# Pharmaceuticals and Medical Devices Safety Information

## No. 364 July 2019

**Table of Contents**



This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only in Japanese).

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

Register here


**Published by**
**Ministry of Health, Labour and Welfare**

Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

**Translated by**
**Pharmaceuticals and Medical Devices Agency**

Office of Informatics and Management for Safety,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan E-mail: safety.info@pmda.go.jp

# Pharmaceuticals and Medical Devices Safety Information

**No. 364 July 2019**

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan


**[ Outline of Information ]**

| No. | Subject | Measures | Outline of Information | Page |
|---|---|---|---|---|
| 1 | **Interstitial lung disease by abemaciclib** | *R*<br>*P*<br>*C* | Cases of serious interstitial lung disease (ILD) have been reported in 14 patients treated with abemaciclib, 3 of which resulted in death, as of May 14, 2019 during the period of early post-marketing phase vigilance since its launch on November 30, 2018.<br>MHLW in response instructed the marketing authorization holder on May 17, 2019 to caution related parties regarding ILD by revising the Precautions of the package insert and a Dear Healthcare Professionals Letter of Rapid Safety Communication. The details are provided below. | 4 |
| 2 | **Review of "glaucoma," as a contraindication for anticholinergic drugs** | *P* | Based on the various text-books, guidelines, and views in the relevant scientific societies, etc., a revision of "glaucoma" as a contraindication for anticholinergic drugs was considered at the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.<br>As a result, MHLW instructed the MAHs on June 18, 2019 to review the current language of the Precautions of the package insert. The details are provided below. | 10 |
| 3 | **Important Safety Information** | *P*<br>*C* | Abemaciclib, and 2 others. Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated May 17 and June 4, 2019, the contents of important revisions and case summaries that served as the basis for these revisions will be presented in this section. | 14 |
| 4 | **Revision of Precautions (No. 304)** | *P* | 1. Eletriptan hydrobromide<br>2. Zolmitriptan<br>3. Naratriptan hydrochloride<br>4. Rizatriptan benzoate (and 6 others) | 25 |
| 5 | **List of Products Subject to Early Post-marketing Phase Vigilance** | | List of products subject to Early Post-marketing Phase Vigilance as of May 31, 2019. | 28 |

*E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries*

**Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of providers of medical care and pharmaceutical products.**

If providers of medical care and pharmaceutical products such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

## Abbreviations

| | |
|---|---|
| ALT | Alanine aminotransferase |
| BP | Blood pressure |
| CA15-3 | Carbohydrate antigen 15-3 |
| CRP | C-reactive protein |
| CT | Computed tomography |
| EPPV | Early Post-marketing Phase Vigilance |
| FDP | Fibrin/fibrinogen degradation product |
| HER2 | Human epidermal growth factor receptor 2 |
| HR | Hormone receptor |
| ILD | Interstitial lung disease |
| JCS | Japan Coma Scale |
| KL-6 | Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6) |
| LDH | Lactate dehydrogenase |
| MAH | Marketing authorization holder |
| MHLW | Ministry of Health, Labour and Welfare |
| NSCLC | Non-small cell lung cancer |
| Neut | Neutrophil |
| PCR | Polymerase chain reaction |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PMDSI | Pharmaceuticals and Medical Devices Safety Information |
| PS | Performance status |
| PT-INR | Prothrombin time - international normalized ratio |
| SP-D | Surfactant protein D |
| SpO2 | Oxygen saturation |
| WBC | White blood cell |

# 1
# Interstitial lung disease by abemaciclib

| | | |
|---|---|---|
| **Name of ingredient Brand name (name of company )** | Name of ingredient | Brand name (name of company ) |
| | Abemaciclib | Verzenio Tablets 50 mg, 100 mg, 150 mg (Eli Lilly Japan K.K.) |
| **Therapeutic category** | Antineoplastics-miscellaneous | |
| **Indications** | Hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer | |

## 1. Introduction

Abemaciclib (hereinafter referred to as “this drug”) was approved in September 2018 for marketing with an indication of “Hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer.” The marketing authorization holder (MAH) estimates that this drug has been used by approximately 2 000 patients as of May 14, 2019 since its launch in Japan (November 30, 2018).

On May 17, 2019, MHLW instructed the MAH to revise its Precautions and distribute the Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue Letter)[1)]. The details are provided below.

## 2. Backgrounds

Interstitial lung disease (hereinafter, “ILD”) by this drug has been cautioned since November 2018, when it was launched, in the sections of “Important Precautions” and “Clinically Significant Adverse Reactions.” The early post-marketing phase vigilance (EPPV) was also performed between November 2018 and May 2019.

The EPPV intends to ensure provision of necessary information and precautions to medical institutions thereby promoting understanding of the proper use of drugs as well as collecting information on adverse reactions, etc. in a timely manner, for 6 months after the product launch in order to take necessary safety measures and minimize adverse reactions and other damage[2)].

There were serious ILD cases reported in 14 Japanese patients, 3 of which resulted in death, during the EPPV period even though such a precaution is stated in the Clinically Significant Adverse Reactions section of the package insert. Therefore, investigations/discussions were implemented to find whether the package insert should be revised.

As a result of the investigations/discussions, the PMDA concluded that revision of the package insert was necessary as an urgent matter based on the following reasons:

- Adverse reactions involving serious ILD have been reported for a short period of time since the launch. The reports related to ILD including patient mortality cases have been increased, particularly since the end of April 2019.
- The causal relationship with this drug cannot be ruled out in 4 of the 14 serious cases, and the causal relationship between serious ILD by this drug and death cannot be ruled out in 1 of the 3 mortality cases.
- Precaution against ILD has been stated in the sections of the Important Precautions and Clinically Significant Adverse Reactions sections of the package insert since the drug’s approval, September 2018. In one of the serious cases the patient continuously received this drug even though pyrexia and other cold-like symptoms occurred, resulting in development of serious ILD.

Based on this, it was considered necessary to disseminate the fact that serious cases involving ILD including patient mortality cases have been reported and to

make well known appropriate measures to be taken, etc. as well as precautions 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. and [2] 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 so that we can strive for early detection and early treatment which will prevent serious outcomes.

Consequently, MHLW required the MAH to revise the Precautions on May 17, 2019 to add necessary precautions in the Warning section and to distribute the Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue Letter)[1)] in order to communicate the precaution details to healthcare professionals quickly in view of the urgency.

## 3. Cases involving ILD by abemaciclib reported in Japan

The clinical course of 2 serious ILD cases are provided below.

**Case 1 ILD**

| No. | Patient | | Daily dose/ Treatment period | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 50s | Right breast cancer (Congenital hearing disorder (with speech disorder), headache) | 300 mg for 33 days | **ILD**<br>Medical history: no smoking history, no radiotherapy history, no allergy history<br>At the first visit: right breast cancer (Stage IV: T4cN3M1, sites of distant metastases: bones, lungs, pleura, and the opposite breast)<br>Previous treatment history:<br>First line: fulvestrant<br>Second line: exemestane + everolimus<br>Third line: exemestane + palbociclib<br>Fourth line: fulvestrant + palbociclib<br>Day 1 of administration: As the relevant tumor marker levels were gradually increased, the patient was started on this drug and fulvestrant (no respiratory symptoms)<br>No findings suggesting ILD were observed in the last PET/CT scan (231 days before administration) or chest X-ray (91 days before administration) before this drug was started.<br>33 days after administration (day of discontinuation): The patient experienced worsened headache, a chronic disease, and discontinued this drug (by her own decision).<br>1 day after discontinuation: The patient slept all day due to anorexia.<br>2 days after discontinuation: The patient slept all day, but communicated with her family until 21:00 as usual. The presence of pyrexia was unknown.<br>3 days after discontinuation: Since she was found unconscious in agony in her room around 7:00 in the morning, the patient was rushed to a hospital (JCS III-200, SpO2 64%, BP 160/80 mmHg, body temperature 38.0°C).<br>Blood pressure was gradually de- |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | creased during transfer to a hospital. |
| | | | | | When she arrived at the hospital, decerebrate rigidity and right concomitant deviation were observed. There were no light reflexes.<br>Tracheal intubation and artificial respiration were introduced.<br>Chest X-ray revealed infiltrative shadows in the right middle lung field and bilateral lower lung field.<br>Contrast CT scan revealed infiltrative shadows in the bilateral lower lung field and ground-glass opacity around them.<br>Sputum culture: negative, blood culture: negative, influenza test: negative<br>KL-6 1425 U/mL, SP-D 556 ng/mL<br>The patient was diagnosed with interstitial pneumonia, acute respiratory distress syndrome (ARDS), and hypoxic encephalopathy due to respiratory failure (brain death).<br>Treatment with steroid pulse (methylprednisolone) was started for interstitial pneumonia.<br>Treatment with concentrated Glycerin/fructose was started for hypoxic encephalopathy.<br>4 days after discontinuation: Cytology of the cerebrospinal fluid: negative, JCS III-300<br>5 days after discontinuation: Administration of steroid pulse (methylprednisolone) was terminated.<br>10 days after discontinuation: The patient died of interstitial pneumonia and hypoxic encephalopathy.<br>No autopsy was performed. |

**Laboratory Examination**

| | 14 days before administration | Day 1 of administration | 14 days after administration | 28 days after administration | 3 days after discontinuation | 4 days after discontinuation |
|---|---|---|---|---|---|---|
| LDH (IU/L) | 216 | 217 | - | 238 | 613 | 618 |
| CRP (mg/dL) | 0.08 | 0.33 | - | 0.10 | 13.45 | 8.51 |
| WBC (/uL) | 3 600 | 3 400 | - | 4 100 | 10 900 | 5 700 |
| Neut (%) | 59.7 | 57.3 | - | 68.9 | 94.2 | 91.7 |
| PT-INR | 0.89 | 0.94 | - | 0.96 | 1.12 | 1.22 |
| ALT (IU/L) | - | - | - | 13 | - | - |
| FDP (ug/ml) | - | - | - | - | 20.1 | 123.0 |
| CA15-3 (U/ml) | 36.6 | - | 32.2 | - | - | - |

Concomitant medications: fulvestrant, denosumab (genetical recombination), oxycodone hydrochloride hydrate, loxoprofen sodium hydrate, amlodipine besilate, sennoside, esomeprazole magnesium hydrate, calcium lactate hydrate

**Case 2 ILD**

| No. | Patient | | Daily dose/ Treatment period | Adverse reactions | |
|---|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 2 | Female 70s | Right breast cancer (with peritoneal dissemination) (Hypertension) | 300 mg for 13 days ↓ Discontinued ↓ 200 mg for 59 days ↓ Discontinued | **ILD**<br>Medical history: No smoking history, allergy history unknown<br>At the first visit: breast-conserving surgery was performed against right breast cancer (Stage IIB) after preoperative chemotherapy (details unknown)<br>Radiotherapy for the right breast was performed to the conserved breast (thoracic, 60 Gy)<br>As for the metastatic lesions, the lumbar spine was resected and ovariohysterectomy was performed.<br>Previous treatment history:<br>First line: anastrozole<br>Second line: capecitabine<br>Third line: fulvestrant<br>Fourth line: eribulin mesilate<br>Fifth line: bevacizumab (genetical recombination)<br>Sixth line: letrozole + palbociclib | |
| | | | | 7 days before administration | No abnormal findings were detected by CT scan. No respiratory symptoms were found. |
| | | | | Day 1 of administration | Treatment with this drug + letrozole was started for breast cancer (with peritoneal dissemination). |
| | | | | 14 days after administration (day of discontinuation) | This drug was discontinued due to increased creatinine level and hypercalcemia. |
| | | | | 11 days after discontinuation (day 1 of readministration) | Treatment with this drug and letrozole was resumed after increased creatinine level and hypercalcemia resolved. |
| | | | | 26 days after readministration | CT scan revealed no interstitial shadows and other findings. The peritoneal dissemination was decreased with no respiratory symptoms. |
| | | | | 72 days after readministration | The patients had a fever of 38.5°C. |
| | | | | 79 days after readministration | The patient had another fever in the 38 degree range, which resolved later, and was followed up but no respiratory symptoms were observed. |
| | | | | 85 days after readministration (day when readministration was discontinued) | The patient felt difficulty breathing since the morning and it worsened in the late afternoon, which resulted in her visit to the emergency room in the evening (37°C, PaO2 58.3 mmHg).<br>CT scan revealed ground-glass opacity in the upper and lower lobes of bilateral lungs and the right middle lobe.<br>Sputum culture: negative, mycoplasma antigen test: negative<br>The patient was admitted to the hospital after being diagnosed with interstitial pneumonia and discontinued this drug. Oxygen inhalation (by reservoir mask 10 L/min.) was |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | started. |
| | | | | 2 days after re-administration was discontinued | Steroid pulse (methylprednisolone) was administered 1000 mg/day for 3 days.<br>Tazobactam/piperacillin hydrate 4.5 g×3/day was administered for 5 days.<br>KL-6 2 979 U/mL, β-D-glucan <6.0 pg/mL, SP-D 955.9 ng/mL |
| | | | | 3 days after re-administration was discontinued | Treatment with oral corticosteroids (prednisolone) 60 mg/day was started. |
| | | | | 10 to 12 days after readministration was discontinued | The dose of oral corticosteroids (prednisolone) was reduced to 40 mg/day. |
| | | | | 20 days after re-administration was discontinued | The dose of oral corticosteroids (prednisolone) was reduced to 30 mg/day.<br>Oxygen inhalation was discontinued. |
| | | | | 28 days after re-administration was discontinued | The dose of oral corticosteroids (prednisolone) was reduced to 25 mg/day. |
| | | | | 33 days after re-administration was discontinued | The dose of oral corticosteroids (prednisolone) was reduced to 20 mg/day.<br>CT scan showed that ground-glass opacity almost improved and interstitial pneumonia recovered. |

Laboratory Examination

| | 4 days after readministration was discontinued | 6 days after readministration was discontinued | 9 days after readministration was discontinued | 13 days after readministration was discontinued | 16 days after re-administration was discontinued | 20 days after readministration was discontinued |
|---|---|---|---|---|---|---|
| WBC (/uL) | 8 140 | 7 090 | 6 290 | 9 750 | 8 290 | 8 190 |
| Neut (/uL) | 6 950 | 5 790 | 4 480 | 7 250 | 6 070 | 5 880 |
| CRP (mg/dL) | 2.0 | 1.1 | 0.32 | 0.09 | 0.05 | 1.52 |
| LDH (IU/L) | 478 | 358 | 368 | 305 | 314 | 286 |

Concomitant medications: letrozole, famotidine, goshajinkigan, hangeshashinto, pregabalin, furosemide tablets, polaprezinc

## 4. Precautions for serious Interstitial lung disease

Healthcare professionals are alerted to the following in the Blue Letter:

1. When using this drug, patients should be carefully monitored for initial symptoms of interstitial lung disease (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc.
2. 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.
3. Patients or their families should be instructed to contact the physician/pharmacist immediately when the initial symptoms of ILD (such as dyspnoea, cough, and pyrexia) occur.

Patients are also alerted as follows in the Letter.

1. Interstitial lung disease may occur while you are taking this drug.
2. Contact your physician/pharmacist if symptoms such as the following suddenly occur or persist:
   Shortness of breath or difficulty breathing when climbing the stairs or with mild overexertion
   Dry cough
   Fever

## 5. Concluding remarks

The revision details for this package insert are provided in 3. Important Safety Information for your reference on page 14 of this issue.

Regarding the use of this drug, we would like you to ensure early detection and early treatment of ILD and continuously cooperate with us for proper use.

<References>

1) Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue Letter): Serious Interstitial lung disease by Verzenio Tablets 50 mg, 100 mg, 150 mg
https://www.pmda.go.jp/files/000229624.pdf
Dear Patients who are to receive Verzenio Tablets for Treatment of Breast Cancer and their Families
http://www.pmda.go.jp/files/000229599.pdf (only in Japanese)

PMDA Investigation report
http://www.pmda.go.jp/files/000229604.pdf (only in Japanese)

2) Information on EPPV
http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0006.html
(only in Japanese)

# 2
# Review of “glaucoma” as a contraindication for anticholinergic drugs

## 1. Introduction

Drugs with an anticholinergic effect (hereinafter referred to as “anticholinergic drugs”) are widely used in the clinical settings as drugs with multiple effects. Anticholinergic drugs are used as antihistamines, anxiolytics, hypnotic and sedatives, common-cold drugs, bronchodilators, and an anti-Parkinson's disease agent for example.

Anticholinergic drugs are known to block muscarinic acetylcholine receptor $M_3$, which relaxes the sphincter pupillae muscle and results in mydriasis. Mydriasis-induced relative pupillary block may cause angle closure. Therefore, a caution has been issued to prevent the applicable patients from using anticholinergic drugs by listing “patients with glaucoma” in the Contraindications section of the package insert to prevent worsened glaucoma or acute glaucoma attack caused by anticholinergic effects.

The package inserts of anticholinergic drugs have been revised based on the discussion at the 2019 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (3rd meeting, hereinafter “Subcommittee on Drug Safety”), which was held in May 31, 2019. The details are provided below.

## 2. Backgrounds

Glaucoma is a disease characterized by distinctive changes in the optical nerve and visual field and the abnormality of the eye’s functions and structure which usually reduce the intraocular pressure sufficiently to improve and control optic nerve disorders. The disease is roughly divided into two types: “open-angle glaucoma” and “angle-closure glaucoma” based on the findings of angle closure features. Of these two, patients with “angle-closure glaucoma” only are considered to have a chance to experience worsened glaucoma or acute glaucoma attack caused by anticholinergic effects. As for “open-angle glaucoma,” the Japanese Ophthalmological Society says that neither Japanese nor foreign textbooks, guidelines, etc. stated that these events develop due to anticholinergic effects. Therefore, we discussed a revision on the caution for patients with glaucoma in the Contraindications section.

As for the package insert in which the term “narrow-angle glaucoma” is used, a review of the term to be used in the package insert was made in accordance with the wording that has been used in Japanese guidelines.

## 3. Details discussed by the Subcommittee on Drug Safety

(1) Changing from “glaucoma” to “angle-closure glaucoma” as a contraindication

The following are the results found after this review of descriptions of glaucoma associated with anticholinergic drugs in various textbooks, guidelines, etc.:

- “Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Edition Chapter 9,” an international pharmacology textbook, reads “Muscarinic receptor antagonists administered systemically have little effect on intraocular pressure except in patients predisposed to narrow-angle glaucoma, in whom the pressure may occasionally rise dangerously. The rise in intraocular pressure occurs when the anterior chamber is narrow and the iris obstructs outflow of aqueous humor into the trabeculae. Muscarinic receptor antagonists may precipitate a first attack in unrecognized cases predisposed to narrow-angle glaucoma. In patients with open-angle glaucoma, an acute rise in intraocular pressure is unusual. Atropine-like drugs generally can be used safely in this latter condition, particularly if the patient also is adequately treated with an appropriate miotic agent.”
- Terminology and Guidelines for Glaucoma, 4th Edition of European Glaucoma Society

reads “None of the systemic drugs with effects on the angle are contraindicated per se in open-angle glaucoma.”

- Anticholinergic drugs are contraindicated in patients with glaucoma in accordance with the current package inserts in some of such guidelines but in general Japanese major medical guidelines state that it basically should not be a problem to administer anticholinergic drugs to patients with open-angle glaucoma.
- Among the drugs approved in Japan for marketing since 2010 with new ingredients intended for COPD, overactive bladder, etc. and that are considered to have an anticholinergic effect as their main effect, no such ingredients (7 in total) are contraindicated for use in “patients with glaucoma.” These drugs are contraindicated in “patients with angle-closure glaucoma” or “patients with narrow-angle glaucoma.”

For revision from “glaucoma” to “angle-closure glaucoma” as a contraindication, the following feedback was given by the Japanese Ophthalmological Society from the specialist viewpoint in response to our request for their views on the change:

- Basically, patients with open-angle glaucoma at Grade 3 or higher in the Shaffer Classification (Table 1) do not have acute glaucoma attack.
- On the other hand, the possibility cannot be ruled out that patients with open-angle glaucoma who have a narrow angle (Grade 1 or 2 in the Shaffer Classification) may experience angle closure and acute glaucoma attack following administration of anticholinergic agents.

Table 1 Angle width and its clinical significance by Shaffer Classification

| | | Angle | Grade | Clinical significance |
|---|---|---|---|---|
| Wide open angle | | 20-45 | 3-4 | Angle closure impossible |
| Moderately narrow angle | | 20 | 2 | Angle closure possible |
| Very narrow angle | | 10 | 1 | Angle closure probable, eventually |
| Closed angle | | 0 | 0 | Angle closed |

Based on the results, the Subcommittee on Drug Safety determined that “angle-closure glaucoma” may be adopted instead of “glaucoma,” which is currently contraindicated in the package inserts of anticholinergic drugs (except ophthalmic topical preparations and drugs in which an anticholinergic effect is not considered the rationale for contraindication). However, since the risk of acute glaucoma attack cannot be completely denied when anticholinergic drugs are administered to patients with open-angle glaucoma, the Group judged that “patients with open-angle glaucoma” should be added to the “Careful Administration” section (Table 2).

(2) Review of the term “narrow-angle glaucoma”

The disease names of “narrow-angle glaucoma” and “angle-closure glaucoma” have been so far considered identical and used interchangeably. The disease name of narrow-angle glaucoma does not clearly indicate whether it is a glaucoma with closed angle or without it. Therefore, “Guidelines for Glaucoma Management” Second Edition (2006) states “Narrow angle only means a condition in which the angle is narrow, and it does not mean the presence of the angle-closure mechanism. Since primary open-angle glaucoma with a narrow angle can occur, the term narrow-angle glaucoma should not be used.” The Japan Glaucoma Society suggested that the diagnostic name of narrow-angle glaucoma should not be used as a diagnostic name that represents angle-closure glaucoma.

Following the suggestion, the Safety Measure Investigation Group judged that the term “narrow-angle glaucoma” in the package insert may be changed to “angle-closure glaucoma” (Table 2).

Table 2. New/old comparison table

○ **"Glaucoma" as a contraindication**

Underlined parts were revised, and crossed-out parts were deleted.

| Before revision | After revision |
|---|---|
| [Contraindications]<br>Patients with glaucoma [snip.] | [Contraindications]<br>Patients with angle-closure glaucoma [Anticholinergic effects may increase the intraocular pressure and worsen the symptoms.] |
| [Contraindications]<br>Patients ~~who have~~ with glaucoma [snip.] | |
| [Careful Administration]<br>(N/A) | [Careful Administration]<br>Patients with open-angle glaucoma [Anticholinergic effects may increase the intraocular pressure and worsen the symptoms.] |

| Before revision | After revision |
|---|---|
| [Contraindications]<br>Patients with glaucoma or likely to retain urine [snip.] | [Contraindications]<br>Patients with angle-closure glaucoma [Anticholinergic effects may increase the intraocular pressure and worsen the symptoms.]<br><br>Patients likely to retain urine [Anticholinergic effects may worsen urinary retention.] |
| [Careful Administration]<br>(N/Ad) | [Careful Administration]<br>Patients with open-angle glaucoma [Anticholinergic effects may increase the intraocular pressure and worsen the symptoms.] |

N/A: Not Applicable, because the section is not included in the current package insert.

○ **Replacement of narrow-angle glaucoma**

| Before revision | After revision |
|---|---|
| [Contraindications]<br>Patients with narrow-angle glaucoma [snip.] | [Contraindications]<br>Patients with angle-closure glaucoma [Anticholinergic effects may increase the intraocular pressure and worsen the symptoms.] |

| Before revision | After revision |
|---|---|
| [Contraindications]<br>Patients with acute narrow-angle glaucoma [snip.] | [Contraindications]<br>Patients with acute angle-closure glaucoma [Anticholinergic effects may increase the intraocular pressure and worsen the symptoms.] |
| [Contraindications]<br>Patients ~~who have~~ with acute narrow-angle glaucoma [snip.] | |

| Before revision | After revision |
|---|---|
| [Careful Administration]<br>Patients with angle closure ~~or narrow-angle~~ glaucoma [snip.] | [Careful Administration]<br>Patients with angle-closure glaucoma [Anticholinergic effects may increase the intraocular pressure and worsen the symptoms.] |

## 4. Handling of over the counter drugs

Ingredients with anticholinergic effects are also contained in over the counter (OTC) drugs such as cold medicines, internal medicine for rhinitis, gastrointestinal drugs, and antivertigo medicines. Healthcare professionals who are consulted by patients with glaucoma concerning products for which “glaucoma” is listed as Precautions in the Consultation section of the package insert should confirm the type of glaucoma of the patient to the extent possible in line with the intention of the revision of package insert for prescription drugs this time and consult a physician if the type of glaucoma cannot be identified or is unknown.

## 5. Concluding remarks

Despite being treated for glaucoma by ophthalmologist, some patients do not know what type of glaucoma they have. Therefore, it is important for the patients to know what type of glaucoma they have. Healthcare professionals are required to understand the gist of this revision, to provide information properly on what type of glaucoma the patient has, and to determine whether to administer anticholinergic drugs after precisely identifying what type of glaucoma the patient has if the drugs are an option. We would like you to continuously cooperate for proper use of anticholinergic drugs.

[Reference information]

- The 2019 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (3rd meeting held on May 31, 2019) Document 2
  https://www.mhlw.go.jp/stf/shingi2/0000183979_00004.html
- Revision of Precautions regarding “glaucoma” as a contraindication for drugs with anticholinergic effects (PSEHB/PSD Notification No.0618-X dated June 18, 2019)
  URL

# 3

# Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated May 17 and June 4, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

## 1 Abemaciclib

| | |
|---|---|
| **Branded name (name of company)** | Verzenio Tablets 50 mg, 100 mg, 150 mg (Eli Lilly Japan K.K.) |
| **Therapeutic category** | Antineoplastics-miscellaneous |
| **Indications** | Hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer |

**PRECAUTIONS (revised language is underlined)**

| | |
|---|---|
| **[Current]** | |
| **Warnings** | N/A |
| **Careful Administration** | N/A |
| **Important Precautions** | 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. |
| **Adverse Reactions (Clinically Significant Adverse Reactions)** | Interstitial lung disease:<br>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. |
| **[Revised]** | |
| **Warnings** | 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.) |
| **Careful Administration** | Patients with interstitial lung disease or a history of the disease (Interstitial lung disease may be exacerbated.) |
| **Important Precautions** | 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.<br>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. |
| **Adverse Reactions (Clinically Significant Adverse Reactions)** | Interstitial lung disease: 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. |
| **Reference information** | Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 6-month period (November 2018 to May 2019).<br>Cases involving interstitial lung disease: 4 (1 patient mortality)<br><br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 2 000<br><br>Japanese market launch: November 2018 |

### Case summary

Please refer to the case summary in “1. Interstitial lung disease (ILD) by abemaciclib” on page 5 of this issue.

## 2 Nivolumab (genetical recombination)

| | |
|---|---|
| **Branded name (name of company)** | Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.) |
| **Therapeutic category** | Antineoplastics-miscellaneous |
| **Indications** | Malignant melanoma<br>Unresectable advanced or recurrent non-small cell lung cancer<br>Unresectable or metastatic renal cell carcinoma<br>Relapsed or refractory classical Hodgkin lymphoma<br>Relapsed or metastatic head and neck cancer<br>Unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy<br>Unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy |

**PRECAUTIONS (revised language is underlined)**

| | |
|---|---|
| **[Under Old instructions]**<br>**Careful Administration (Newly added)** | Patients with tuberculosis infection or its history |
| **Adverse Reactions (Clinically Significant Adverse Reactions) (Newly added)** | **Tuberculosis**: Tuberculosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug. |
| **[Under New instructions]**<br>**9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS**<br>**9.1 Patients with Complication or History of Diseases, etc.**<br>**(Newly added)** | Patients with tuberculosis infection or its history |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions**<br>**(Newly added)** | **Tuberculosis** |
| **Reference information** | Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 35-month period (April 2016 to February 2019).<br>Cases involving tuberculosis: 6 (no patient mortalities)<br><br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 17 000<br><br>Japanese market launch: September 2014 |

Case summary

Case 1

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | |
|---|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and Therapeutic measures | |
| 1 | Male 70s | Non-small cell lung cancer (with inguinal hernia, emphysema, metastasis to left adrenal gland, metastases to lymph nodes, drinking history, and smoking history) | 3 mg/kg 15 times at 2-week intervals ↓ Discontinued ↓ 3 mg/kg 31 times at 2-week intervals | **Rash, Pulmonary tuberculosis** | |
| | | | | Day 1 of administration | Nivolumab was administered (3 mg/kg/day) to the patient with unresectable advanced and recurrent Non-small cell lung cancer (NSCLC) (histology: adenocarcinoma, treatment site: right upper lobe, stage 4, TNM classification: T3bN2M1b (the name of organ metastasized: left adrenal gland, *EGFR* gene mutation: negative). Past history of tuberculosis: none, PS: 1-2 |
| | | | | 196 days after administration | The patient received the 15th dose of nivolumab. |
| | | | | 197 days after administration (day of final discontinuation) | The patient developed productive cough, pyrexia, and purulent sputum, and visited the hospital for suspected tuberculosis. Because of Ziehl–Neelsen staining of sputum: (+) and PCR test: (+), the patient was diagnosed with pulmonary tuberculosis. The patient was admitted to the hospital for treatment. Tuberculosis bacteria were detected by the fluorescence method in a sputum culture at the time of hospital admission thus the diagnosis was confirmed bacteriologically (week of determination: Week 4). Nivolumab was discontinued. |
| | | | | 6 days after discontinuation | Combination therapy with 4 agents - isoniazid, rifampicin, ethambutol hydrochloride, and pyrazinamide - was performed. At the time of administration of antituberculosis drugs, the patient had hypoalbuminaemia, anaemia, and lymphopenia. |
| | | | | 16 days after discontinuation | Pyrexia higher than 38°C was present as an axillary temperature. Pulse rate was 114, compared with basal pulse rate of 98, showing tachycardia. New shadows were noted in the central and lower regions of the right lung. Lymphocyte count increased was not seen. As the shadows were diagnosed as bacterial pneumonia, ampicillin sodium and sulbactam sodium were prescribed. |
| | | | | Date unknown | As improvement of pyrexia was not observed, administration of ampicillin sodium and sulbactam sodium was discontinued in consideration of the possibility of drug-induced pyrexia. |
| | | | | 20 days after discontinuation | As improvement of pyrexia was not seen, administration of pyrazinamide was discontinued in consideration of the possibility of drug-induced pyrexia. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 22 days after discontinuation | As improvement of pyrexia was not seen, administration of rifampicin was discontinued in consideration of the possibility of drug-induced pyrexia, and administration of moxifloxacin hydrochloride was added as antituberculosis treatment. |
| | | | | Date unknown: | Pyrexia persisted and the lung shadows increased. |
| | | | | 28 days after discontinutation | Administration of prednisolone (30 mg/day) was started. Pyrexia improved promptly. Administration of moxifloxacin hydrochloride was discontinued, and administration of rifampicin was initiated. |
| | | | | 33 days after discontinuation | Sputum smear stained: (-), sputum culture: (-) |
| | | | | 46 days after discontinuation | KL-6: 411 U/mL. Based on the above clinical course, the pyrexia and shadows were judged to suggest paradoxical response (PR). |
| | | | | Date unknown | During a washout interval of antituberculosis treatment, drug-susceptibility testing for tuberculosis bacteria was performed and susceptibility to all drugs other than levofloxacin hydrate was confirmed. Combination therapy with 4 agents was resumed for 2 months. |
| | | | | Date unknown | Three months after the initiation of antituberculosis treatment, a sputum culture for tuberculosis bacteria: (-). The lung shadows in the central and lower regions of the right lung disappeared. Administration of prednisolone (5 mg/day) was terminated. |
| | | | | 116 days after discontinuation (Day 1 of readministration) | The hepatic function was good (PS: 1), the response to nivolumab was seen in the past, and the patient requested readministration of nivolumab. For these reasons, nivolumab (3 mg/kg/day) was resumed for unresectable advanced and recurrent NSCLC with permission of the cancer board. |
| | | | | Date unknown | Combination therapy with 2 agents - isoniazid and rifampicin - was performed for 7 months as a long-term antituberculosis treatment plan. |
| | | | | Date unknown | One year after the introduction of antituberculosis treatment, antituberculosis treatment was discontinued. |
| | | | | 329 days after readministration | The shadows improved. |
| | | | | 401 days after readministration | The patient received the 46th dose of nivolumab. Tuberculosis infection did not recur. For NSCLC, partial response (PR) was maintained. |
| | Concomitant medications: unknown | | | | |

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | |
|---|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and Therapeutic measures | |
| 2 | Male 50s | Classical Hodgkin's lymphoma (with emphysema, old pulmonary tuberculosis, tuberculous lymphadenitis, and smoking history) | 3 mg/kg 5 times at 2-week intervals ↓ Discontinued ↓ 3 mg/kg 3 times at 2-week intervals. | **Malignant neoplasm progression, thyroiditis, tuberculosis, altered state of consciousness** | |
| | | | | Day 1 of administration | Nivolumab (3 mg/kg/day) was administered for recurrent or refractory classical Hodgkin's lymphoma (Ann Arbor classification: Stage III). PS: 1 |
| | | | | 85 days after administration (day of termination) | The patient received the 5th dose of nivolumab. |
| | | | | 88 days after administration | Pyrexia of 38°C and increased hepatobiliary enzymes were observed. As cholecystitis was suspected, abdominal CT was performed. From the diagnostic results, any finding suggestive of cholecystitis or cholangitis could not be pointed out. |
| | | | | 92 days after administration (day of discontinuation) | Acid-fast bacteria testing was performed. Abscess in the psoas major muscle was punctured, and acid-fast bacteria were seen in a sputum smear. The patient was diagnosed with tuberculous abscess in the psoas major muscle. Ziehl–Neelsen staining: (+) G1, sputum culture: (-) (week of determination: Week 8). Nivolumab was suspended. |
| | | | | 2 days after discontinuation | Acid-fast bacteria testing was performed. Ziehl–Neelsen staining: (-), PCR testing: (-), sputum culture: (-) (week of determination: Week 8). |
| | | | | 3 days after discontinuation | Administration of isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1.5 g/day), and ethambutol hydrochloride (1 000 mg/day) was initiated. |
| | | | | 8 days after discontinuation | Chest CT was performed, and the patient was diagnosed with old pulmonary tuberculosis. There was no exacerbated tuberculous lesion. |
| | | | | Date unknown | Pyrexia was gradually alleviated and resolved. |
| | | | | 83 days after discontinuation (Day 1 of readministration) | The patient received the 6th dose of nivolumab. |
| | | | | 29 days after readministration (day of final administration) | The patient received the 8th dose of nivolumab. |
| | | | | 2 days after termination of readministration | Tuberculous abscess in the psoas major muscle remitted. |
| | | | | 50 days after termination of readministration | Administration of pyrazinamide (1.5 g/day) and ethambutol hydrochloride (1 000 mg/day) was terminated. |
| | | | | 59 days after termination of readministration | Administration of isoniazid (300 mg/day) and rifampicin (600 mg/day) was terminated. Pulmonary tuberculosis did not relapse. |
| | Concomitant medications: unknown | | | | |

## 3 Baloxavir marboxil

| | |
|---|---|
| **Branded name (name of company)** | Xofluza Tablets 10 mg, 20 mg, Xofluza granule 2% portions (Shionogi & Co., Ltd.) |
| **Therapeutic category** | Antivirals |
| **Indications** | Influenza A or B viral infections |

**PRECAUTIONS (revised language is underlined)**

**[Under Old instructions]**

**Adverse Reactions (Clinically Significant Adverse Reactions) (N/A)**

**Shock, anaphylaxis**:
Shock or anaphylaxis may occur. If any abnormalities are observed, appropriate measures should be taken.

**[Under New instructions]**

**11. ADVERSE REACTIONS**

**11.1 Clinically Significant Adverse Reactions (N/A)**

**Shock, anaphylaxis**

**Reference information**

Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 36-month period (April 2016 to March 2019).
Cases involving shock, anaphylaxis: 16 (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 7 800 000

Japanese market launch: March 2018

Case summary (anaphylactic shock)

| No. | Patient | | Daily dose/ Treatment duration | **Adverse reactions** | |
|---|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and Therapeutic measures | |
| 1 | Female 40s | Influenza (none) | 40 mg Once | **Anaphylactic shock** | |
| | | | | Day 1 of administration | The patient developed influenza A virus infection. |
| | | | | (day of termination) | After returning home, baloxavir marboxil 40 mg/day was administered. |
| | | | | 30 minutes later | Vomiting occurred. |
| | | | | 45 minutes later | Itching associated with redness on the face, upper limbs, and chest occurred. The patient seemed to have tears in the eyes and also had hoarseness. |
| | | | | Approximately 3 hours later | The patient revisited the medical institution. Consciousness lucid: Upper limb blood pressure decreased to 80/mmHg, compared with a usual level of around 96/mmHg, without respiratory distress. Because of skin eruption and blood pressure, the patient was diagnosed with anaphylactic shock and treated with antihistamine and fluid replacement. (Anaphylactic shock occurred.) |
| | | | | Approximately 5 hours later | Skin eruption became tolerable and blood pressure recovered to 92. There were circumstances where hospitalisation was not possible and normal activities became possible, the patient returned home. |
| | | | | 1 day after termination | Continued improvement was confirmed over the phone.<br>(anaphylactic shock resolved) |
| | | | | 4 days after termination: | Medical examination was terminated. |
| | Laboratory Examination: - | | | | |
| | Concomitant medications: none | | | | |

Case summary (anaphylactoid symptoms)

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | |
|---|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and Therapeutic measures | |
| 2 | Female 20s | Influenza (none) | 40 mg Once | **Anaphylactoid symptoms** | |
| | | | | Time unknown | The patient developed influenza A virus infection. |
| | | | | Day 1 of administration | The patient was diagnosed with influenza at a nearby hospital. |
| | | | | (day of termination) | Baloxavir marboxil 40 mg/day was administered. Dyspnoea feeling and systemic pruritus developed. Nausea, vomiting, and abdominal pain were present. (Anaphylactoid symptoms occurred.) Dyspnoea feeling decreased, but eyelid oedema and systemic pruritus persisted. The patient was transported to the emergency unit. |
| | | | | Approximately 1 hour later | At the time of transportation: consciousness lucid<br>Body temperature (36.6°C), blood pressure (systolic 92/mmHg, diastolic 53/mmHg), circulatory failure absent, SpO2 95% (room air), heart rate 74, redness of pharynx present. Laryngeal oedema and swelling were not observed. Dyspnoea was absent. Eyelid oedema, nausea, vomiting, abdominal pain, and wheals (abdomen, back, lower legs) were observed.<br>Breath sounds: clear, without airway narrowing. Heart sounds: clear, without cardiac murmur. Abdomen: flat and soft, without tenderness. Diarrhoea was absent.<br>For suspected anaphylaxis, infusion treatment was initiated.<br>Main tube: Continuous infusion of saline injection 500 mL was initiated.<br>From the side tube, the following drugs were infused:<br>Saline injection 100 mL, famotidine injection 20 mg, d-chlorpheniramine maleate injection, betamethasone valerate sodium injection 2 mg. The patient was admitted to the hospital for follow-up observation in consideration of the possibility of a second attack.<br>As vomiting occurred within 1 hour after administration of baloxavir marboxil, inhalation of zanamivir hydrate was attempted but was given up because inhalation was difficult due to severe nausea. Treatment of influenza with other agents was not performed.<br>The symptoms resolved on the same day. |
| | | | | 1 day after termination | The patient was discharged from the hospital. (Anaphylactoid symptoms resolved.) |

| | |
|---|---|
| | Laboratory Examination<br>Day 1 of administration: (at the time of transportation) / 1 day after termination:<br>WBC (/μL): 6 500 / 5 600<br>Hemoglobin (g/dL): 17.0 / 13.7<br>Neutrophils (%): 92.3 / 89.6<br>CRP (mg/dL): 1.39 / 3.00 |
| | Concomitant medications: none |

# Revision of Precautions (No. 304)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated June 4, 2019.

## 1 Vasoconstrictors

## [1] Eletriptan hydrobromide
## [2] Zolmitriptan
## [3] Naratriptan hydrochloride
## [4] Rizatriptan benzoate

**Branded name**

[1] Relpax Tablets 20 mg (Pfizer Japan Inc.), and the others
[2] Zomig Tablets 2.5 mg, Zomig RM Tablets 2.5 mg (Sawai Pharmaceutical Co.,Ltd.),and the others
[3] Amerge Tablets 2.5 mg (GlaxoSmithKline K.K.)
[4] Maxalt Tablets 10 mg, Maxalt RPD Tablets 10 mg (Kyorin Pharmaceutical Co.,Ltd.),and the others

**[Under Old instructions]**

**Important Precautions (newly added)**

Triptans including this drug may lead to an exacerbation of headache. If headache does not improve, consider a possibility of “medication overuse headache” and appropriate measures such as discontinuation of administration should be taken.

**Adverse Reactions**
**Clinically Significant Adverse Reactions (newly added)**

**Medication overuse headache**: Medication overuse headache may occur. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

## 2 Vasoconstrictors

## [1] Sumatriptan
## [2] Sumatriptan succinate (oral dosage form)
## [3] Sumatriptan succinate (injectable dosage form, ampules)

**Branded name**

[1] Imigran Nasal Spray 20 mg (GlaxoSmithKline K.K.)
[2] Imigran Tablets 50 mg (GlaxoSmithKline K.K.), and the others
[3] Imigran (GlaxoSmithKline K.K.), and the others

**[Under Old instructions]**

**Important Precautions (newly added)**

Triptans including this drug may lead to an exacerbation of headache. If headache does not improve, consider a possibility of “medication overuse headache” and appropriate measures such as discontinuation of administration should be taken.

**Adverse Reactions**
**Clinically Significant Adverse Reactions (newly added)**

Medication overuse headache may occur. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

## 3 Vasoconstrictors

## Sumatriptan succinate (injectable dosage form, kit)

| | |
|---|---|
| **Branded name** | Imigran Kit Subcutaneous Injection 3 mg (GlaxoSmithKline K.K.), and the others |
| **[Under Old instructions]** | |
| **Important Precautions (newly added)** | Triptans including this drug may lead to an exacerbation of headache. If headache does not improve, consider a possibility of "medication overuse headache" and appropriate measures such as discontinuation of administration should be taken. |
| **Adverse Reactions Clinically Significant Adverse Reactions (newly added)** | Medication overuse headache may occur. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken. |

4 Antineoplastics-miscellaneous

## Avelumab (genetical recombination)

| | |
|---|---|
| **Branded name** | Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd.) |
| **[Under New instructions]** | |
| **11. Adverse Reactions 11.1 Clinically Significant Adverse Reactions (newly added)** | **Pancreatitis** |

5 Antineoplastics-miscellaneous

## Nivolumab (genetical recombination)

| | |
|---|---|
| **Branded name** | Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.) |
| **[Under Old instructions]** | |
| **Careful Administration (newly added)** | Patients with tuberculosis infection or its history |
| **ADVERSE REACTIONS Clinically Significant Adverse Reactions (newly added)** | **Tuberculosis**:<br>Tuberculosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug. |
| **[Under New instructions]** | |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)** | Patients with tuberculosis infection or its history. |
| **11. ADVERSE REACTIONS** | |

| | |
|---|---|
| **11.1 Clinically Significant Adverse Reactions （newly added）** | Tuberculosis |

6 Antineoplastics-miscellaneous

## Pembrolizumab (genetical recombination)

| | |
|---|---|
| **Branded name** | Keytruda Injection 20 mg, 100 mg (MSD K.K.) |
| **[Under Old instructions]** | |
| **Careful Administration （newly added）** | Patients with tuberculosis infection or its history |
| **Adverse Reactions Clinically Significant Adverse Reactions** | **Tuberculosis**: Tuberculosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug. |

7 Antivirals

## Baloxavir marboxil

| | |
|---|---|
| **Branded name** | Xofluza Tablets 10 mg, 20 mg, Xofluza granule 2% portions (Shionogi & Co., Ltd.) |
| **[Under Old instructions]** | |
| **Adverse Reactions (Clinically Significant Adverse Reactions) （newly added）** | **Shock, anaphylaxis**:<br>Shock or anaphylaxis may occur. If any abnormalities are observed, appropriate measures should be taken. |
| **[Under New instructions]** | |
| **11. ADVERSE REACTIONS** | |
| **11.1 Clinically Significant Adverse Reactions** | **Shock, anaphylaxis** |

5

# List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 31 May, 2019)
◎: Products for which EPPV was initiated after May 1, 2019

| | Nonproprietary name<br>Branded name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | Apalutamide<br>Erleada Tablets 60 mg | Janssen Pharmaceutical K.K. | May 30, 2019 |
| ◎ | Thiotepa<br>Rethio Intravenous Infusion 100 mg | Sumitomo Dainippon Pharma Co., Ltd. | May 28, 2019 |
| ◎ | Risankizumab（genetical recombination）<br>Skyrizi Subcutaneous Injection 75 mg Syringe 0.83 mL | AbbVie GK | May 24, 2019 |
| ◎ | Fluticasone furoate/ vilanterol trifenatate/ umeclidinium bromide<br>Trelegy 100 Ellipta 14 doses, 30 doses | Glaxo Smith Kline K.K. | May 22, 2019 |
| ◎ | Esaxerenone<br>Minnebro Tablets 1.25mg, 2.5mg, 5mg | Daiichi Sankyo Co., Ltd. | May 13,2019 |
| | Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate<br>Biktarvy Combination Tablets | Gilead Sciences Inc. | April 8, 2019 |
| | Tafamidis meglumine*1<br>Vyndaqel capsules 20 mg | Pfizer Japan Inc. | March 26, 2019 |
| | Landiolol hydrochloride*2<br>Onoact for Intravenous Infusion 50 mg, 150 mg | Ono Pharmaceutical Co., Ltd. | March 26, 2019 |
| | Dupilumab (genetical recombination) *3<br>Dupixent Subcutaneous Injection 300 mg Syringe | Sanofi K.K. | March 26, 2019 |
| | Dapagliflozin propylene glycolate hydrate*4<br>Forxiga Tablets 5 mg, 10 mg | AstraZeneca K.K. | March 26, 2019 |
| | Nalmefene hydrochloride hydrate<br>Selincro tablets 10 mg | Otsuka Pharmaceutical Co., Ltd | Match 5, 2019 |
| | Romosozumab (genetical recombination)<br>Evenity subcutaneous injection 105 mg syringe | Amgen Astellas BioPharma K.K. | March 4, 2019 |
| | Dacomitinib Hydrate<br>Vizimpro Tablets 15 mg, 45 mg | Pfizer Japan Inc. | March 1, 2019 |
| | Relugolix | Takeda Pharmaceutical | March 1, 2019 |

| Nonproprietary name<br>Branded name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| Relumina Tablets 40 mg | Company Limited. | |
| Lorazepam<br>Lora-pita Intravenous Injection 2mg | Pfizer Japan Inc. | March 1, 2019 |
| Binimetinib<br>Mektovi Tablets 15 mg | Ono Pharmaceutical Co., Ltd. | February 26, 2019 |
| Encorafenib<br>Braftovi Capsules 50 mg | Ono Pharmaceutical Co., Ltd. | February 26, 2019 |
| Sofosbuvir/velpatasvir<br>Epclusa Combination Tablets | Gilead Sciences Inc. | February 26, 2019 |
| Metirosine<br>Demser Capsules 250 mg | Ono Pharmaceutical Co., Ltd. | February 26, 2019 |
| Damoctocog alfa pegol (genetical recombination)<br>Jivi for i.v. injection 250, 500, 1000, 2000, 3000 | Bayer Yakuhin Ltd | February 12, 2019 |
| Secukinumab (genetical recombination) *1<br>Cosentyx for s.c. injection 150 mg syringe | Novartis Pharma K.K. | December 21, 2018 |
| Ipragliflozin L–proline *2<br>Suglat Tablets 25 mg, 50 mg | Astellas Pharma Inc. | December 21 2018 |
| Dolutegravir sodium/rilpivirine hydrochloride<br>Juluca Combination Tablets | Viiv Healthcare K.K. | December 20, 2018 |
| Gilteritinib fumarate<br>Xospata Tablets 40 mg | Astellas Pharma Inc. | December 3, 2018 |
| Abemaciclib<br>Verzenio Tablets 50 mg, 100 mg, 150 mg | Eli Lilly Japan K.K. | November 30, 2018 |
| Dexmedetomidine hydrochloride<br>a. Precedex Intravenous Solution 200 μg [Pfizer], b. Precedex Intravenous Solution 200 μg/50 mL syringe [Pfizer], c. Precedex Intravenous Solution 200 μg [Maruishi], d. Precedex Intravenous Solution 200 μg/50 mL syringe [Maruishi] | a, b Pfizer Japan Inc.<br>c, d Maruishi Pharmaceutical Co., Ltd. | November 29, 2018 |
| Macrogol 4000/sodium chloride/sodium bicarbonate/potassium chloride<br>Movicol Combination Powder | EA Pharma Co., Ltd. | November 29, 2018 |
| Omidenepag isopropyl<br>Eybelis Ophthalmic Solution 0.002% | Santen Pharmaceutical Co., Ltd. | November 27, 2018 |
| Vibegron<br>Beova Tablets 50 mg | Kyorin Pharmaceutical Co.,Ltd. | November 27, 2018 |
| Blinatumomab (genetical recombination)<br>Blincyto I.V. Infusion 35 μg | Amgen Astellas BioPharma K.K. | November 27, 2018 |
| Lorlatinib<br>Lorbrena Tablets 25 mg, 100 mg | Pfizer Japan Inc. | November 20, 2018 |
| Icatibant acetate<br>Firazyr subcutaneous injection 30 mg syringe | Shire Japan KK | November 20, 2018 |
| Vedolizumab (genetical recombination)<br>Entyvio for I.V. Infusion 300 mg | Takeda Pharmaceutical Company Limited. | November 7, 2018 |
| Nonacog beta pegol (genetical recombination)<br>Refixia I.V. Injection 500, 1000, 2000 | Novo Nordisk Pharma Ltd. | November 1, 2018 |

*1 Transthyretin cardiac amyloidosis (wild type and mutant type)

*2 The following life-threatening arrhythmias when they are refractory and time-critical

Ventricular fibrillation, ventricular tachycardia accompanied by haemodynamic instability

*3 Bronchial asthma (only for sever or refractory cases whose symptoms are not adequately controlled with existing treatments)

*4 Type 1 diabetes mellitus

*5 Ankylosing spondylitis that does not adequately respond to existing treatments