Investigation Results on Abemaciclib

May 17, 2019

Pharmaceuticals and Medical Devices Agency

Summary of drug

[Branded name]	Verzenio Tablets 50 mg, 100 mg, 150 mg
[Non-proprietary name]	Abemaciclib
[Approval holder]	Eli Lilly Japan K.K.
[Indications]	Hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer
[Estimated number of patients using the drug]	Approximately 2 000 (November 30, 2018 to May 14, 2019)

Outline of Investigation

Abemaciclib (this drug) is a drug to treat breast cancer. It is a low-molecular compound that inhibits cyclin-dependent kinases (CDK) 4 and 6 (4/6), which regulate cell cycles. This dug inhibits the activity of the complex of CDK 4/6 and cyclin D, which inhibits phosphorylation of the retinoblastoma (Rb) protein. By this process this drug halts cell cycle progression and consequently inhibits tumor proliferation as currently understood.

Regarding interstitial lung disease (ILD) associated with this drug, a precaution has been in place under the Important Precautions and the Clinically Significant Adverse Reactions section of the package insert since the approval of the product in Japan in September 2018. Interstitial lung disease occurred nonetheless and 14 serious cases have been reported in Japan from November 2018 to May 2019 while the drug has been under the early post-marketing phase vigilance, with 3 of the 14 serious cases leading to patient mortalities. PMDA concluded that revision of the package insert was necessary based on the results of its investigation of the currently available evidence and in consultation with expert advisors.

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Results of Investigation

PMDA concludes that this revision of the package insert is an emergency matter based on the following and opinions of expert advisors:

- Serious adverse reactions involving ILD have been reported in a short period of time after the product launch in Japan and such reports have particularly increased since the end of April 2019 including instances of patient mortality.
- Causal relationship to the product could not be ruled out in 4 of the 14 serious cases and causal relationship between serious ILD and death could not be ruled out in 1 of the 3 cases that resulted in patient mortality.
- Despite the cautionary statement regarding ILD that has been in place under the Important Precautions and the Clinically Significant Adverse Reactions sections of the package insert since the product approval in September 2018, in 1 of the serious cases, administration of this drug continued while the patient had cold-like symptoms including pyrexia who had serious ILD as a result.

Consequently, in order to disseminate information on the reported serious adverse reaction cases involving ILD including instances of patient mortality and for early detection and early treatment of the disease to prevent serious outcomes, it is necessary to ensure awareness and implementation of required responses such as;

1. When using this drug, patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc.
2. If any abnormalities are observed, administration of this drug should be discontinued and a chest CT scan or serum marker test, etc. should be performed as necessary and appropriate measures should be taken.

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Proposed revision for abemaciclib

Revised language is underlined.

Proposed revision	Current
Warnings 1. This drug should be administered in a medical institution sufficiently capable of responding to emergency situations, under physicians with adequate knowledge and experience of cancer therapy, and only to patients for whom administration of this drug is considered appropriate. In addition, patients or their families should be sufficiently informed of the effectiveness and risks of this drug and their consent should be obtained prior to administration. 2. Cases of interstitial lung disease resulting in mortality have been reported. Patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. If any abnormalities are observed, administration of this drug should be discontinued and a chest CT scan or serum marker test, etc. should be performed as necessary and appropriate measures should be taken. (See Careful Administration, Important Precautions, Clinically Significant Adverse Reactions sections.)	**Warnings** This drug should be administered in a medical institution sufficiently capable of responding to emergency situations, under physicians with adequate knowledge and experience of cancer therapy, and only to patients for whom administration of this drug is considered appropriate. In addition, patients or their families should be sufficiently informed of the effectiveness and risks of this drug and their consent should be obtained prior to administration.

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Precautions **1. Careful Administration (this drug should be administered with caution to the following patients)** (1) Patients with severe hepatic impairment (snip.) (2) Patients with interstitial lung disease or a history of the disease (Interstitial lung disease may be exacerbated. (See Warnings, Important Precautions, and Clinically Significant Adverse reactions sections.)	**Precautions** **1. Careful Administration (this drug should be administered with caution to the following patients)** Patients with severe hepatic impairment (snip.)
2. Important Precautions (2) Interstitial lung disease may occur. When using this drug, patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. A chest CT scan or serum marker test, etc. should be performed as necessary. Patients should be adequately informed of adverse reactions associated with this drug and instructed to immediately contact medical institutions when they experience any initial symptoms of the disease. (See Warnings, Important Precautions, and Clinically Significant Adverse reactions sections.)	**2. Important Precautions** (2) Interstitial lung disease may occur. When using this drug, patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. A chest CT scan or serum marker test, etc. should be performed as necessary.
4. Adverse Reactions (1) Clinically Significant Adverse Reactions 4) Interstitial lung disease (2.7%): Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, this drug should be discontinued and a chest CT scan or serum marker test, etc. should be performed as necessary, and appropriate measures should be taken. (See the Warning, Careful Administration, and Important Precautions sections.)	**4. Adverse Reactions** (1) Clinically Significant Adverse Reactions 4) Interstitial lung disease (2.7%): Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug.