U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer

Safety Announcement

[9-13-2019] The U.S. Food and Drug Administration (FDA) is warning that Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) used to treat some patients with advanced breast cancers may cause rare but severe inflammation of the lungs. We have approved new warnings about this risk to the prescribing information and Patient Package Insert for the entire class of these cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor medicines. The overall benefit of CDK 4/6 inhibitors is still greater than the risks when used as prescribed.

CDK 4/6 inhibitors are a class of prescription medicines that are used in combination with hormone therapies to treat adults with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer that has spread to other parts of the body. CDK 4/6 inhibitors block certain molecules involved in promoting the growth of cancer cells. FDA approved Ibrance in 2015, and both Kisqali and Verzenio in 2017. CDK 4/6 inhibitors have been shown to improve the amount of time after the start of treatment the cancer does not grow substantially and the patient is alive, called progression-free survival (**See List of FDA-Approved CDK 4/6 Inhibitors below**).

Patients should notify your health care professional right away if you have any new or worsening symptoms involving your lungs, as they may indicate a rare but life-threatening condition that can lead to death. Symptoms to watch for include:

- Difficulty or discomfort with breathing
- Shortness of breath while at rest or with low activity

Do not stop taking your medicine without first talking to your health care professional. All medicines have side effects even when used correctly as prescribed, but in general the benefits of taking these medicines outweigh these risks. It is important to know that people respond differently to all medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. Specific risk factors to determine how likely it is that a particular person will experience severe lung inflammation when taking Ibrance, Kisqali, or Verzenio have not been identified.

Health care professionals should monitor patients regularly for pulmonary symptoms indicative of interstitial lung disease (ILD) and/or pneumonitis. Signs and symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in

patients in whom infectious, neoplastic, and other causes have been excluded. Interrupt CDK 4/6 inhibitor treatment in patients who have new or worsening respiratory symptoms, and permanently discontinue treatment in patients with severe ILD and/or pneumonitis.

We reviewed CDK 4/6 inhibitors cases from completed and ongoing clinical trials undertaken by manufacturers and their postmarket safety databases* that described specific types of inflammation of the lungs, called interstitial lung disease and pneumonitis. Across the entire drug class, there were reports of serious cases, including fatalities.

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

List of FDA-Approved CDK 4/6 Inhibitors

Brand Name	**Active Ingredient(s)**
Ibrance	palbociclib
Kisqali	ribociclib
Kisqali Femara Co-Pack	ribociclib and letrozole
Verzenio	abemaciclib

Facts about Cyclin-Dependent Kinase 4/6 (CDK 4/6) Inhibitors

- CDK 4/6 inhibitors are a class of medicines used in combination with hormonal therapies to treat adult patients with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer that has spread to other parts of the body.
- Medicines in this class include Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib).
- CDK 4/6 inhibitors work by blocking certain molecules involved in promoting the growth of cancer cells. This may help stop or slow the spread of cancer cells.
- CDK 4/6 inhibitors are available as tablets or capsules taken by mouth.
- Common side effects of CDK 4/6 inhibitors include nausea, vomiting, diarrhea, constipation, decreased appetite, abdominal pain, infections, low red blood cell counts, low white blood cell counts, low platelet count, headache, dizziness, hair thinning or loss, rash, tiredness, and weakness.

Additional Information for Patients

- The class of breast cancer medicines known as cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors may cause rare but severe inflammation of the lungs that can lead to death. See List of FDA-Approved CDK 4/6 Inhibitors above.

- Notify your health care professional right away if you have any new or worsening symptoms involving the lungs such as:
    - Difficulty or discomfort with breathing
    - Shortness of breath while at rest or with low activity
- Do not stop taking your medicine without first talking to your health care professional.
- Read the Patient Package Insert every time you receive a prescription for a CDK 4/6 inhibitor. It explains the important things that you need to know. 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.
- Talk to your health care professional if you have any questions or concerns about CDK 4/6 inhibitors.
- To help FDA track safety issues with medicines, report side effects from CDK 4/6 inhibitors 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

- Rare but severe, life-threatening or fatal interstitial lung disease (ILD) and pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors. See List of FDA-Approved CDK 4/6 Inhibitors above.
- Monitor patients regularly for pulmonary signs or symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, or other causes have been excluded.
- In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt CDK 4/6 inhibitor treatment immediately and evaluate the patient.
- Permanently discontinue the CDK 4/6 inhibitor in all patients with severe ILD or pneumonitis.
- Advise patients to immediately report new or worsening respiratory symptoms.
- Encourage patients to read the Patient Package Insert they receive with their CDK 4/6 inhibitor prescriptions, which explain the safety risks and provides other important information.
- To help FDA track safety issues with medicines, report adverse events involving CDK 4/6 inhibitors or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Data Summary

FDA reviewed cases of interstitial lung disease (ILD) and pneumonitis with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors that were identified in the manufacturers' completed and ongoing clinical trials and their postmarket safety databases.[*] Although rare, there were serious cases and/or deaths with Ibrance (palbociclib), Verzenio (abemaciclib), and Kisqali (ribociclib). Across clinical trials of the three CDK 4/6 inhibitors, 1 to 3 percent of patients had ILD/pneumonitis of any grade and less than 1 percent had fatal outcomes. Among patients who developed ILD/pneumonitis, including

fatal cases, there were patients who had no risk factors for lung disease, but some patients had at least one risk factor.

*The cases were identified in the Pfizer Safety Database, Novartis Argus Safety Database, and Lilly Safety System Databases.

Related Information

Ibrance Labeling

Kisqali Labeling

Kisqali Femara Co-Pack Labeling

Verzenio Labeling

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines