NEW DRUG APPROVAL

Brand Name	Rezlidhia™
Generic Name	olutasidenib
Drug Manufacturer	Metrics Contract Services

New Drug Approval

FDA approval date: December 01, 2022

Review designation: Standard; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215814

Dispensing restriction: Specialty Pharmacy Required

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Acute myeloid leukemia (AML) is characterized by a clonal proliferation of myeloid precursors with a reduced capacity to differentiate into more mature cellular elements. As a result, there is an accumulation of leukemic blasts or immature forms in the bone marrow, peripheral blood, and occasionally in other tissues, with a variable reduction in the production of normal red blood cells, platelets, and mature granulocytes. The increased production of malignant cells, along with a reduction in these mature elements, results in a variety of systemic consequences including anemia, bleeding, and an increased risk of infection.

AML is one of the most common types of leukemia in adults, with about 20,000 new cases reported in the United States each year. Isocitrate dehydrogenase-1 (IDH1) mutations are seen in about 6% to 10% of patients with AML and tend to be associated with a poorer prognosis. Although the majority of patients with AML initially respond to induction chemotherapy and achieve a complete remission, most will eventually relapse.

Efficacy

Acute Myeloid Leukemia

The efficacy of Rezlidhia™ was evaluated in an open-label, single-arm, multicenter clinical trial (Study 2102-HEM-101, NCT02719574) in 147 adult patients with relapsed or refractory AML with an IDH1 mutation. IDH1 mutations in blood or bone marrow were confirmed retrospectively using the Abbott RealTimeTM IDH1 Assay. Rezlidhia™ was given orally at a dose of 150 mg twice daily until disease progression, development of unacceptable toxicity, or hematopoietic stem cell transplantation. Sixteen of the 147 patients (11%) underwent stem cell transplantation following Rezlidhia™ treatment.

The baseline demographic and disease characteristics are shown in Table 1.

Table 1: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML (Study 2102-HEM-101)

Demographic and Disease Characteristics	Rezlidhia™ (150 mg twice daily) N=147
Demographics	
Age (Years) Median (Min, Max)	71 (32, 87)
Age Categories, n (%)	
<65 years	37 (25)

≥65 years to <75 years	65 (44)
≥75 years	45 (31)
Sex, n (%)	
Male	74 (50)
Female	73 (50)
Race, n (%)	
White	67 (46)
Black or African American	5 (3)
Asian	5 (3)
Native Hawaiian/Other Pacific Islander	0 (0)
Other/Not provided	70 (48)
Disease Characteristics	
ECOG PS, n (%)	
0	45 (31)
1	76 (52)
2	23 (16)
IDH1 Mutation, n (%)[1]	
R132C	85 (58)
R132H	35 (24)
R132G	12 (8)
R132S	11 (7)
R132L	4 (3)
Type of AML, n (%)	
De novo AML	97 (66)
Secondary AML	50 (34)
Cytogenetic Risk Status[2], n (%)	
Favorable	6 (4)
Intermediate	107 (73)
Poor	25 (17)
Unknown	9 (6)
Relapsed/Refractory Patient Category	
Primary Refractory	46 (31)
Untreated Relapse[3]	81 (55)
Refractory Relapse[3]	20 (14)
Demographic and Disease Characteristics	**Rezlidhia™ (150 mg twice daily) N=147**
Relapse Number	
0	46 (31)
1	87 (59)
2	11 (8)
≥3	3 (2)
Prior Stem Cell Transplantation for AML, n (%)	17 (12)

Transfusion Dependent at Baseline[4], n (%)	86 (59)
Median Number of Prior Therapies (Min, Max)	2 (1,7)

[1]Using central IDH1 assay testing results.
[2]Cytogenetic risk categorization was investigator reported by NCCN or ELN guidelines.
[3]May be first or subsequent relapse
[4]Transfusion-Dependent at Baseline is defined as receiving a transfusion within 8 weeks prior to first dose of olutasidenib or noting transfusion dependence prior to coming on study.

Efficacy was established on the basis of the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 2. The median follow-up was 10.2 months (range: 0.2 to 38.1 months) and median treatment duration was 4.7 months (range: 0.1 to 26.0 months).

Table 2: Efficacy Results in Patients with Relapsed or Refractory AML (Study 2102-HEM-101)

Endpoint	Rezlidhia™ (150 mg twice daily) N=147
CR+CRh[1,2] n (%) **95% CI** **Median DOCR+CRh[3] (months)** **95% CI**	51 (35) (27, 43) 25.9 (13.5, NR)
CR[1] n (%) **95% CI** **Median DOCR[3] (months)** **95% CI**	47 (32) (25, 40) 28.1 (13.8, NR)
CRh[1] n (%) **95% CI** **Observed DOCRh[3] (months)**	4 (2.7) (0.7, 6.8) 1.8, 5.6, 13.5, 28.5+

CI: confidence interval; NR = not reached
[1] CR (complete remission) was defined as 100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter); CRh (complete remission with partial hematologic recovery) was defined as < 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).
[2] CR+CRh rate was consistent across all baseline demographic and baseline disease characteristic subgroups with the exception of IDH1 R132H mutation (CR+CRh 17%).
[3] Duration of response is defined as the time from the date of the first response to the date of the relapse or death. Patients who did not relapse were censored at the date of last response assessment. + indicates censored observation.
Of the patients who achieved a CR or CRh, the median time to CR or CRh was 1.9 months (range: 0.9 to 5.6 months). All patients that achieved a best response of CR or CRh did so within 5.6 months of initiating Rezlidhia™.
Overall, among the 86 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 29 (34%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 61 patients who were independent of both RBC and platelet transfusions at baseline, 39 (64%) remained transfusion independent during any 56-day postbaseline period.
The most common (20%) adverse reactions, including laboratory abnormalities, are aspartate aminotransferase increased, alanine aminotransferase increased, potassium decreased, sodium decreased, alkaline phosphatase increased, nausea, creatinine increased, fatigue/malaise, arthralgia, constipation, lymphocytes increased, bilirubin

increased, leukocytosis, uric acid increased, dyspnea, pyrexia, rash, lipase increased, mucositis, diarrhea and transaminitis.

Safety

ADVERSE EVENTS

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WARNINGS & PRECAUTIONS

Differentiation Syndrome

Rezlidhia™ can cause differentiation syndrome. In the clinical trial of Rezlidhia™ in patients with relapsed or refractory AML, differentiation syndrome occurred in 16% (25/153) of patients, with grade 3 or 4 differentiation syndrome occurring in 8% of patients treated, and fatalities in 1% of patients.Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal. Symptoms of differentiation syndrome in patients treated with Rezlidhia™ included leukocytosis, dyspnea, pulmonary infiltrates/pleuropericardial effusion, kidney injury, fever, edema, pyrexia, and weight gain. Of the 25 patients who experienced differentiation syndrome, 19 (76%) recovered after treatment or after dosage interruption of Rezlidhia™. Differentiation syndrome occurred as early as 1 day and up to 18 months after Rezlidhia™ initiation and has been observed with or without concomitant leukocytosis.
If differentiation syndrome is suspected, temporarily withhold Rezlidhia™ and initiate systemic corticosteroids (e.g., dexamethasone 10 mg IV every 12 hours) for a minimum of 3 days and until resolution of signs and symptoms. If concomitant leukocytosis is observed, initiate treatment with hydroxyurea, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms. Differentiation syndrome may recur with premature discontinuation of corticosteroids and/or hydroxyurea treatment. Institute supportive measures and hemodynamic monitoring until improvement; withhold dose of Rezlidhia™ and consider dose reduction based on recurrence.

Hepatotoxicity

Rezlidhia™ can cause hepatotoxicity, presenting as increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood alkaline phosphatase, and/or elevated bilirubin. Of 153 patients with relapsed or refractory AML who received Rezlidhia™, hepatotoxicity occurred in 23% of patients; 13% experienced grade 3 or 4 hepatotoxicity. One patient treated with Rezlidhia™ in combination with azacitidine in the clinical trial, a combination for which Rezlidhia™ is not indicated, died from complications of drug-induced liver injury. The median time to onset of hepatotoxicity in patients with relapsed or refractory AML treated with Rezlidhia™ was 1.2 months (range: 1 day to 17.5 months) after Rezlidhia™ initiation, and the median time to resolution was 12 days (range: 1 day to 17 months). The most common hepatotoxicities were elevations of ALT, AST, blood alkaline phosphatase, and blood bilirubin. Monitor patients frequently for clinical symptoms of hepatic dysfunction such as fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Obtain baseline liver function tests prior to initiation of Rezlidhia™, at least once weekly for the first two months, once every other week for the third month, once in the fourth month, and once every other month for the duration of therapy. If hepatic dysfunction occurs, withhold, reduce, or permanently discontinue Rezlidhia™ based on recurrence/severity

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Olutasidenib is a small-molecule inhibitor of mutated isocitrate dehydrogenase-1 (IDH1). In patients with AML, susceptible IDH1 mutations are defined as those leading to increased levels of 2- hydroxyglutarate (2-HG) in the leukemia cells and where efficacy is predicted by 1) clinically meaningful remissions with the recommended dose of olutasidenib and/or 2) inhibition of mutant IDH1 enzymatic activity at concentrations of olutasidenib sustainable at the recommended dosage according to validated methods. The most common of such mutations in patients with AML are R132H and R132C substitutions. In vitro, olutasidenib inhibited mutated IDH1 R132H, R132L, R132S, R132G, and R132C proteins; wild-type IDH1 or mutated IDH2 proteins were not inhibited. Olutasidenib inhibition of mutant IDH1 led to decreased 2-HG levels in vitro and in in vivo xenograft models.

Dose & Administration

ADULTS

150 mg orally twice daily, until disease progression or unacceptable toxicity.
Take on an empty stomach at least 1 hour before or 2 hours after a meal.

PEDIATRICS

The safety and effectiveness of Rezlidhia™ have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage modification is recommended for patients with mild to moderate renal impairment.

HEPATIC IMPAIRMENT

No dosage modification is recommended for patients with mild (total bilirubin ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 150 mg