110 mg strength tablet contains 110 mg revumenib, equivalent to 146.5 mg revumenib citrate, and the following inactive ingredients: microcrystalline cellulose, dicalcium phosphate, crospovidone, hypromellose, sodium bicarbonate, hydrophobic colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, red iron oxide, and yellow iron oxide.

Each 160 mg strength tablet contains 160 mg revumenib equivalent to 213.2 mg revumenib citrate, and the following inactive ingredients: microcrystalline cellulose, dicalcium phosphate, crospovidone, hypromellose, sodium bicarbonate, hydrophobic colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, red iron oxide, and FD&C blue #2/indigo carmine aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Revumenib 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.

12.2 Pharmacodynamics

Revumenib exposure-response relationships have not been fully characterized and the time course of pharmacodynamic response is unknown.

Cardiac Electrophysiology

The effect of REVUFORJ on the QTc interval was evaluated across a dose range of 113 mg to 339 mg twice daily (1.2 times the highest adult approved recommended dosage) with and without strong CYP3A4 inhibitors in patients with relapsed or refractory acute leukemia with KMT2Ar.

The increase in QTc interval was concentration dependent with an increase in QTc predicted to be 27 msec (upper bound of 90% confidence interval: 30 msec) at the mean steady-state maximum concentration (C_{max}) observed in patients at the highest approved recommended dosage without CYP3A4 inhibitors. The increase in QTc interval was predicted to be 19 msec (upper bound of 90% confidence interval: 22 msec) at steady-state C_{max} after administration of 163 mg twice daily with strong CYP3A4 inhibitors *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

The pharmacokinetics of revumenib were characterized in patients with relapsed or refractory acute leukemia following single and multiple oral administration of revumenib with or without strong CYP3A4 inhibitors. Steady-state pharmacokinetic parameters are presented as geometric mean [coefficient of variation (%CV)] unless otherwise specified.

Table 9. Revumenib Pharmacokinetics in Patients with Relapsed or Refractory Acute Leukemia

Parameter	Dosage	
	163 mg twice daily (with strong CYP3A4 inhibitors)[a]	**276 mg twice daily (without strong CYP3A4 inhibitors)[a]**
General Information		
Exposure[b]		
C_{max} (ng/mL)	3220 (34%)	2052 (79%)
AUC_{0-12h} (ng•h/mL)	22,610 (50%)	10,150 (69%)
Dose Proportionality[c]	Dose proportional increases in C_{max} and AUC_{0-12h}	
Time to Steady-State	2-3 days	
Accumulation[b]	2-fold	
Absorption		
T_{max} Median (range) hours	2 (0-6)	1 (0.5-4)
Effect of Food		
Low fat meal[d]	No clinically significant differences in revumenib pharmacokinetics observed (C_{max} and AUC decreased by 27% and 12% respectively)	
Distribution		
Apparent Volume of Distribution[b] (L)	78 (50%)	
Protein Binding[e]	90%	
Blood to plasma ratio	0.8	
Elimination		

Half-Life[b] (hours)	7.5 (57%)	3.6 (36%)
Apparent Clearance[b] (L/h)	7 (51%)	27 (69%)
Metabolism		
Primary Pathway	CYP3A4	
Active Metabolite	M1[f]	
Excretion[g]		
Feces	Approximately 49% (7% unchanged)	
Urine	Approximately 27% (7% unchanged)	

Abbreviations: C_{max} = maximum plasma concentration; AUC = area under the time concentration curve; T_{max} = time to peak concentration

[a] - 1.02 times the highest adult approved recommended dosages

[b] - Steady-state

[c] - Dosage range of 113 mg to 339 mg (1.26 times the highest adult approved recommended dosage)

[d] - Approximately 400-500 calories, 25% of calories from fat

[e] - Independent of concentration

[f] - M1 contributes to revumenib's clinically significant effects on QTc *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]* but does not contribute to its efficacy at the approved recommended dosage

[g] - A single dose of radiolabeled revumenib 276 mg (1.02 times the highest adult approved recommended dosage) to adult patients with relapsed/refractory acute leukemia

Specific Populations

No clinically significant differences in the pharmacokinetics of revumenib were observed based on age (1 to 82 years), race (71% White, 8% Asian, 8% Black), sex, mild to moderate (CLcr 30 to 89 mL/min) renal impairment, and mild (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin > 1 to 1.5 × ULN and any AST) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment. The effect of severe renal impairment (CLcr less than 30 mL/min), end-stage renal disease (CLcr less than 15 mL/min), or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment is unknown.

Body weight (8-146 kg) has a significant effect on the pharmacokinetics of revumenib, with higher revumenib exposures in patients with lower body weight (less than 40 kg). This supports the use of BSA-based dosage in patients weighing less than 40 kg.

Pediatric Patients

Revumenib geometric mean (CV%) steady-state C_{max} was 3137 (39%) ng/mL and $AUC_{0\text{-}tau}$ was 14,630 (55%) ng·hr/mL following 95 mg/m^2 twice daily (approximately 1.02 times the highest approved recommended adult dosage) with strong CYP3A4 inhibitors.

Revumenib predicted geometric mean (%CV) steady-state C_{max} was 1597 (70%) ng/mL and $AUC_{0\text{-}tau}$ was 12,570 (56%) ng·hr/mL following 160 mg/m^2 twice daily (approximately 1.02 times the highest approved recommended adult dosage) without strong CYP3A4 inhibitors.

Drug Interaction Studies

Clinical Studies

Strong CYP3A4 Inhibitors: Revumenib AUC and C_{max} is increased by 2-fold following concomitant use of multiple doses of revumenib with certain azole antifungals that are strong CYP3A4 inhibitors (i.e., posaconazole, itraconazole, and voriconazole). Similarly, revumenib AUC and C_{max} is increased

by 2.5-fold following concomitant use of multiple doses of revumenib with cobicistat (strong CYP3A4 inhibitor).

Strong and Moderate CYP3A4 Inducers: Revumenib exposure is expected to decrease and M1 exposure is expected to increase with strong and moderate CYP3A4 inducers.

Other Drugs: No clinically significant differences in revumenib pharmacokinetics were observed when used concomitantly with fluconazole (moderate CYP3A4 inhibitor), isavuconazole (moderate CYP3A4 inhibitor).

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Revumenib inhibits CYP3A4, but does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

Revumenib does not induce CYP1A2, CYP2B6, and CYP3A4.

Transporter Systems: Revumenib is a substrate of OCT1, OCT2, OAT1, OAT3, and MATE1, but is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, MATE2-K, or BSEP. M1 is a substrate of OATP1B1, but is not a substrate of P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B3, MATE1, or MATE2-K.

Revumenib inhibits MATE1, but does not inhibit P-gp, BCRP, OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, BSEP, and MATE2-K. M1 inhibits MATE1, but does not inhibit OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and MATE2-K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with revumenib. In a repeat dose toxicity study in rats treated with revumenib for 13 weeks, lymphoma was observed in multiple organs in one animal.

Revumenib was not genotoxic in an in vitro bacterial reverse mutation (Ames) assay, an in vitro micronucleus assay in human peripheral blood lymphocytes, or an in vivo rat peripheral blood reticulocyte micronucleus assay.

Fertility studies in animals have not been conducted with revumenib.

In a repeat dose toxicity study in dogs treated with revumenib at 12.5, 25 or 40 mg/kg/day for 13 weeks, microscopic findings in the testes and epididymis consisted of depletion of germ cells and decreased sperm at ≥12.5 mg/kg/day. In females, microscopic changes of atrophy in the mammary glands, uterus, and vagina and decreased number of corpora lutea in the ovaries were observed at ≥12.5 mg/kg/day. At the end of the 13-week recovery period, the findings in the female reproductive organs were reversed at all doses, and the testicular and epididymal effects were reversed at 12.5 mg/kg/day. At the dose of 12.5 mg/kg/day in dogs, exposures (AUC) were approximately 1.3 times the human exposure (AUC) at the recommended dose.

13.2 Animal Toxicology and/or Pharmacology

In a repeat dose toxicity study in dogs treated with revumenib at 12.5, 25, or 40 mg/kg/day for 13 weeks, microscopic findings of nerve fiber degeneration in the brain, sciatic nerves, and spinal cord segments were observed at ≥ 12.5 mg/kg/day and were not reversed at the end of a 13-week recovery period.

In a repeat dose toxicity study in rats treated with revumenib at 75, 150, 300 mg/kg/day for 13 weeks, dose dependent ocular findings of lens opacities were observed at ≥ 75 mg/kg/day; the findings progressed during the dosing and recovery periods and were not reversed.

Hyperplasia was observed in multiple organs including the testes, mammary gland, uterus, pancreas, and kidney in rats treated at ≥ 75 mg/kg/day for up to 13 weeks. The findings were irreversible in the testes, mammary gland, and pancreas. Revumenib exposures at 75 mg/kg/day in rats are approximately 2 times the human exposure (AUC) at the recommended dose.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory Acute Leukemia with a KMT2A Translocation

SNDX-5613-0700

The efficacy of REVUFORJ was evaluated in a single-arm cohort of an open-label, multicenter trial (SNDX-5613-0700, NCT04065399; AUGMENT-101) in adult and pediatric patients at least 30 days old with relapsed or refractory (R/R) acute leukemia with a KMT2A translocation. Patients with an 11q23 partial tandem duplication were excluded. Eligibility required a QTcF < 450 msec at study baseline. Treatment consisted of REVUFORJ at a dose approximately equivalent to 160 mg in adults orally twice daily 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).

The baseline demographic and disease characteristics of the 104 treated patients are shown in Table 10. Twenty-four (23%) patients underwent HSCT following treatment with REVUFORJ.

Table 10. Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory Acute Leukemia with KMT2A translocation (Study SNDX-5613-0700)

Demographic and Disease Characteristics	REVUFORJ N = 104
Demographics	
Median Age (years) (Range)	37 (1, 79)
Age, n (%)	
< 17 years old	25 (24)
≥ 17 years old	79 (76)
Sex, n (%)	
Male	37 (36)
Female	67 (64)
Race, n (%)	
Black or African American	8 (8)
Asian	10 (10)
White	75 (72)
Multiple	1 (1)

Demographic and Disease Characteristics	REVUFORJ N = 104
Unknown	10 (10)
Ethnicity, n (%)	
Hispanic or Latino	23 (22)
Not Hispanic or Latino	76 (73)
Unknown	5 (5)
Disease Characteristics	
Leukemia morphological type, n (%)	
Acute myeloid leukemia (AML)	86 (83)
Acute lymphoblastic leukemia (ALL)	16 (15)
Mixed phenotype acute leukemia (MPAL)	2 (2)
Translocations[1], n (%)	
t(9;11)	23 (22)
t(11;19)	20 (19)
t(6;11)	10 (10)
t(10;11)	10 (10)
t(4;11)	7 (7)
t(1;11)	3 (3)
t(11;17)	2 (2)
t(11;22)	2 (2)
t(11;16)	1(1)
KMT2A fusion partner unknown	26 (25)
Disease status, n (%)	
Primary refractory	22 (21)
Untreated relapse	21 (20)
Refractory relapse	61 (59)
Prior treatment	
Number of prior regimens, median (range)	2 (1, 11)
Prior stem cell transplantation, n (%)	46 (44)
Number of prior relapses, n (%)	
0	22 (21)
1	55 (53)
2	20 (19)
≥3	7 (7)

1. One patient did not have a translocation type reported.

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 (range, 0.3 to 28.9

months). The efficacy results are shown in Table 11. On subgroup analysis, CR+CRh was achieved by 18/86 (21%) of patients with AML, 3/16 (19%) of patients with ALL, and 1/2 (50%) of patients with MPAL.

Table 11. Efficacy Results in Patients with Relapsed or Refractory Acute Leukemia with KMT2A translocation (Study SNDX-5613-0700)

Endpoint	REVUFORJ N = 104
CR[1]+CRh[2] n (%)	22 (21.2)
95% CI	(13.8, 30.3)[6]
Median DOCR+CRh[3] (months)	6.4[6]
95% CI	(2.7, NE)
CR n (%)	13 (12.5)
95% CI	(6.8, 20.4)[6]
Median DOCR[4] (months)	4.3[6]
95% CI	(1.0, NE)
CRh n (%)	9 (8.7)
95% CI	(4.0, 15.8)[6]
Median DOCRh[5] (months)	6.4[6]
95% CI	(1.9, NE)

CI: confidence interval; NE = not estimable; DOCR = duration of CR; DOCRh = duration of CRh.
1. CR is defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L and platelet count ≥100 × 10^9/L.
2. CRh is defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; residual neutropenia (>0.5 × 10^9/L) and thrombocytopenia (>50 × 10^9/L), but the count recovery criteria for CR are not met.
3. Duration of CR+CRh is defined as the time from first CR or CRh to the first documented relapse or death, whichever occurs first.
4. Duration of CR is defined as the time from first CR to the first documented relapse or death, whichever occurs first.
5. Duration of CRh is defined as the time from first CRh to the first documented relapse or death, whichever occurs first.
6. The 95% CI of the response rate is derived using the exact method based on binomial distribution. The median of the response duration is derived using Kaplan-Meier method.

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

25 mg: Pink modified oval film-coated tablet debossed with “S” on one side and “25” on the other side.

- 30-count bottles with a desiccant and child resistant closure (NDC 73555-500-00)

110 mg: Beige modified oval film-coated tablet debossed with “S” on one side and “110” on the other side.

- 30-count bottles with a desiccant and child resistant closure (NDC 73555-501-00)

160 mg: Purple modified oval film-coated tablet debossed with “S” on one side and “160” on the other side.

- 30-count bottles with a desiccant and child resistant closure (NDC 73555-502-00)

Store tablets at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Keep in original container until dispensed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) and Instructions for Use.

Differentiation Syndrome

Advise patients of the risks of developing differentiation syndrome as early as 1 day after the start of therapy and during treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, rash, low blood pressure, rapid weight gain, swelling of their arms or legs, or decreased urinary output, to their healthcare provider for further evaluation *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Prolonged QT Interval

Advise patients to consult their healthcare provider immediately if they feel faint, lose consciousness, or have signs or symptoms suggestive of arrhythmia. Advise patients with a history of hypokalemia or hypomagnesemia of the importance of monitoring their electrolytes *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to notify their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with REVUFORJ and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with REVUFORJ and for 4 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation
Advise women not to breastfeed during treatment with REVUFORJ and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility
Advise females and males of reproductive potential of the potential for impaired fertility from REVUFORJ *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Drug Interactions
Advise patients to inform their healthcare providers of all concomitant products, including over-the counter products and supplements *[see Drug Interactions (7.1)]*.

Dosing Instructions

Advise patients to swallow tablets whole with a cup of water and not to cut or chew tablets. If patients are unable to swallow the tablets, they may be crushed and dispersed in water *[see Instructions for Use].* Instruct patients that, if they miss a dose of REVUFORJ, to take it as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose, and return to the normal schedule the following day *[see Dosage and Administration (2.2)]*.

Manufactured for
Syndax Pharmaceuticals, Inc., Waltham, MA 02451
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218944-SYND-USPI-001

Medication Guide

REVUFORJ (REV-you-forge)

(revumenib)

tablets, for oral use

What is the most important information I should know about REVUFORJ?

REVUFORJ may cause serious side effects including:

- **differentiation syndrome.** Differentiation syndrome is a serious, but common condition that affects your blood cells which may be life threatening or lead to death if not treated. Differentiation syndrome has happened as early as 3 days and up to 41 days after starting REVUFORJ. Tell any healthcare provider caring for you that you are taking a medicine that can cause differentiation syndrome. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome during treatment with REVUFORJ:
  - fever
  - cough
  - shortness of breath
  - severe headache
  - confusion
  - dizziness or lightheadedness
  - fast weight gain
  - swelling of arms, legs, neck, groin, or underarm area
  - decreased urination

  If you develop any of these symptoms of differentiation syndrome, your healthcare provider may start you on a medicine given through a vein (intravenous) called corticosteroids and may monitor you in the hospital.

See **"What are the possible side effects of REVUFORJ?"** for more information about side effects.

What is REVUFORJ?

REVUFORJ is a prescription medicine used to treat adults and children 1 year and older with acute leukemia with a lysine methyltransferase 2A gene translocation (KMT2A) whose disease has come back or has not improved after previous treatment(s).

Your healthcare provider will perform a test to make sure that REVUFORJ is right for you.

It is not known if REVUFORJ is safe and effective in children less than 1 year of age.

Before taking REVUFORJ, tell your healthcare provider about all of your medical conditions, including if you:

- have any heart problems, including a condition called long QT syndrome.
- have been told you have low blood levels of potassium or magnesium.
- are pregnant or plan to become pregnant. REVUFORJ can harm your unborn baby.
  - Your healthcare provider will perform a pregnancy test within 7 days before you start treatment with REVUFORJ. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with REVUFORJ.
  - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with REVUFORJ and for 4 months after the last dose of REVUFORJ.
  - **Males** who have female partners who are able to become pregnant should use effective birth control during treatment with REVUFORJ and for 4 months after the last dose of REVUFORJ.
  - Talk to your healthcare provider about birth control methods you can use during this time.
- are breastfeeding or plan to breastfeed. It is not known if REVUFORJ passes into your breast milk. **Do not** breastfeed during your treatment with REVUFORJ or for 1 week after your last dose of REVUFORJ.

Tell your healthcare provider about any other medications you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

REVUFORJ and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take REVUFORJ?

- **Take REVUFORJ exactly as your healthcare provider tells you to**. **Do not** change your dose or stop taking REVUFORJ unless your healthcare provider tells you to.
- REVUFORJ tablets come in different strengths. Each strength is a different color. Your healthcare provider may prescribe more than 1 strength of REVUFORJ tablets for you, so it is important that you understand how to take your medicine the right way. Be sure that you understand exactly how many tablets you need to take, and what strengths to take.
- Take REVUFORJ 2 times a day at about the same time each day about 12 hours apart.

- REVUFORJ can be taken fasted or with a low-fat meal.
- Swallow REVUFORJ tablets whole with a cup of water. If you are unable to swallow tablets, crush the tablets and break them apart in water. See the **Instructions for Use** for detailed instructions on how to prepare and give REVUFORJ tablets. **Do not** cut or chew tablets.
- If you miss a dose of REVUFORJ or did not take it at the usual time, take your dose as soon as possible and at least 12 hours before your next dose. **Do not** take 2 doses within 12 hours. Return to your normal scheduled dose the following day.

What are the possible side effects of REVUFORJ?

REVUFORJ may cause serious side effects including:

- see **"What is the most important information I should know about REVUFORJ?"**
- **changes in electrical activity of your heart called QT prolongation.** QT prolongation is a serious, but common side effect that can cause irregular heartbeats that can be life-threatening or lead to death. Your healthcare provider will check the electrical activity of your heart with a test called an electrocardiogram (ECG) and will also do blood tests to check your potassium and magnesium levels before and during treatment with REVUFORJ. Tell your healthcare provider right away if you feel faint, lightheaded, dizzy, or if you feel your heart beating irregularly or fast during treatment with REVUFORJ.

The most common side effects of REVUFORJ include:

- bleeding (hemorrhage)
- nausea and vomiting
- muscle pain
- infections, including bacterial and viral infections
- low white blood cell counts with fever
- diarrhea
- changes in liver function tests
- swelling in the arms and legs
- decreased appetite
- constipation
- tiredness

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with REVUFORJ if you develop certain side effects.

REVUFORJ may cause fertility problems in females and males. Talk to your healthcare provider if this is a concern for you.

These are not all possible side effects of REVUFORJ.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store REVUFORJ?

- Store REVUFORJ at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the tablets in the bottle that it comes in until you are ready to take it.
- The REVUFORJ bottle has a drying agent (desiccant) and child resistant closure.

Keep REVUFORJ and all medicines out of reach of children.

General information about the safe and effective use of REVUFORJ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REVUFORJ for a condition for which it is not prescribed. Do not give REVUFORJ to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or health professionals for information about REVUFORJ that is written for healthcare professionals.

What are the ingredients in REVUFORJ?

Active ingredient: revumenib

Inactive ingredients: microcrystalline cellulose, dicalcium phosphate, crospovidone, hypromellose, sodium bicarbonate, hydrophobic colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and red iron oxide.

The 110 mg tablet also includes yellow iron oxide.

The 160 mg tablet also includes FD&C blue #2/indigo carmine aluminum lake.

Manufactured for: Syndax Pharmaceuticals, Inc., Waltham, MA 02451
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For more information, go to www.revuforj.com or call Syndax at 1-888-539-3REV.
218944-SYND-MG-001

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INSTRUCTIONS FOR USE
REVUFORJ (REV-you-forge)
revumenib tablets, for oral use

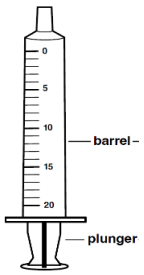
Read these Instructions for Use to prepare and take or give a dose of REVUFORJ tablets broken apart (dispersed) in water and each time you or your child get a prescription refill. There may be new information. This information does not take the place of talking with your healthcare provider about you or your child's medical condition or your treatment.

Important information you need to know before preparing to break apart the REVUFORJ tablets in water:

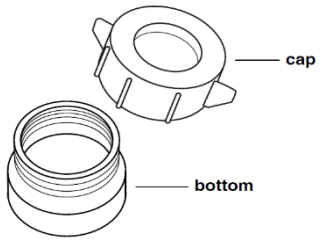
- For more information about REVUFORJ tablets, see the Medication Guide.
- **REVUFORJ tablets broken apart in water should be prepared for people who are unable to swallow whole REVUFORJ tablets. People who can swallow the tablets whole should not cut, chew, or break the tablets apart in water.**
- Take or give REVUFORJ tablets exactly as your healthcare provider tells you to. **Do not** change your dose or stop taking REVUFORJ unless your provider tells you to.
- REVUFORJ tablets come in different strengths. Each strength is a different color. Your healthcare provider may prescribe more than 1 strength of REVUFORJ tablets for you or your child, so it is important that you understand how to take or give the medicine the right way. Be sure that you understand exactly how many tablets you need to take, and what strengths to take.
- Check the expiration date on the REVUFORJ tablet bottles. **Do not** use REVUFORJ if the expiration date on the bottles have passed. Contact your healthcare provider or pharmacist.
- The REVUFORJ tablets should be crushed in a clean and dry pill crusher.
- Use room temperature water to dissolve the REVUFORJ tablets.
- Use a teaspoon to measure the room temperature water. Use a 20 mL oral syringe to administer the medicine.
  - Oral syringes can look different. Talk to your pharmacist if you are not sure if you have the correct oral syringe size.
  - Replace the oral syringe if there are signs of damage. **See Step 15**.

Supplies needed to prepare and break apart the REVUFORJ tablets in water. You will need to get the 20 mL oral syringe and pill crusher, which are available from your pharmacy.

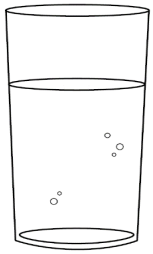
Figure A



20 mL Oral Syringe

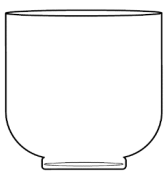


Pill Crusher

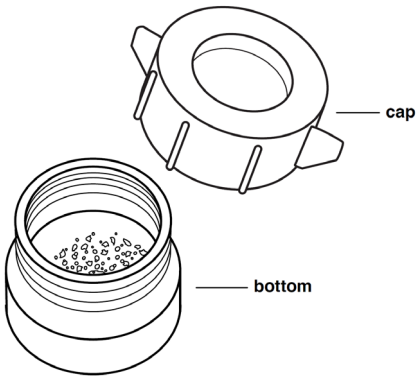
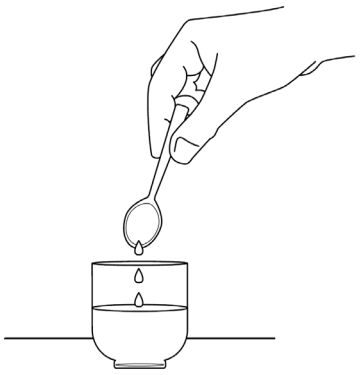
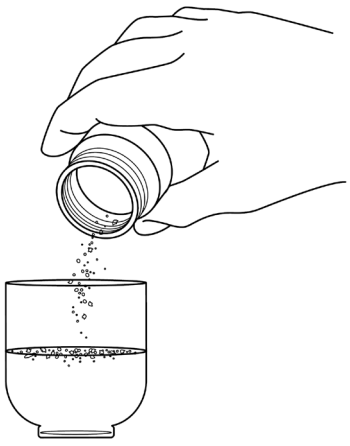


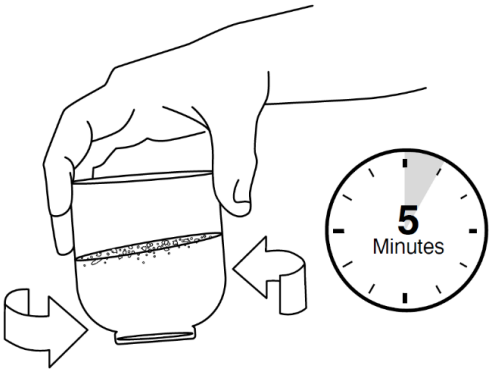
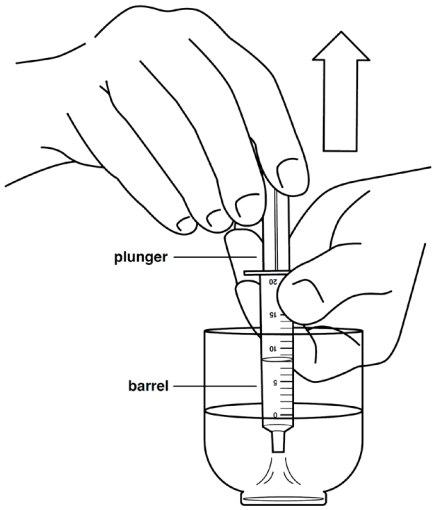
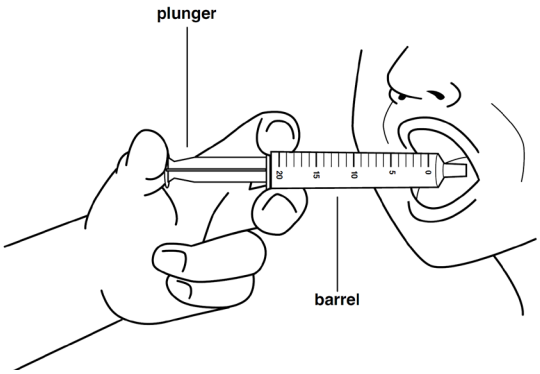
Room Temperature Water

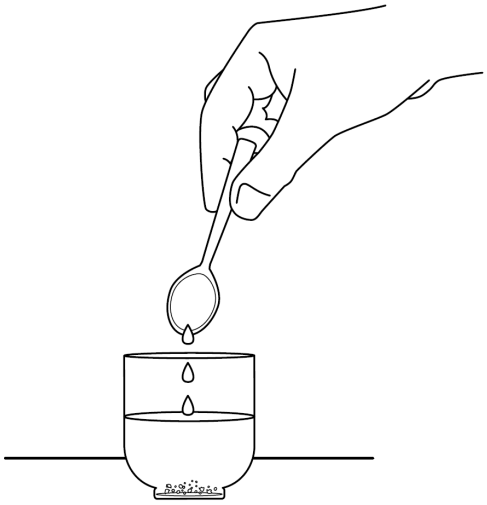
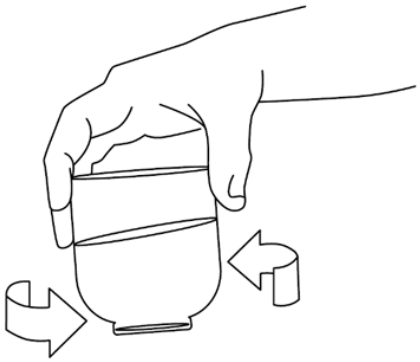
1 Teaspoon

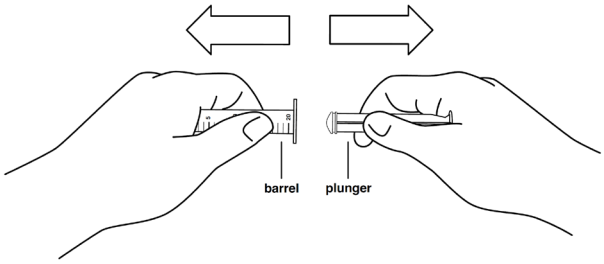
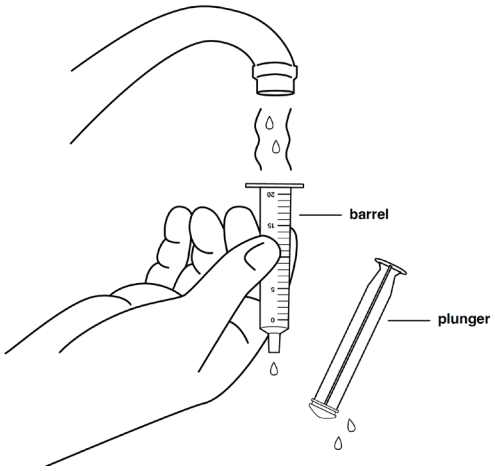
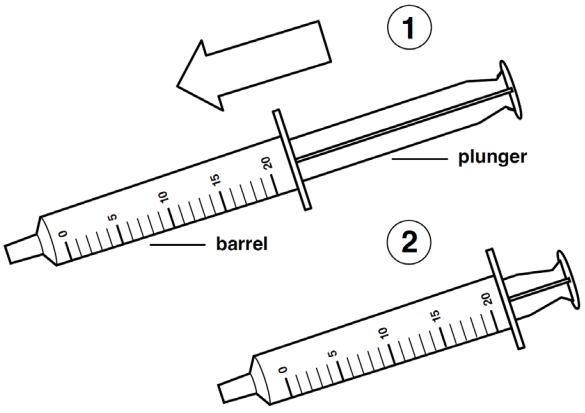


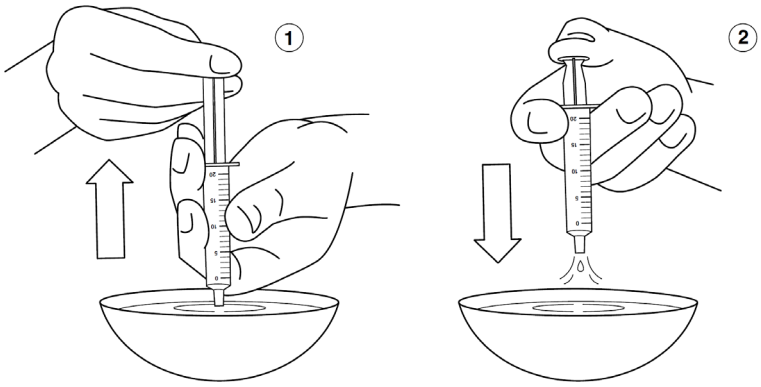
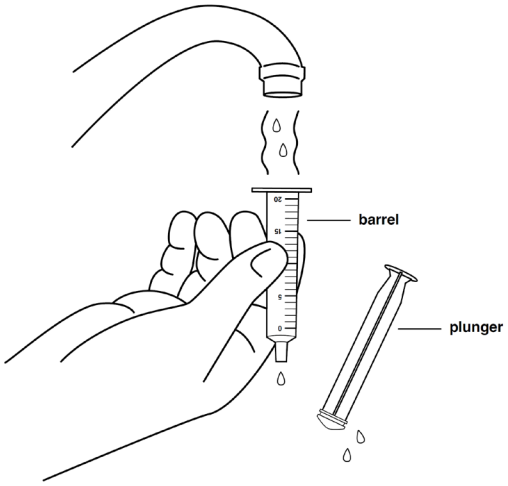
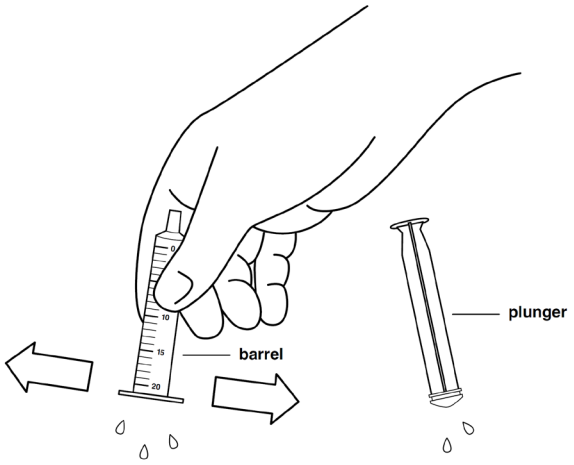
Small Plastic or Glass Cup

Preparing to dissolve the REVUFORJ tablets	
Step 1: Gather and place the REVUFORJ bottles and supplies on a clean, flat surface. Check your prescribed dose. Count out the strengths and number of REVUFORJ tablets needed for the prescribed dose. Add all the REVUFORJ tablets to a clean and dry pill crusher. Screw the top of the pill crusher down until it touches the REVUFORJ tablets. Turn the pill crusher cap back and forth to crush the REVUFORJ tablets. Continue turning the pill crusher cap back and forth, increasing the crushing pressure on the REVUFORJ tablets each time. Repeat until all large REVUFORJ tablet pieces are broken up. The crushed REVUFORJ tablets should be like the consistency of flour.	**Figure B** 
Step 2: Use **two** teaspoons to measure 10 mL of room temperature water. Add the 10 mL of water to the small cup. **Add water to the cup first and then add the crushed REVUFORJ tablets.** **Do not add the crushed REVUFORJ tablets first followed by the room temperature water.**	**Figure C** 
Step 3: Tip the crushed REVUFORJ tablets from the pill crusher into the small cup that contains 10 mL of water. Carefully add all of the crushed REVUFORJ tablets to the small cup. Hold the pill crusher upside down over the small cup. Tap the pill crusher to make sure no more crushed REVUFORJ tablet pieces are left in the pill crusher.	**Figure D** 

Step 4: Carefully swirl the cup right after adding the crushed REVUFORJ tablets to the small cup with water. Swirl the small cup every 30 seconds to 1 minute for a total of **5 minutes**. The crushed REVUFORJ tablets in water will look cloudy**.**	**Figure E** 
Step 5: Draw up the medicine into the 20 mL oral syringe right away. Push the plunger of the oral syringe all the way up towards the tip. Place the tip of the oral syringe in the small cup. Pull the oral syringe plunger to draw up all of the medicine in the small cup. The medicine must be taken within **2 hours** of preparation. Turn the oral syringe upside down and back several times before taking or giving the medicine.	**Figure F** 
Step 6: The adult or child should sit up straight or stand before taking the medicine. Place the tip of the oral syringe into the mouth against the inside of the cheek. Slowly and gently press down on the plunger to gently squirt the medicine into the mouth. Allow the adult or child to swallow the medicine. Make sure that no medicine is left in the mouth. The adult or child should remain sitting up straight or standing for 2 to 3 minutes right after receiving a dose of the medicine. If the medicine is vomited or all of the medicine is not swallowed, do not give another dose. Wait until the next scheduled dose.	**Figure G** 

Step 7: The small cup must be rinsed to make sure the adult or child receives the full dose of REVUFORJ tablets. Place **two** teaspoons (10 mL) of room temperature water in the cup rinsing down the sides (Figure H) Swirl the water around the sides of the small cup to make sure any remaining crushed REVUFORJ tablets is mixed with the water (Figure I).	**Figure H**  **Figure I** 
Step 8: Repeat **Step 5** and **Step 6 until no more medicine is left in the cup**.	

Cleaning the oral syringe after use	
Follow the instructions below for cleaning and storing the oral syringe (**Step 9 through Step 15**). Throw away the oral syringe in your household trash if it is damaged (**See Step 15**), and use a new 20 mL oral syringe.	
Step 9: Remove the plunger from the barrel of the oral syringe.	**Figure J** 
Step 10: Rinse the barrel and plunger in warm running water to help make sure all of the medicine has been removed from the oral syringe. **Do not** boil the oral syringe.	**Figure K** 
Step 11: Put the plunger into the barrel of the oral syringe.	**Figure L** 

Step 12: Hold the oral syringe tip under water and draw warm water several times into the oral syringe and squirt out again until all of the medicine has been removed from the oral syringe. **Repeat this Step until the oral syringe is clean.**	**Figure M** 
Step 13: Remove the plunger from the barrel of the oral syringe. Rinse the barrel and plunger again with warm water.	**Figure N** 
Step 14: Shake off excess water or wipe off the outside of the plunger and barrel. Place the barrel and plunger on a clean, dry paper towel to dry.	**Figure O** 

Step 15: Make sure the oral syringe parts are fully dry before putting the plunger back into the barrel of the oral syringe. Store the oral syringe in a clean place until the next use. Replace the oral syringe if: • there is any damage to the barrel, plunger, or tip. • you cannot see the dosage markings or it becomes difficult to move the plunger.
Cleaning the pill crusher after use
Step 16: Rinse both parts of the pill crusher with water after use. Shake off excess water or wipe both parts of the pill crusher. Place both parts of the pill crusher on a clean, dry paper towel to dry.

Storing REVUFORJ

- Store REVUFORJ at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the tablets in the bottle that it comes in until you are ready to take it.
- The REVUFORJ bottle has a drying agent (desiccant) and child resistant closure.

Keep REVUFORJ and all medicines out of reach of children.

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