



## **FDA warns that symptoms of a serious condition affecting the blood cells are not being recognized with the leukemia medicine Idhifa (enasidenib)**

### **Safety Announcement**

**[11-29-2018]** The U.S. Food and Drug Administration (FDA) is warning that signs and symptoms of a life-threatening side effect called differentiation syndrome are not being recognized in patients receiving the acute myeloid leukemia medicine Idhifa (enasidenib). The Idhifa [prescribing information](#) and [patient Medication Guide](#) already contain a warning about differentiation syndrome. However, we have become aware of cases of differentiation syndrome not being recognized and patients not receiving the necessary treatment.

As a result, we are alerting health care professionals and patients about the need for early recognition and aggressive management of differentiation syndrome to lessen the likelihood of serious illness and death. We are continuing to monitor this safety concern.

**Health care professionals** should describe to patients the symptoms of differentiation syndrome listed in the [Medication Guide](#) when starting Idhifa and at follow-up visits, and inform them to call their health care professional if such symptoms occur. Differentiation syndrome has occurred as early as 10 days and up to 5 months after starting the medicine. If patients experience unexplained respiratory distress or other symptoms, consider a diagnosis of differentiation syndrome and treat promptly with oral or intravenous corticosteroids (See Additional Information for Health Care Professionals).

**Patients** should contact your health care professional or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome while you are taking Idhifa:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs
- Swelling around the neck, groin, or underarm area
- Fast weight gain of more than 10 pounds within a week
- Bone pain
- Dizziness or feeling lightheaded

Idhifa was approved in August 2017 to treat patients with acute myeloid leukemia (AML) with a specific genetic mutation called isocitrate dehydrogenase (IDH)-2 whose disease has come back or has not improved after treatment with other chemotherapy medicines. AML is a rapidly progressing cancer that forms in the bone marrow and results in an increased number of abnormal white blood cells. Idhifa works by blocking several enzymes that promote this abnormal blood cell growth.

In the clinical trial conducted for Idhifa's approval, at least 14 percent of patients experienced differentiation syndrome. The manufacturer's safety report, which included the period of May 1, 2018 to July 31, 2018, reported five cases of death associated with differentiation syndrome in patients taking Idhifa (See Data Summary). Until Idhifa was approved, differentiation syndrome had been associated only with induction chemotherapy in patients with a rare form of cancer called acute promyelocytic leukemia. Health care professionals and patients may not recognize the signs and symptoms of differentiation syndrome associated with Idhifa. Another recently approved drug for AML with a specific genetic mutation called isocitrate dehydrogenase (IDH)-1, Tibsovo (ivosidenib), also carries a risk of differentiation syndrome. Health care professionals should also be vigilant in monitoring for differentiation syndrome when prescribing Tibsovo and patients should alert their health care professional of any symptoms.

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving Idhifa or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

### **Facts about Idhifa (enasidenib)**

- Idhifa is approved to treat a certain type of acute myeloid leukemia (AML), a type of cancer involving the white blood cells, that has come back or has not improved after treatment with other chemotherapy medicines.
- Idhifa works by blocking an enzyme that promotes abnormal cell growth.
- Idhifa has a Boxed Warning for differentiation syndrome.
- Idhifa is available as a tablet to take by mouth once daily.
- Common side effects of Idhifa include nausea, vomiting, diarrhea, yellowing of the skin or whites of the eyes, and decreased appetite.

### **Additional Information for Patients**

- Idhifa (enasidenib) can cause a serious condition called differentiation syndrome, which may be life-threatening if not treated quickly.
- Go to the nearest hospital emergency room right away if you develop any of the following symptoms while you are taking Idhifa and tell them you may have differentiation syndrome:
  - Fever
  - Cough
  - Shortness of breath

- Swelling of arms and legs
- Swelling around the neck, groin, or underarm area
- Fast weight gain of more than 10 pounds within a week
- Bone pain
- Dizziness or feeling lightheaded
- If you develop any of these symptoms, your health care professional will start you on oral or intravenous corticosteroid medicines if they suspect that you have differentiation syndrome, and may monitor you in the hospital.
- Read the patient [Medication Guide](#) every time you receive a prescription for Idhifa because there may be new or important additional information about your medicine. The Medication Guide explains the important things you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- To help FDA track safety issues with medicines, report side effects from Idhifa or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Additional Information for Health Care Professionals**

- Idhifa (enasidenib) can cause differentiation syndrome, which may be life-threatening or fatal if not treated quickly. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells.
- Differentiation syndrome has been observed as early as 10 days and up to 5 months after initiation of Idhifa.
- Encourage patients to read the [Medication Guide](#) they receive with their Idhifa prescriptions, which helps patients understand differentiation syndrome and provides other important information.
- Advise patients about the signs and symptoms of differentiation syndrome.
- Symptoms of differentiation syndrome include:
  - Acute respiratory distress represented by dyspnea and/or hypoxia and a need for supplemental oxygen
  - Pulmonary infiltrates and pleural effusion
  - Fever
  - Lymphadenopathy
  - Bone pain
  - Peripheral edema with rapid weight gain
  - Pericardial effusion
  - Hepatic, renal, and multiorgan dysfunction can also occur
- The initial presentations of differentiation syndrome may mimic and be difficult to distinguish from cardiogenic pulmonary edema, pneumonia, or sepsis.
- Initiate systemic corticosteroids (e.g., dexamethasone 10 mg every 12 hours) at the earliest suspicion of differentiation syndrome. Monitor hemodynamics until improvement and provide supportive care as needed.
- If renal dysfunction or severe pulmonary symptoms requiring intubation or ventilator support persist for more than 48 hours after initiation of systemic

corticosteroids, interrupt Idhifa treatment until signs and symptoms are no longer severe.

- Taper corticosteroids only after the symptoms resolve completely. Differentiation syndrome may recur with premature discontinuation of corticosteroid treatment.
- To help FDA track safety issues with medicines, report adverse events involving Idhifa or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

## Data Summary

In the manufacturer's latest Idhifa (enasidenib) quarterly safety report (May 1, 2018 to July 31, 2018) submitted to FDA, there were five cases of death associated with differentiation syndrome in patients treated with the drug. In two cases, differentiation syndrome was listed as the only cause of death, while the three other cases were confounded by hemorrhagic stroke, pneumonia and sepsis, and sepsis alone. One patient received systemic corticosteroids without delay, however may possibly have died of sepsis during the hospitalization. Another patient died after a delay in diagnosis and treatment, and treatment details are unavailable for the remaining three patients.

In the clinical trial conducted for Idhifa's approval, symptoms reported in patients with differentiation syndrome included acute respiratory distress represented by dyspnea and/or hypoxia (68%) and need for supplemental oxygen (76%), pulmonary infiltrates (73%) and pleural effusion (45%), renal impairment (70%), fever (36%), lymphadenopathy (33%), bone pain (27%), peripheral edema with rapid weight gain (21%), and pericardial effusion (18%). Hepatic, renal, and multi-organ dysfunction were also observed. Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, and as early as 10 days and up to 5 months after Idhifa initiation.

A recent systematic analysis by FDA identified a differentiation syndrome incidence with Idhifa of 19 percent, with 5 percent of these cases fatal.<sup>1</sup>

## References

1. Norsworthy KJ, Mulkey F, Ward AF, Przepiorka D, Deisseroth AB, Farrell AT, and Pazdur R. Incidence of differentiation syndrome with ivosidenib (IVO) and enasidenib (ENA) for treatment of patients with relapsed or refractory (R/R) isocitrate dehydrogenase (IDH)1- or IDH2-mutated acute myeloid leukemia (AML): a systematic analysis by the U.S. Food and Drug Administration (FDA). Oral presentation at: American Society of Hematology Annual Meeting; December, 2018; San Diego, CA. Available at: <https://ash.confex.com/ash/2018/webprogram/Paper117426.html>

## **Related Information**

[The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)

[Think It Through: Managing the Benefits and Risks of Medicines](#)