CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215814Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
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Reviewer Name(s)	Celeste Karpow, PharmD, MPH
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Review Completion Date	November 29, 2022
Subject	Evaluation of Need for a REMS
Established Name	olutasidenib
Trade Name	Rezlidhia
Name of Applicant	Forma Therapeutics, Inc.
Therapeutic Class	Isocitrate dehydrogenase-1 (IDH1) inhibitor
Formulation(s)	Capsules
Dosing Regimen	150 mg orally every 12 hours

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rezlidhia (olutasidenib) is necessary to ensure the benefits outweigh its risks. Forma Therapeutics, Inc. submitted a New Drug Application (NDA) 215814 for olutasidenib with the proposed indication for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (R/R AML) with a susceptible IDH1 mutation. The FDA approved indication will be for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test. The risks associated with olutasidenib include differentiation syndrome and hepatotoxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Hematologic Malignancies I (DHMI) determined that a REMS is not needed to ensure the benefits of olutasidenib outweigh its risks. The efficacy of olutasidenib in adult patients with relapsed or refractory AML with a susceptible isocitrate dehydrogenase -1 (IDH1) mutation patients was supported by Study 2102-HEM-101 in which the primary endpoint of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), or CR+CRh was achieved in 51/147 (35%). As with other isocitrate dehydrogenase (IDH) inhibitors for this indication, the serious risk of differentiation syndrome will be addressed in a boxed warning, and the warnings and precautions section of the label will include recommendations for management. There will be a medication guide included with the labeling to inform patients on the risks. The likely prescribers will be oncologists and hematologists who are expected to be familiar managing the serious adverse events including differentiation syndrome and hepatotoxicity reported with olutasidenib as they are similar to other IDH inhibitors approved to treat adult patients with relapsed or refractory AML with a susceptible IDH mutation.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rezlidhia (olutasidenib) is necessary to ensure the benefits outweigh its risks. Forma Therapeutics, Inc. submitted a New Drug Application (NDA) 215814 for olutasidenib with the proposed indication treatment of adult patients with relapsed or refractory acute myeloid leukemia (R/R AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation. The FDA approved indication will be for the treatment of adult patients with relapsed or refractory AML with a susceptible IDH1 mutation as detected by an FDA-approved test. This application is under review in the Division of Hematologic Malignancies 1 (DHM1). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Rezlidhia (olutasidenib), a new molecular entity[a], is an isocitrate dehydrogenase-1 (IDH1) inhibitor, proposed for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.[1] Isocitrate dehydrogenases (IDH) catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) during cellular metabolism. Mutations of the IDH1 isoform are found in 6-16% of patients with AML.[12] Increased cellular 2-hydroxyglutarate (2-HG) levels contribute to epigenetic mechanisms of pathogenesis by inhibiting α-KG-dependent enzymes important for normal DNA methylation.[12] Olutasidenib lowers 2-hydroxyglutarate (2-HG) levels by inhibition of mutated IDH1 leading to restoration of normal cellular differentiation.[12]

Olutasidenib is proposed as 150 mg capsule to be taken orally every 12 hours, until disease progression or unacceptable toxicity.[b,1] Olutasidenib is not currently approved in any jurisdiction, and has not been granted breakthrough therapy or fast track designation.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215814 relevant to this review:

- 04/27/2017: Orphan drug designation granted
- 02/15/2022: NDA 215814 submission for treatment of adult patients with relapsed or refractory AML with susceptible IDH1 mutation.
- 07/28/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for olutasidenib.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

AML is a group of aggressive blood cancers characterized by infiltration of the blood, bone marrow, and other tissues by proliferative, clonal, poorly differentiated cells of the hematopoietic system.[2,3] The cause of AML is predominantly idiopathic however it can arise in patients with an underlying hematological disorder or as a consequence of prior chemotherapy.[3,4] The pathophysiology of AML

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

consists of a maturational arrest of bone marrow cells in the earliest stages of development. The mechanism of this arrest is under study, but in many cases, it involves the activation of abnormal genes through chromosomal translocations and other genetic abnormalities. This developmental arrest results in two disease processes. First, the production of normal blood cells markedly decreases, which results in varying degrees of anemia, thrombocytopenia, and neutropenia. Second, the rapid proliferation of these cells, along with a reduction in their ability to undergo programmed cell death, results in their accumulation in the bone marrow, the blood, the spleen, and the liver.[4,5]

While AML is the second most common category of leukemia in adults and the most common type of acute leukemia, it is rare.[2] The American Cancer Society estimates approximately 20,050 new cases of AML and approximately 11,540 deaths from AML in the United States in 2022.[c,6] According to the National Cancer Institute's SEER database, between 2012-2018, the 5-year relative survival rate for patients diagnosed with AML was 30.5%.[d,6]

The median age at diagnosis is approximately 68 years of age and is uncommon before the age of 45.[2] Age is an important prognostic factor for AML with significantly worse outcomes among patients older than 60 years due to differences in tumor biology which confers resistance and patient characteristics (e.g., impaired performance status) that reduce treatment tolerance.[7] In addition, multidrug resistance gene expression, WBC greater than 100,000 cells/mm^3, and patients who develop "secondary" leukemia after treatment of another malignancy generally have an unfavorable prognosis.[7]

3.2. Description of Current Treatment Options

The primary goal of AML treatment is to rapidly achieve a complete clinical and hematologic remission defined as the disappearance of all clinical and bone marrow evidence (normal cellularity more than 20% with less than 5% blasts) of leukemia, with restoration of normal hematopoiesis (neutrophils more than or equal to 1,000 cells/mm^3 [1×10^9/L] and platelets more than 100,000 cells/mm^3 [100×10^9/L]).[7] Once complete remission is achieved, the goal is to maintain the patient in continuous complete remission.[7] Relapse in the bone marrow reduces the likelihood of cure. If relapse occurs, the treatment options include clinical trials, additional chemotherapy, and supportive care depending on the patient's clinical status.[7] Recent advances in antineoplastic therapy and supportive care has resulted in 20% - 40% becoming long-term survivors.[7]

Standard treatment for AML has not changed in several decades.[7] AML treatment consists of induction and post remission therapy, such as consolidation and intensification.[7] The most common regimen combines daunorubicin administered as a short infusion of 60 to 90 mg/m^2/day on days 1 to 3, along with cytarabine administered as a continuous 24 hour infusion of 100 to 200 mg/m^2/day on days 1 to 7.[7]

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is the most aggressive post remission therapy for AML.[7]

Treatment of relapsed or refractory AML is a therapeutic challenge.[7] The most common cause of treatment failure in AML receiving either chemotherapy or HSCT is relapse.[7] Furthermore, older patients may have refractory disease in which they are unable to achieve complete remission after 2 courses of induction therapy.[7] Salvage chemotherapy regimens that may be used in relapsed or refractory AML include:

- Fludarabine, cytarabine, idarubicin and a granulocyte colony stimulating factor
- Mitoxantrone, etoposide, cytarabine
- Clofarabine, high dose cytarabine, and priming granulocyte colony stimulating factor

In patients unfit to receive the aforementioned regimens, a less aggressive option is the azacitidine or decitabine.[7] There are also novel classes for treatment of relapsed or refractory AML including FLT3 inhibitors (e.g., midostaurin, gilteritinib), IDH (e.g., enasidenib, ivosidenib), Hedgehog inhibitors (glasdegib) and BCL2 inhibitors (venetoclax).[7] Products used to treat relapsed or refractory AML are summarized in Table 1 in the Appendix.

4. Benefit Assessment

The efficacy of olutasidenib was evaluated in Study 2102-HEM-101 (NCT02719574), an ongoing Phase 1/2, multicenter, open-label, single-arm study in patients with AML or myelodysplastic syndrome with an IDH1-R132 mutation.[8] Cohort 1 included adult patients with R/R AML who received olutasidenib at the proposed dose of 150 mg twice daily until disease progression, relapse, unacceptable toxicity, HSCT, withdrawal of consent, or other withdrawal criteria were met.[8] Efficacy was established on the basis of the rate of CR+CRh, the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence.[1] The primary endpoint of CR+CRh was achieved in 51/147 (35%). Secondary endpoints of CR was achieved in 47/147 (32%) of patients and CRh was achieved in 4/147 (2.7%).[8] The clinical reviewer's conclusion is that study HEM 101 showed similar CR+CRh rate (32% with 95% CI: 25, 40) compared to the approved ivosidenib (33% with 95% CI: 26, 40; data source: ivosidenib USPI).[e,8] The results from the interim analysis passed the efficacy criteria.[8] In addition, Study HEM 101 showed similar CR+CRh time to response (median 1.9 months; range, 0.9 to 5.6 months; data source: draft prescribing information for olutasidenib) compared to ivosidenib (median 2 months; range, 0.9 to 5.6 months; data source: ivosidenib USPI).[1,8] The duration of CR+CRh was 25.9 months (95% confidence interval (13.5, not reached)).[1] The rate of conversion from transfusion dependence to transfusion independence is characterized among the 86 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, in which 29 (34%) became independent of RBC and platelet transfusions during any 56-day post-baseline period.[1] The clinical reviewer concluded the Applicant provided substantial evidence of effectiveness based on the rate of CR+CRh, the duration of CR+CRh, and the rate of

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

conversion from transfusion dependence to transfusion independence, and recommends approval of olutasidenib for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test.[1]

5. Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for olutasidenib. The safety of olutasidenib was evaluated in 153 adults with R/R AML with an IDH1 mutation in Study 2102-HEM-101, who received olutasidenib 150 mg twice daily.[1] The median duration of exposure to olutasidenib was 4.7 months (range: 0.1 to 34 months).[1] Thirty-five percent of patients were exposed to olutasidenib for at least 6 months and 21% were exposed for at least 1 year.[1] The most common adverse reactions (≥20%) were aspartate aminotransferase increased, alanine aminotransferase increased, potassium decreased, sodium decreased, nausea, creatinine increased, fatigue/malaise, arthralgia, constipation, lymphocytes increased, bilirubin increased, leukocytosis, uric acid increased, dyspnea, rash, lipase increased, mucositis, diarrhea and transaminitis.[1]

Deaths

There were a total of 73/153 (48%) deaths.[8] Most of the deaths due to TEAEs were due to disease progression 21/153 (14%) and death from AML.[8] There were 45/153 (29%) of TEAEs leading to death.[8] Most of the deaths were related to complications from AML, such as infection and/or bleeding complications.[8] Fatal adverse reactions occurred in (b) (4)% of patients who received olutasidenib, including (b) (4) differentiation syndrome (1%).[1] The TEAEs that caused death in more than 1 patient included intracranial hemorrhage 4/153 (2.6%), pneumonia 3/153 (2%), dyspnea 3/153 (2%), and sepsis. 3/153 (2%).[8]

Serious Adverse Events (SAE)

Serious adverse reactions in ≥5% included differentiation syndrome (9%) and transaminitis (6%). Adverse reactions leading to permanent discontinuation occurred in 8% of patients. The adverse reactions leading to permanent discontinuation in ≥ 1% of patients included transaminitis, differentiation syndrome, and dyspnea. Adverse reactions leading to dosage interruptions occurred in 32% of patients. The adverse reactions which required dosage interruption in >5% of patients included transaminitis and differentiation syndrome. Adverse reactions leading to dose reductions occurred in 11% of patients. Adverse reactions which required dose reductions in ≥ 2% of patients included transaminitis.

5.1. Differentiation Syndrome

Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal.[1] Symptoms of differentiation syndrome in patients treated with olutasidenib included leukocytosis, dyspnea, pulmonary infiltrates/pleuropericardial effusion, kidney injury, fever, edema, pyrexia, and weight gain.[1] In the clinical trial, differentiation syndrome occurred in 16% of patients, with grade 3 or 4 differentiation syndrome occurring in 8% of patients treated, and

fatalities in 1% of patients.[1] Of the 25 patients who experienced differentiation syndrome, 19 (76%) recovered after treatment or after dosage interruption of olutasidenib.[1] Differentiation syndrome occurred as early as 1 day and up to 18 months after olutasidenib initiation and has been observed with or without concomitant leukocytosis.[1]

Similar to the other approved IDH inhibitors, ivosidenib and enasidenib, labeling will include the risk of differentiation syndrome as a Boxed Warning.[9,10] Management of differentiation syndrome, including recommendations for initiating intravenous steroids and hemodynamic monitoring will be communicated in the Warnings and Precautions section of the label.[1] In addition, a Medication Guide as part of labeling will be included to inform patients regarding the potential risks of differentiation syndrome will also be included as part of the labeling. Monitoring and dosage modifications for toxicities to address the safety issues with olutasidenib will be included in the Dosage and Administration section of the label.[1]

5.2. Hepatotoxicity

In the clinical trial, hepatotoxicity occurred in 23% of patients, with grade 3 or 4 hepatotoxicity occurring in 13% of patients.[1] Hepatotoxicity presented as increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood alkaline phosphatase, and/or elevated bilirubin.[1] There were no Hy's Law cases, transplants, or deaths related to hepatoxicity. The median time to onset of hepatotoxicity was 1.2 months (range: 1 day to 17.5 months) after olutasidenib initiation, and the median time to resolution was 12 days (range: 1 day to 17 months).[1]

Many patients with hepatic TEAEs continued on treatment with or without dose reduction. Five patients discontinued olutasidenib due to hepatotoxicity. Of the 5 patients, 4 cases resolved and there is no follow-up information on the 5th patient. Labeling includes recommendations for monitoring and dose adjustments should hepatic dysfunction occur in the Warnings and Precautions, Dosing and Administration, and Patient Counseling sections. Specifically, labeling recommends that for Grade 3* hepatotoxicity:

- Withhold olutasidenib and monitor liver function tests, twice per week, until laboratory values have returned to baseline or Grade 1* toxicity.
- Resume olutasidenib at a reduced dose of 150 mg once daily and continue monitoring; may increase to 150 mg twice daily if hepatotoxicity resolves to baseline for at least 28 days.
- If hepatotoxicity (Grade 3) recurs at 150 mg once daily, discontinue olutasidenib.

If Grade 4 hepatotoxicity or AST or ALT >3x ULN and total bilirubin >2x ULN and alkaline phosphatase <2x ULN in the absence of a clear alternative explanation, labeling recommends to permanently discontinue olutasidenib.[1] In addition, Patient Counseling Information advises that patients should be counseled for the potential for hepatic effects and to immediately report any associated signs and symptoms such as right upper abdominal discomfort, dark urine, jaundice, anorexia, or fatigue to their healthcare provider for further evaluation.[1]

6. Expected Postmarket Use

If approved, olutasidenib will primarily be prescribed by oncologists or hematologists who are familiar with the management of chemotherapeutic toxicities such as differentiation syndrome and hepatotoxicity. We expect this product will be dispensed from both inpatient and outpatient pharmacy settings.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for olutasidenib beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of olutasidenib on the basis of the efficacy and safety information currently available.

AML is a group of aggressive blood cancers characterized by infiltration of the blood, bone marrow, and other tissues by proliferative, clonal, poorly differentiated cells of the hematopoietic system.[2,3] The estimated number of new cases of AML in the United States in 2022 is 20,050. Although recent advances in antineoplastic therapy and supportive care has resulted in 20% - 40% of AML patients becoming long-term survivors, relapse is the most common treatment failure.[7]

Olutasidenib is an IDH1 inhibitor proposed for the treatment of adult patients with relapsed or refractory AML with a susceptible IDH1 mutation as detected by an FDA-approved test. The efficacy of olutasidenib was supported by Study 2102-HEM-101 in which the primary endpoint of CR+CRh was achieved in 51/147 (35%), similar to other approved therapies for this indication.

The serious risks associated with olutasidenib include differentiation syndrome and hepatotoxicity. As with other products in the class, differentiation syndrome will be addressed in a boxed warning and warnings and precautions. The percent of patients who experienced serious adverse reactions who received olutasidenib in the clinical trial is lower than the percent of patients who experienced serious adverse reactions receiving other IDH inhibitors ivosidenib (34%) and enasidenib (77.1%) in their respective clinical trials.[1,9,10] In addition, the 16% of patients who experienced differentiation syndrome that received olutasidenib in the clinical trial is similar or lower than the percent of patients who experienced differentiation syndrome receiving other IDHI inhibitors ivosidenib (15%) and enasidenib (14%) in their respective clinical trial programs.[1,9,10] In another study, an analysis found that both ivosidenib and enasidenib cause differentiation syndrome in 19% of patients.[11] Overall, the results from Study 2102-HEM-101 suggest that olutasidenib is not more toxic compared to other approved and marketed IDH1 inhibitors ivosidenib and enasidenib.

The likely prescribers are oncologists and hematologists who are expected to have experience managing the adverse events reported with olutasidenib. Based on the efficacy and risks associated with olutasidenib for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test, this reviewer's recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, short-term benefits are meaningful for patients seeking improved quality of life while the median duration of treatment at this time is relatively short at 4.7 months, so long-term benefits are unknown. The risk evaluation suggests that olutasidenib is not more toxic than other approved products in the class. Therefore, a REMS is not necessary for olutasidenib at this time to ensure the benefits outweigh the risks. The management of the risks associated with olutasidenib can be communicated through labeling. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. Table 1

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Xospata (gilteritinib) 11/28/2018	treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.	120 mg orally once daily with or without food. Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response.	Differentiation syndrome, Posterior Reversible Encephalopathy Syndrome, Prolonged QT Interval , Pancreatitis, Embryo-Fetal Toxicity	Boxed warning, Warnings and Precautions, Medication Guide
Idhifa (enasidenib) 08/01/2017	treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.	100 mg taken orally once daily with or without food 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.	Differentiation syndrome, embryo-fetal toxicity	Boxed warning, Warnings and Precautions, Medication Guide
Tibsovo (ivosidenib) 07/20/2018	treatment of newly-diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive	500 mg taken orally once daily 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.	Differentiation Syndrome, QTc Interval Prolongation, Guillain-Barré Syndrome	Boxed warning, Warnings and Precautions, Medication Guide

	induction chemotherapy and relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test			
Depocyt (cytarabine) 04/01/1999	for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients. It has also been found useful in the treatment of acute non-lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of Cytarabine Injection (preservative free preparations only) is indicated in the prophylaxis and treatment of meningeal leukemia.	Standard-dose cytarabine 100–200 mg/m^2 continuous infusion x 7 days in conjunction with other therapies	Chemical Arachnoiditis, Neurotoxicity, Transient Elevations in CSF Protein and CSF White Blood Cells, Embryo-fetal Toxicity	Boxed warning, Warnings and Precautions
Novantrone (mitoxantrone) 12/23/1987	for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis; in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias.	12 mg/m^2 x 3 days in conjunction with other therapies	Cardiac Effects, Multiple Sclerosis, Leukemia, Hormone-Refractory Prostate Cancer, Pregnancy, Secondary Leukemia	Boxed warning, Warnings and Precautions, Medication Guide

Idamycin (idarubicin) 09/27/1990	in combination with other approved antileukemic drugs is indicated for the treatment of acute myeloid leukemia (AML) in adults.	12 mg/m^2 daily for 3 days by slow (10 to 15 min) intravenous injection in combination with cytarabine.	Myelosuppression, Gastrointestinal, Dermatologic, Hepatic and Renal changes, Cardiac dysfunction, Pregnancy	Boxed warning, Warnings and Precautions
Fludara or Oforta (fludarabine) 04/18/1991	treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.	30 mg/m^2 IV for days 2–6 in conjunction with other therapies	bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, Pregnancy category D	Boxed warning, Warnings and Precautions
Vepesid (etoposide) 11/10/1983	indicated for management of refractory testicular tumors and small cell lung cancer	50 mg/m^2 days 1 to 5x (1 cycle)	Myelosuppression, Pregnancy, Renal Impairment	Boxed warning, Warnings and Precautions
Clolar (clofarabine) 12/28/2004	for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.	10 mg/m^2 on days 1–5) for patients with AML between the ages of 18 to 65 years	Myelosuppression, Hemorrhage, Infections, Tumor Lysis Syndrome, Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome, Venous Occlusive Disease of the Liver, Hepatotoxicity, Renal Toxicity, Enterocolitis, Skin Reactions, Embryo-Fetal Toxicity	Warnings and Precautions

Venclexta (venetoclax) 04/11/2016	for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older in combination with azacitidine, or decitabine, or low-dose cytarabine, or who have comorbidities that preclude use of intensive induction chemotherapy; treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)	100 mg on day 1, 200 mg on day 2, 400 mg on day 3 followed by 400 mg orally once daily of each 28-day cycle in combination with azacitidine or decitabine or 600 mg orally once daily of each 28-day cycle in combination with low-dose cytarabine on day 4 and beyond	Tumor Lysis Syndrome, Neutropenia, Infections, Immunization, Embryo-Fetal Toxicity, Increased Mortality in Patients with Multiple Myeloma when added to Bortezomib and Dexamethasone	Warnings and Precautions, Medication Guide
Rydapt (midostaurin) 04/28/2017	in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by an FDA approved test	50 mg orally twice daily with food on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with high-dose cytarabine.	Embryo-Fetal Toxicity, Pulmonary Toxicity, Risk of Prolonged Severe Neutropenia and Thrombocytopenia in Pediatric Patients Treated With Combination Chemotherapy	Warnings and Precautions
Daurismo (glasdegib) 11/21/2018	in combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.	100 mg orally once daily on days 1 to 28 in combination with cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of each 28-day cycle in the absence of unacceptable toxicity or loss of disease control. For patients without unacceptable toxicity, treat for a minimum of 6 cycles to allow time for clinical response.	Embryo-Fetal Toxicity, QTc Interval Prolongation	Boxed warning, Warnings and Precautions, Medication Guide

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