# Pharmaceuticals and Medical Devices Safety Information

**September 2026**

**No. 432**

**Table of contents**


1. Revision of PRECAUTIONS for acetaminophen-containing preparations ..... 5

2. Revision of "Q&A on Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents" ..... 8

3. Important Safety Information ..... 12

1. (1) Avelumab (genetical recombination) ..... 12
   (2) Atezolizumab (genetical recombination)
   (3) Durvalumab (genetical recombination)
   (4) Tremelimumab (genetical recombination)
2. (1) Tislelizumab (genetical recombination) ..... 14
   (2) Retifanlimab (genetical recombination)
   (3) Avelumab (genetical recombination)
   (4) Durvalumab (genetical recombination)
   (5) Ipilimumab (genetical recombination)
   (6) Tremelimumab (genetical recombination)
3. Apalutamide ..... 17
4. Nivolumab (genetical recombination) ..... 19
5. Atezolizumab (genetical recombination) ..... 20

4. Revisions of PRECAUTIONS (No. 372) ..... 22

Viltolarsen, and 33 others

5. List of Products Subject to Early Post-marketing Phase Vigilance.... 39



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# Pharmaceuticals and Medical Devices Safety Information No.432

**Ministry of Health, Labour and Welfare**

## [ Outline of Information ]

| No. | Subject | Measures | Outline of Information | Page |
|---|---|---|---|---|
| 1 | **Revision of PRECAUTIONS for acetaminophen-containing preparations** | *P* | Acetaminophen is a drug widely used as an antipyretic analgesic and has been used in a wide range of patients from children to the elderly. Although its safety is considered relatively high, serious adverse reactions may occur in specific patients.<br>Cases of high anion gap metabolic acidosis (HAGMA) that occurred during treatment with acetaminophen have been reported overseas, and based on the review of these cases and findings concerning the mechanism of this event, 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS in the package insert, which was electronized on August 25, 2026, was revised to provide relevant precautions.<br>HAGMA is considered to be induced by accumulation of pyroglutamic acid driven by underlying states such as depletion of glutathione. Patients with specific backgrounds such as serious renal impairment, liver impairment, sepsis, and malnutrition may be at an increased risk of occurrence of HAGMA.<br>This document introduces findings concerning HAGMA associated with acetaminophen-containing preparations and safety measures taken to address this event. | 5 |
| 2 | **Revision of "Q&A on Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents"** | | The handling of labeling items and brand name of drugs, which marketing authorization holders must comply with to prevent medical accidents, has been announced in "Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents" (PMSB Notification No. 935 issued by the Director of Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated September 19, 2000; hereinafter referred to as "Notification No. 935") and "Q&A on Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents" (Joint Administrative Notice issued by Evaluation and Licensing Division and Safety Division of the Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated October 31, 2000).<br>Recently, based on the report on "Research on medical safety related to brand names/packaging, etc. of prescription drugs", a research project funded by Health and Labour Sciences Research Grants conducted in FY 2024 and FY 2025 (research project on regulatory science for drugs, medical devices, etc.), this Q&A was revised on June 17, 2026.<br>This research investigated the handling in | 8 |

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| | | | | |
|---|---|---|---|---|
| | | | clinical settings, and this revision reflects the actual use status in clinical settings and opinions of healthcare professionals. Among the revised contents, three items that are deeply relevant to the clinical settings are presented. | |
| 3 | **(1) Avelumab (genetical recombination), (2) Atezolizumab (genetical recombination), (3) Durvalumab (genetical recombination), (4) Tremelimumab (genetical recombination) and 4 others** | *P*<br>*C* | Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated August 25, 2026, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions. | 12 |
| 4 | **Viltolarsen and 33 others** | *P* | Revisions of PRECAUTIONS (No. 372) | 22 |
| 5 | **List of Products Subject to Early Post-marketing Phase Vigilance** | | List of products subject to Early Post-marketing Phase Vigilance as of July 31, 2026 | 39 |

*E:* Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of PRECAUTIONS, *C*: Case Reports

**Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of healthcare professionals.**

If healthcare professionals such as physicians, dentists, and pharmacists detect adverse reactions, infections, or malfunctions associated with drugs, medical devices, or regenerative medical products, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As healthcare professionals, drugstore and pharmacy personnel are also required to report adverse reactions, etc.

Please utilize the  Report Reception Site for reporting.
(This service is available only in Japanese.)





https://www.pmda.go.jp/safety/reports/hcp/0002.html

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# 1.

# Revision of PRECAUTIONS for acetaminophen-containing preparations

## 1. Introduction

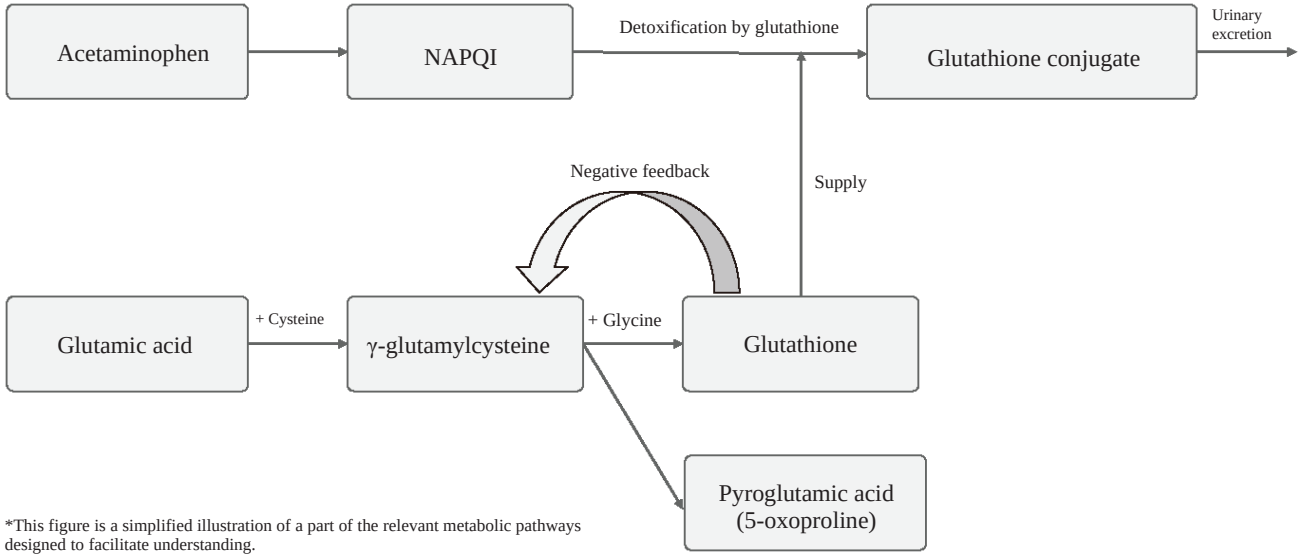
Acetaminophen is a drug widely used as an antipyretic analgesic and has been used in a wide range of patients from children to the elderly. Although its safety is considered relatively high, serious adverse reactions may occur in specific patients.
Cases of high anion gap metabolic acidosis (HAGMA) that occurred during treatment with acetaminophen have been reported overseas, and based on the review of these cases and findings concerning the mechanism of this event, 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS in the package insert, which was electronized on August 25, 2026, was revised. This document introduces the details of the revision.

## 2. HAGMA and background of this revision

HAGMA is metabolic acidosis with a high anion gap that, if advanced, can result in a serious outcome.
Acetaminophen is usually metabolized by glucuronidation and sulfate conjugation, and a portion of the amount administered undergoes oxidative metabolism to produce N-acetyl-p-benzoquinone imine (NAPQI), a reactive metabolite. The NAPQI is detoxified by glutathione conjugation and excreted in urine. In the process of glutathione conjugation, pyroglutamic acid (5-oxoproline) is produced (Figure 1).
When acetaminophen is administered to patients with specific conditions such as serious renal impairment, liver impairment, sepsis, and malnutrition, accumulation of pyroglutamic acid may be promoted by decreased urinary excretion of pyroglutamic acid or disruption of negative feedback regulation resulting from depletion of glutathione. Pyroglutamic acid is an organic acid and is known to make blood tend to be acidic when accumulated, causing pyroglutamic acidosis, which leads to onset of HAGMA (Figure 2).
Overseas, cases of HAGMA through this mechanism have been reported, and healthcare professionals are required to pay attention to HAGMA as an event related to acetaminophen. In Japan, however, the awareness of HAGMA itself is not consistently high, and the risk of the occurrence of HAGMA associated with acetaminophen has not been well announced. Although the frequency of HAGMA is low, it was judged necessary to revise the package insert to provide relevant precautions for healthcare professionals in clinical settings because progression to a serious condition may occur in patients with specific backgrounds and HAGMA is considered to be an event that is explicable given the mechanism of onset.

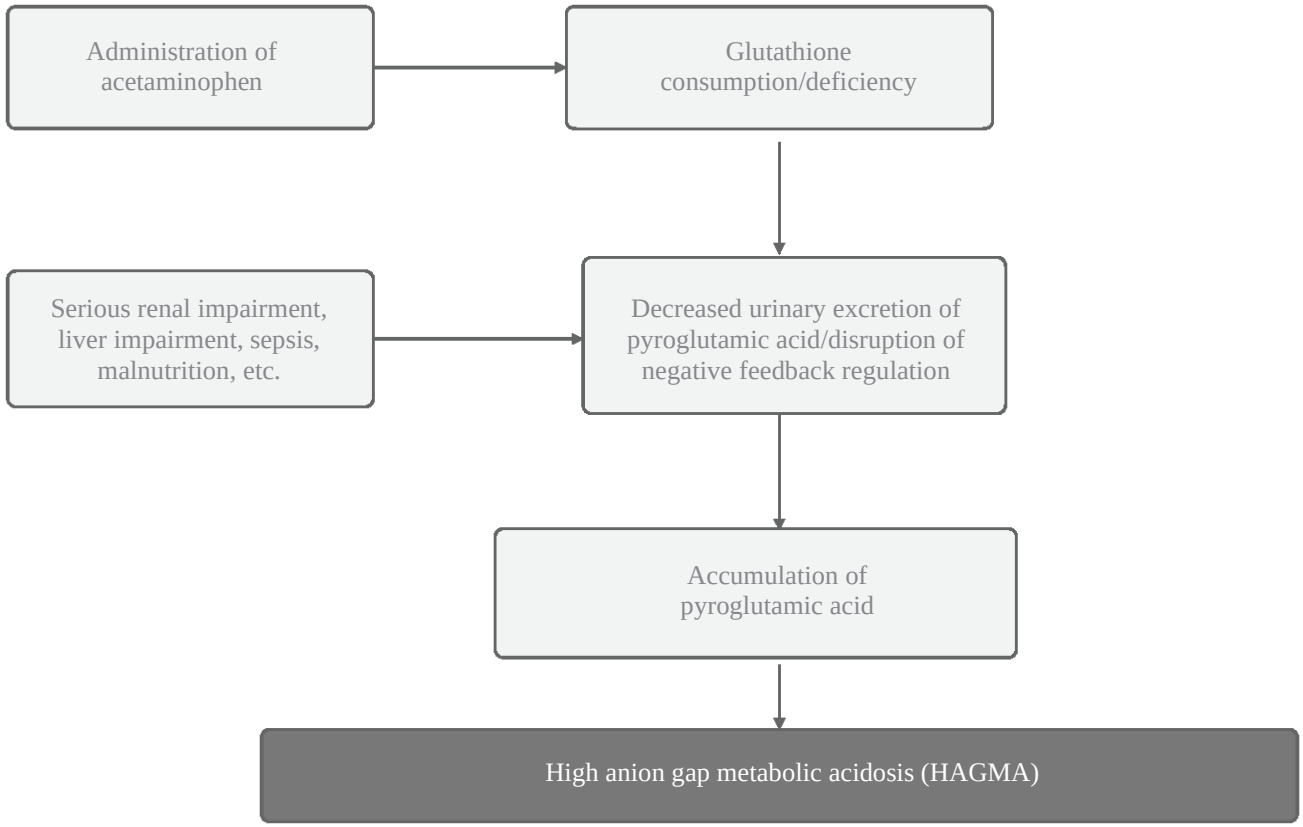
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**Figure 1 Part of the pathways of acetaminophen metabolism (acetaminophen metabolism and glutathione pathway)**




NAPQI produced by acetaminophen undergoes glutathione conjugation and is excreted in urine. Pyroglutamic acid is produced in the glutathione pathway.

**Figure 2 Mechanism of onset of HAGMA (mechanism of onset of HAGMA mediated by pyroglutamic acid)**




In patients who have serious conditions as a background factor, a decrease in urinary excretion of pyroglutamic acid or disruption of negative feedback regulation associated with the background factor may occur, and when these conditions coexist with consumption of glutathione due to administration of acetaminophen, accumulation of pyroglutamic acid is promoted, possibly leading to HAGMA.

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## 3. Details of the revision

Recently, the following precautionary statements have been newly added to the electronized package inserts of acetaminophen-containing preparations (prescription drug).
It is considered unnecessary, at this time, to revise package inserts of OTC drugs containing acetaminophen because patients with specific backgrounds who may experience HAGMA are considered to correspond to (1) Persons receiving treatment by a physician or dentist in the “Consultation” section of the package insert.

A changed description is underlined

| Current | Revision |
|---|---|
| 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS<br>9.1 Patients with Complication or History of Diseases, etc.<br>(newly added) | 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS<br>9.1 Patients with Complication or History of Diseases, etc.<br><u>9.1. Patients with a predisposition to accumulation of pyroglutamic acid due to serious renal impairment, liver impairment (excluding serious liver impairment), sepsis, malnutrition, etc. Pyroglutamic acid excretion is inhibited or glutathione deficiency occurs in these patients. Administration of this drug may promote accumulation of pyroglutamic acid to cause high-anion gap metabolic acidosis.</u> |

## 4. Points to be noted in clinical settings

As shown in this revision, patients with a predisposition to accumulation of pyroglutamic acid due to specific conditions such as serious renal impairment, liver impairment, sepsis, and malnutrition may be at an increased risk of occurrence of HAGMA.
If metabolic acidosis is observed during administration of acetaminophen, it is important to consider the possibility of HAGMA due to accumulation of pyroglutamic acid in addition to the possibility of metabolic acidosis due to common causes such as lactic acidosis, diabetic ketoacidosis, and renal failure and make an appropriate diagnosis and take appropriate actions.
In particular, if high anion gap metabolic acidosis of unknown cause (symptoms: dyspnoea/tachypnoea, general malaise, inappetence/nausea/vomiting, headache/depressed level of consciousness/delirium/confusion, etc.) is observed, the patient background and the use status of acetaminophen should be checked.

## 5. In closing

Although the frequency of HAGMA associated with acetaminophen is not high, serious metabolic acidosis may occur in patients with specific backgrounds.
Healthcare professionals are requested to understand the purpose of the revision this time and pay careful attention to administration of acetaminophen to patients with a predisposition to accumulation of pyroglutamic acid and continuously cooperate in ensuring the proper use of the drug.

## 6. References


• Revisions of PRECAUTIONS (PSB/PSD Notification No. 0825-1 dated August 25, 2026)
https://www.mhlw.go.jp/content/11120000/001742182.pdf.



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# 2.

# Revision of “Q&A on Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents”

## 1. Introduction

The handling of labeling items and brand name of drugs, which marketing authorization holders must comply with to prevent medical accidents, has been announced in “Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents” (PMSB Notification No. 935 issued by the Director of Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated September 19, 2000; hereinafter referred to as “Notification No. 935”) and “Q&A on Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents” (Joint Administrative Notice issued by Evaluation and Licensing Division and Safety Division of the Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated October 31, 2000).
Recently, based on the report on “Research on medical safety related to brand names/packaging, etc. of prescription drugs”, a research project funded by Health and Labour Sciences Research Grants conducted in FY 2024 and FY 2025 (research project on regulatory science for drugs, medical devices, etc.), this Q&A was revised on June 17, 2026. This research investigated the handling in clinical settings, and this revision reflects the actual use status in clinical settings and opinions of healthcare professionals.
This document introduces the following three items that are deeply relevant to the clinical settings.

(1) Labels to be applied to syringes, which are provided as an attachment of oral/external preparations contained in a vial or ampule
(2) Information to be described on the PTP sheet (inner bag) and where to describe the information
(3) Labeling items and brand names to prevent misuse of sustained-release preparations, enteric-coated preparations, etc.

For products whose labeling, etc. are to be changed in response to this revision, the marketing authorization holder will find an appropriate timing to change the labeling and proceed with the changing process gradually. For this reason, products with old labelling and products with new labelling will coexist in clinical settings for the time being.

## 2. Labels to be applied to syringes, which are provided as an attachment of oral/external preparations contained in a vial or ampule

(1) Previous handling

Preparations filled in a vial or an ampule, even if they are oral or external preparations, may be injected by mistake because they are similar to injections in appearance. For this reason, Notification No. 935 specifies that the words “injection prohibited” and words indicating the method of handling or route of administration of the preparation be described on the label of the immediate container and that a label required to be applied to a syringe after the drug solution is drawn into the syringe be included in the package of the product (see the figure below). These measures are specified to prevent such syringes from being mixed up with syringes for injection.

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Excerpted from Notification No. 935
Figure 1 An example of describing the information on a label of the immediate container

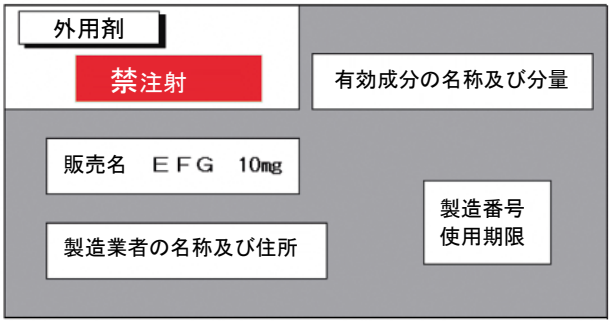
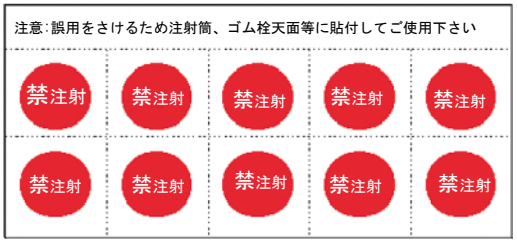



Figure 2 An example of a label required to be applied to a syringe




(2)　Details of this revision
Until now, the labels to be applied to syringes had been specified to be “a circle-shaped label with a diameter of about 15 mm,” and it had been interpreted that the number of labels and how to include the labels in the package of the products are also strictly specified. Accordingly, the handling was arranged as follows considering the actual status and the use conditions, etc. of the products (Q8 to Q10).

| Item | Handling before and after the revision |
|---|---|
| Shape/size | (Before the revision) Circle-shaped label with a diameter of about 15 mm<br>(**After the revision**) The labels of shapes other than a circular shape are acceptable if they are in a shape and size that can be easily recognized when being applied to a syringe. |
| Number of labels to be included | (Before the revision) The number should be the same as the number of vials, etc. in the package.<br>(**After the revision**) The number may be the same as the number of vials, etc. in the package or larger. |
| How to include the labels in the packages | (Before the revision) Labels should be included in each package of the product, such as the outer box.<br>(**After the revision**) Labels may be provided separately from the product or an arrangement may be made so that a part of a label of the immediate container of the product can be detached and the detached part can be used as a label for a syringe. |

**[Points to be noted in clinical settings]**
The healthcare professionals may encounter the following situations for products whose package has included labels required to be applied to syringes as an attachment so far: Labels with different shapes and sizes from previous ones may be included in the package; A label of the immediate container (vials or ampules) may be designed so that a part of the label can be detached and the detached part can be applied to a syringe. In any case, a label should be applied to a syringe each time it is used as before.

## 3. Information to be described on the PTP sheet (inner bag) and where to describe the information

The PTP sheet is a package repeatedly seen in the processes from dispensing of a drug/inspection of the dispensed drug to administration of the drug to a patient, and Notification No. 935 specifies items to be described on a PTP sheet, such as Japanese brand name, specification/content, and precautionary notes, and where to describe these items. In this revision, some adjustments were made to these requirements as follows:

(1)　Description of specification/content (Q17 to Q20)
It has been required so far that specification/content be described separately from the brand name uniformly from the

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viewpoint of distinguishability, even if the brand name contains the specification/content. Currently, however, there are many products whose brand name contains specification information, which may cause duplication of information. On the other hand, the investigation conducted by the research group found that healthcare professionals have cautious opinions regarding the omission of specification/content; they insisted on the necessity of describing the specification independently from the viewpoints of visibility and prevention of misuse.
Based on these situations, it was decided to maintain the requirement of describing specification/content on a PTP sheet as a basic rule and **allow omitting the specification/content from the items described on a PTP sheet only if the Japanese brand name contains the information on specification/content**. In this case, the brand name should contain the unit such as "mg", and should contain the description of content even if only one strength is available for the product (excluding combination drugs).
If a product symbol specific to the product contains the specification/content (for products whose Japanese brand name does not contain the specification/content information), the symbol cannot be a substitute for description of the specification/content

**[Points to be noted in clinical settings]**
The handling of description on a PTP sheet has been revised, but a brand name or a specification/content as independent information will be described on the PTP sheet, and therefore it is possible to identify the specification/content by looking at the PTP sheet as before.

(2) Where to describe the information (Q25 to Q28)
The inner bags of drugs include PTP sheets without margin, SP packages, etc. that make it difficult to distinguish between front and back surfaces, and those for which it is difficult to describe information on the surface due to manufacturing designs. For handling in these cases, it was defined that where to describe the information does not have to always follow the requirements specified in Notification No. 935 if necessary information is provided in a way that enables the information to be recognized appropriately at the time of dispensing or at the time of administration. However, **Japanese brand name, specification/content, and precautionary notes are supposed to be seen once per area for about 2 tablets (capsules) on the PTP sheet**. This is to make it possible to identify the drug even after separating the PTP sheet.

**[Points to be noted in clinical settings]**
This revision was made to clarify the handling of cases to which the unified rules for the information description cannot be applicable. Where the information is described may vary depending on the product, but the brand name, etc. will remain identifiable even after the sheet is separated. Healthcare professionals are requested to continue the operation of checking the information described on the PTP sheet even in the case where the products are dispensed as a one dose package or divided into individual tablets or capsules to be carried by a patient.

(3) English brand name (Q16)
It has been required so far that the English brand name be described on the PTP sheet unless prescription in English brand name cannot be assumed; for example, prescription of Chinese medicine, etc.
The investigation conducted by the research group found that there are some advantages of describing English brand name such as facilitation of drug administration guidance for non-Japanese patients and enhancement of communication with multinational staff, but on the other hand, the following opinion was frequently presented: the information has basically been checked with Japanese brand name in the processes from prescription to inspection and situations where description of English brand name directly contributes to the improvement in safety are limited. Based on these situations, the necessity for uniformly requiring description of English brand name is considered low, and therefore **description of English brand name is specified to be optional**.

**[Points to be noted in clinical settings]**
Products without an English brand name on the PTP sheet will be delivered. If a description of English brand name is utilized in drug administration guidance, etc. for non-Japanese patients, please consider utilizing electronic package inserts, drug information provision documents, materials in multiple languages, etc.

## 4. Labeling items and brand names to prevent misuse of sustained-release preparations and enteric-coated preparations (Q22, Q31)

(1) Background
Some sustained-release or enteric-coated preparations cannot be clearly identified as such from their brand name and appearance. If they are administered after being crushed or divided by mistake, the administration may lead to significant consequences such as rapid increase in the blood concentrations or failure to obtain the expected drug effect. Since such cases have occurred, PMDA Medical Safety Information No. 65 was issued in March 2023 to

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provide precautions in the handling of sustained-release preparations for healthcare professionals in clinical settings.

(2) Details of this revision

Based on the above, the handling of PTP sheet, etc. and brand name is presented below to prevent misuse of sustained-release preparations.

- For sustained-release preparations and enteric-coated preparations, **it is desirable to describe precautionary notes such as “Do not chew” or “Do not crush” on the inner bag such as PTP sheet**. Taking actions with respect to existing products should also be considered when there is an opportunity to change the labeling.
- For drugs to be approved in the future, in principle, marketing authorization holders should **create the brand names so that they contain such words as “sustained-release tablets” and “enteric-coated tablets”** instead of expressing formulation characteristics with alphabets alone.

**[Points to be noted in clinical settings]**

The existing products include those whose brand name does not contain words such as “sustained-release” and “enteric-coated”, and even if alphabets indicating a sustained-release preparation (e.g. LA, CR, SR, R, L, etc.) are contained, the meaning differs by product, and therefore it may be difficult to judge whether the drug may be crushed/divided only from the brand name.

The number of products for which precautionary notes such as "Do not chew" or "Do not crush" are described on the PTP sheet will increase in the future. However, it cannot be judged that crushing is allowed just because of the absence of such precautionary notes. **Whether crushing a drug or using a simple suspension method can be acceptable or not should be determined by checking the descriptions in the electronic package insert and information provided by the marketing authorization holder.**

On PTP sheets, etc., words representing the dosage form such as "sustained-release tablets" and "enteric-coated tablets" may be omitted from the Japanese brand names because of space limitations, etc. It has been specified that precautionary notes be described so that misuse can be prevented even in such cases, and therefore please check the information on the entire sheet including the presence or absence of the precautionary notes.

## 5. In closing

This revision was made from the viewpoint of improving the distinguishability and visibility in the actual clinical settings based on the actual use status in clinical settings and opinions of healthcare professionals while maintaining necessary safety measures including labeling and providing precautions.

Healthcare professionals are requested to confirm the details of this revision and, as necessary, review the procedures for identification/differentiation of drugs at each institution and the contents to be announced to staff members.

## 6. References


- “Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents” (PMSB Notification No. 935 issued by the Director of Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated September 19, 2000)
- “Partial Revision of Q&A on Handling of Labeling Items and Brand Name of Drugs to Prevent Medical Accidents” (Joint Administrative Notice issued by Evaluation and Licensing Division and Safety Division of the Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated on June 17, 2026)
- PMDA Medical Safety Information No. 65 (March 2023)
- “Research on medical safety related to brand names/packaging, etc. of prescription drugs” funded by Health and Labour Sciences Research Grants. FY2025 General research report


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# 3.

# Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated August 25, 2026, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

## 1 (1) Avelumab (genetical recombination)
## (2) Atezolizumab (genetical recombination)
## (3) Durvalumab (genetical recombination)
## (4) Tremelimumab (genetical recombination)

| | |
|---|---|
| **Brand name (name of company)** | (1) Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)<br>(2) Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.)<br>(3) Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)<br>(4) Imjudo Injection 25 mg, 300 mg (AstraZeneca K.K.) |
| **Therapeutic category** | Other antitumor agents |
| **Indications** | (1) ○ Radically unresectable Merkel cell carcinoma<br>○ Radically unresectable or metastatic renal cell carcinoma<br>○ Maintenance treatment of radically unresectable urothelial carcinoma following chemotherapy<br>(2) < Common to drug products ><br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Adjuvant treatment for PD-L1 positive non-small cell lung cancer<br>○ Extensive stage small cell lung cancer<br>○ Unresectable alveolar soft part sarcoma<br>○ Recurrent or refractory extranodal NK/T-cell lymphoma/nasal type<br>< Tecentriq for Intravenous Infusion 1200 mg ><br>○ Unresectable hepatocellular carcinoma<br>○ Unresectable thymic carcinoma<br>< Tecentriq for Intravenous Infusion 840 mg ><br>○ PD-L1 positive, hormone receptor negative and HER2 negative inoperable or recurrent breast cancer<br>(3) ○ Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy<br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Neoadjuvant and adjuvant treatment for non-small cell lung cancer<br>○ Extensive stage small cell lung cancer<br>○ Maintenance treatment of limited-stage small cell lung cancer following definitive chemoradiation therapy<br>○ Unresectable hepatocellular carcinoma<br>○ Unresectable biliary tract cancer<br>○ Advanced or recurrent endometrial cancer<br>○ Neoadjuvant and adjuvant treatment for bladder cancer<br>○ High-risk non-muscle-invasive bladder cancer<br>○ Neoadjuvant and adjuvant treatment for gastric cancer<br>(4) < Imjudo Injection 25 mg ><br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Unresectable hepatocellular carcinoma<br>< Imjudo Injection 300 mg ><br>○ Unresectable hepatocellular carcinoma |

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**PRECAUTIONS (Revised language is underlined.)**

| | |
|---|---|
| **8. IMPORTANT PRECAUTIONS (newly added)** | Uveitis may occur. Whether ocular abnormalities occur should be examined periodically. In addition, patients should be instructed to immediately seek medical attention if any ocular abnormalities are observed. |
| **11. ADVERSE REACTIONS** | Uveitis |
| **11.1 Clinically Significant Adverse Reactions (newly added)** | |

**Reference**

Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database

(1) Cases involving uveitis reported in Japan:
0 patients (No patient mortalities)
(2) Cases involving uveitis reported in Japan:
3 patients (No patient mortalities)
(3) Cases involving uveitis reported in Japan:
1 patient (No patient mortalities)
(4) Cases involving uveitis reported in Japan:
1 patient (No patient mortalities)

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

(1) approximately 1,421
(2) approximately 18,920
(3) approximately 12,580
(4) approximately 3,230

Japanese market launch:

(1) Bavencio intravenous infusion 200 mg: November 2017
(2) Tecentriq for Intravenous Infusion 840 mg: November 2019, Tecentriq for Intravenous Infusion 1200 mg: April 2018
(3) Imfinzi Injection 120 mg, 500 mg: August 2018
(4) Imjudo Injection 25 mg, 300 mg: March 2023

**Case summary**

| No. | Patient | | Daily dose/ Administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 1 | Male 70s | Unresectable hepatocellular carcinoma (hepatic cirrhosis, hepatitis C, renal impairment, hypertension, arrhythmia, lumbar spinal stenosis, chronic kidney disease, cataract) | Durvalumab 1500 mg 2 cycles every 4 weeks<br><br>Tremelimumab 300 mg single dose | Uveitis<br>Allergy history: None<br>Other: The patient had a history of alcohol drinking and was an ex-tobacco user | |
| | | | | 5 years and 10 months before administration | Hepatocellular carcinoma was diagnosed, and hepatectomy was performed. |
| | | | | 4 years and 6 months before administration | Treatment with transcatheter arterial chemoembolization (TACE) + lenvatinib was performed for hepatocellular carcinoma. |
| | | | | 4 years before administration | Transcatheter arterial embolization (TAE) was performed for hepatocellular carcinoma. |
| | | | | 16 days before administration | Best-corrected visual acuity: Right 1.0, left 0.3 |
| | | | | Day 1 of administration (Day 1 of administration of durvalumab, day of single dose of tremelimumab) | Treatment with durvalumab and tremelimumab was started for unresectable hepatocellular carcinoma.<br>Child-Pugh classification: Class A, total score: 6. |
| | | | | Day 28 of administration | The second dose of durvalumab was administered.<br>After the administration, blurred vision and visual acuity reduced in the right eye were noted. |

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| | | | | | |
|---|---|---|---|---|---|
| | | | | Date unknown | Macular oedema following central retinal vein occlusion in the left eye, aphakia in the right eye, left cataract, and macular oedema associated with central retinal vein occlusion (CRVO ME) in the left eye occurred. |
| | | | | Day 47 of administration | The patient visited the department of ophthalmology. Grade 3 uveitis was diagnosed. Mutton fat-like keratic precipitates and vitreous opacities were observed in the right eye. Treatment with betamethasone sodium phosphate eye drop and tropicamide and phenylephrine hydrochloride eye drop was started.<br>Best-corrected visual acuity: Right 0.3, left 0.3 |
| | | | | Day 54 of administration | Inflammation of the anterior part of the right eye improved, but findings of uveitis were noted also in the left eye. Treatment with eye drops was continued. |
| | | | | Day 57 of administration | While uveitis tended to improve, macular oedema slightly persisted. The third dose of durvalumab scheduled for the same day was not administered. |
| | | | | Day 71 of administration | While uveitis in the left eye had improved, vitreous opacities in the right eye persisted. Therefore, subtenon steroid injection (triamcinolone acetonide) in the right eye was performed.<br>Best-corrected visual acuity: Right 0.3, left 0.4 |
| | | | | Day 85 of administration | Vitreous opacities in the right eye had almost resolved, and improvement in uveitis based on ophthalmological examination was noted. Uveitis was resolving. |
| | Concomitant suspect drugs: Durvalumab, tremelimumab<br>Concomitant drugs: None | | | | |

## 2 (1) Tislelizumab (genetical recombination)<br>(2) Retifanlimab (genetical recombination)<br>(3) Avelumab (genetical recombination)<br>(4) Durvalumab (genetical recombination)<br>(5) Ipilimumab (genetical recombination)<br>(6) Tremelimumab (genetical recombination)

| | |
|---|---|
| **Brand name<br>(name of company)** | (1) Tevimbra I.V. Infusion 100 mg (BeOne Medicines Japan)<br>(2) Zynyz for Intravenous Infusion 500 mg (Incyte Biosciences Japan G.K.)<br>(3) Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)<br>(4) Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)<br>(5) Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)<br>(6) Imjudo Injection 25 mg, 300 mg (AstraZeneca K.K.) |
| **Therapeutic category** | Other antitumor agents |
| **Indications** | (1) ○ Radically unresectable, advanced or recurrent oesophageal carcinoma<br>○ Unresectable, advanced or recurrent gastric cancer<br>(2) Unresectable advanced or recurrent squamous cell carcinoma of the anal canal<br>(3) ○ Radically unresectable Merkel cell carcinoma<br>○ Radically unresectable or metastatic renal cell carcinoma<br>○ Maintenance treatment of radically unresectable urothelial carcinoma following chemotherapy<br>(4) ○ Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy<br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Neoadjuvant and adjuvant treatment for non-small cell lung cancer<br>○ Extensive stage small cell lung cancer<br>○ Maintenance treatment of limited-stage small cell lung cancer following definitive chemoradiation therapy<br>○ Unresectable hepatocellular carcinoma<br>○ Unresectable biliary tract cancer<br>○ Advanced or recurrent endometrial cancer<br>○ Neoadjuvant and adjuvant treatment for bladder cancer<br>○ High-risk non-muscle-invasive bladder cancer<br>○ Neoadjuvant and adjuvant treatment for gastric cancer |

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| | |
|---|---|
| | (5) ○ Radically unresectable malignant melanoma<br>○ Radically unresectable or metastatic renal cell carcinoma<br>○ Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer<br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Unresectable, advanced or recurrent malignant pleural mesothelioma<br>○ Radically unresectable, advanced or recurrent oesophageal carcinoma<br>○ Unresectable hepatocellular carcinoma<br>(6) < Imjudo Injection 25 mg ><br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Unresectable hepatocellular carcinoma<br>< Imjudo Injection 300 mg ><br>○ Unresectable hepatocellular carcinoma |

**PRECAUTIONS (Revised language is underlined.)**

| | |
|---|---|
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions**<br>**(newly added)** | Haemophagocytic lymphohistiocytosis |

**Reference**

Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database
(1) No cases have been reported in Japan to date.
(2) No cases have been reported in Japan to date.
(3) No cases have been reported in Japan to date.
(4) Cases involving haemophagocytic lymphohistiocytosis reported in Japan: 3 patients (No patient mortalities)
(5) Cases involving haemophagocytic lymphohistiocytosis reported in Japan: 2 patients (No patient mortalities)
(6) Cases involving haemophagocytic lymphohistiocytosis reported in Japan: 1 patient (No patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period:
(1) approximately 669
(2) approximately 6
(3) approximately 1,421
(4) approximately 12,580
(5) approximately 9,583
(6) approximately 3,230

Japanese market launch:
(1) Tevimbra I.V. Infusion 100 mg: July 2025
(2) Zynyz for Intravenous Infusion 500mg: March 2026
(3) Bavencio intravenous infusion 200 mg: November 2017
(4) Imfinzi Injection 120 mg, 500 mg: August 2018
(5) Yervoy Injection 20 mg: November 2021, Yervoy Injection 50 mg: August 2015
(6) Imjudo Injection 25 mg, 300 mg: March 2023

**Case summary**

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/<br>Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/<br>age</th><th>Reason for use<br>(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td rowspan="2">1</td><td rowspan="2">Male<br>70s</td><td rowspan="2">Hepatocellular carcinoma<br>(prostatic hyperplasia, hypertension, diabetes mellitus, lipids blood increased)</td><td rowspan="2">Durvalumab<br>1500 mg<br>1 cycle<br><br>Tremelimumab<br>300 mg</td><td colspan="2">Haemophagocytic lymphohistiocytosis, immune-mediated enterocolitis<br>Medical history: Dyslipidaemia<br>Past medication history: Atezolizumab (hypothyroidism occurred)</td></tr>
<tr><td>Day 1 of administration</td><td>Durvalumab 1500 mg and tremelimumab 300 mg were administered as fourth-line treatment for hepatocellular carcinoma.</td></tr>
</table>

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| | | | | | |
|---|---|---|---|---|---|
| | | | single dose | Day 7 of administration | Inappetence and diarrhoea occurred. |
| | | | | Day 14 of administration | The patient made an emergency visit at night. The patient was found to have dehydration and pyrexia (38.4 degrees C.) and was admitted to the hospital on the same day. After various tests, administration of tazobactam and piperacillin was started. Diarrhoea was aggravated after hospital admission. Immune-mediated enterocolitis developed. |
| | | | | Day 17 of administration | Ferritin: 3,354 ng/mL, platelet: 36,000/μL. Haemophagocytic lymphohistiocytosis developed. |
| | | | | Day 18 of administration | Lower gastrointestinal endoscopy and biopsy were performed. |
| | | | | Day 19 of administration | The results of pathological examination of specimens from the intestinal mucosa suggested that the condition was consistent with enterocolitis as an immune-mediated adverse event. Prednisolone 50 mg/day was started (approximately 1 mg/kg/day). |
| | | | | Day 21 of administration | Bone marrow aspiration was performed. |
| | | | | Day 22 of administration | The results of bone marrow aspiration demonstrated features indicative of haemophagocytosis, and haemophagocytic lymphohistiocytosis associated with the immune-mediated adverse event was diagnosed. Prednisolone was switched to dexamethasone 11.55 mg administered via intravenous drip infusion. The clinical course of diarrhoea and enterocolitis was uneventful. |
| | | | | Day 36 of administration | The dose of dexamethasone was reduced to 6.25 mg administered via intravenous drip infusion. |
| | | | | Day 40 of administration | The dose of dexamethasone was reduced to 5 mg administered orally. |
| | | | | Day 47 of administration | The patient was discharged from the hospital. |
| | | | | Day 50 of administration | The dose of dexamethasone was reduced to 4 mg administered orally. |
| | | | | Day 53 of administration | The patient was re-admitted to the hospital for respite care. Platelet count remained low. The patient was discharged from the hospital while continuing treatment with dexamethasone 4 mg/day. The disease activity might have contributed to low platelets. |
| | | | | Date unknown | Haemophagocytic lymphohistiocytosis had not resolved. |

**Laboratory test values**

| Test item (unit) | Day 1 of administration | Day 14 of administration | Day 15 of administration | Day 17 of administration | Day 22 of administration | Day 41 of administration | Day 46 of administration | Day 53 of administration |
|---|---|---|---|---|---|---|---|---|
| Hb (g/dL) | 10.3 | 13.8 | - | 12.1 | 8.4 | - | 10.9 | 13.4 |
| Neu (/μL) | 2,780 | 6,314 | - | 6,075 | 5,580 | - | 3,375 | 4,300 |
| Platelets ($10^4$/μL) | 18.9 | 12.1 | 10.2 | 3.6 | 4.5 | 10.7 | 6.9 | 4.6 |
| ALT (IU/L) | 25 | 55 | 108 | 156 | 146 | 261 | - | - |
| LDH (IU/L) | 117 | 436 | 539 | 495 | 290 | 266 | - | - |
| Ferritin (ng/mL) | - | - | - | 3,354 | 684 | 587 | - | 2,514 |
| sIL-2R (U/mL) | - | - | - | - | - | - | 638 | 1,328 |
| TG (mg/dL) | 99 | - | - | - | 106 | - | 70 | 163 |
| Fibrinogen (mg/dL) | 511 | - | - | - | - | - | - | - |
| Na (mEq/L) | 139 | 138 | - | 137 | 131 | - | 131 | 130 |

Concomitant drugs: Ursodeoxycholic acid, dried thyroid/levothyroxine sodium hydrate, rabeprazole sodium, clostridium butyricum preparation, l-isoleucine, l-leucine and l-valine, lactulose, levocarnitine chloride, azilsartan, metformin hydrochloride, rosuvastatin calcium, silodosin, cilnidipine

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## 3 Apalutamide

| | |
|---|---|
| **Brand name (name of company)** | Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.) |
| **Therapeutic category** | Other antitumor agents |
| **Indications** | ○ Non-metastatic castration-resistant prostate cancer<br>○ Metastatic prostate cancer |

**PRECAUTIONS (Revised language is underlined.)**

| | |
|---|---|
| **8. IMPORTANT PRECAUTIONS (newly added)** | Agranulocytosis, neutropenia, or leukopenia may occur. Patients should be carefully monitored through periodic blood tests, etc. during treatment with this drug. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | Agranulocytosis, neutropenia, leukopenia |

**Reference**

Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database
< Agranulocytosis >
Cases involving agranulocytosis reported in Japan:
1 patient (No patient mortalities)
< Neutropenia >
Cases involving neutropenia reported in Japan:
7 patients (No patient mortalities)
< Leukopenia >
Cases involving leukopenia reported in Japan:
5 patients (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 6,442
Japanese market launch: Erleada Tablets 60 mg: May 2019

**Case summary**

| No. | Patient | | Daily dose/ Administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 1 | Male 70s | Metastatic prostate cancer (renal failure, dialysis, chronic kidney disease, metastases to bone, metastases to lymph nodes, infection, hand injury) | 120 mg 47 days ↓ Discontinuation | Febrile neutropenia<br>Medical history: Ex-smoker, cardiac failure | |
| | | | | Day 1 of administration | Administration of apalutamide (120 mg/day) was started. As the patient was on maintenance dialysis for chronic kidney disease, treatment was started at half the usual dose. |
| | | | | Day 46 of administration | Pyrexia of 38 degrees C. occurred. Pain was severe.<br>Administration of cefalexin was started for cellulitis. |
| | | | | Day 47 of administration (day of discontinuation) | Febrile neutropenia was noted. As difficulty in walking was also observed, the patient was transported by an ambulance and was admitted to the hospital. Severe redness and swelling were observed on the back of the left hand. Cellulitis was suspected because CT showed few findings suggestive of other sources of fever.<br>Treatment with filgrastim, tazobactam and piperacillin sodium, and vancomycin hydrochloride was started.<br>White blood cell count had decreased to 800/μL. |
| | | | | 1 day after discontinuation | Pyrexia subsided, and white blood cell count had increased to 2,000/μL. Therefore, administration of filgrastim was completed. |
| | | | | 2 days after discontinuation | Hemodialysis was provided. |
| | | | | 4 days after discontinuation | Hemodialysis was provided. |

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|---|---|---|---|---|---|
| | | | | 6 days after discontinuation | Hemodialysis was provided. |
| | | | | 9 days after discontinuation | Administration of vancomycin hydrochloride was completed. Hemodialysis was provided. |
| | | | | 11 days after discontinuation | Administration of tazobactam and piperacillin sodium was completed. Hemodialysis was provided. |
| | | | | 12 days after discontinuation | Cellulitis (the left upper limb) had resolved. |
| | | | | 13 days after discontinuation | Oral administration of levofloxacin hydrate was started. Hemodialysis was provided. |
| | | | | 14 days after discontinuation | Febrile neutropenia had resolved. The symptoms of cellulitis were alleviated with administration of antibiotics, and the patient was discharged from the hospital. |

**Laboratory test values**

| Test item (unit) | Day 15 of administration | Day 43 of administration | Day 46 of administration | Day of discontinuation | 1 day after discontinuation | 2 days after discontinuation | 4 days after discontinuation | 6 days after discontinuation | 9 days after discontinuation |
|---|---|---|---|---|---|---|---|---|---|
| White blood cell count (/μL) | 5,500 | 1,400 | - | 800 | 2,000 | 2,700 | 5,500 | 7,800 | 9,300 |
| Neutrophil count (/μL) | - | - | - | - | - | 1,071 | 3,685 | - | - |

Concomitant suspect drugs: None
Concomitant drugs: Eldecalcitol, lanthanum carbonate hydrate, vonoprazan fumarate, polaprezinc, epinastine hydrochloride, amezinium metilsulfate

## Case summary

| No. | Patient: Sex/ age | Patient: Reason for use (complication) | Daily dose/ Administration duration | Adverse reaction: Clinical course and treatment | |
|---|---|---|---|---|---|
| 2 | Male 80s | Castration-resistant prostate cancer (none) | 180 mg 44 days ↓ Discontinuation | Agranulocytosis<br>Medical history: Angina pectoris, gallstones, orchidectomy, ex-tobacco user. | |
| | | | | Day 1 of administration | The patient started receiving apalutamide (180 mg/day) for castration-resistant prostate cancer. |
| | | | | Day 44 of administration (day of discontinuation) | Administration of apalutamide was discontinued. |
| | | | | 1 day after discontinuation | The patient visited the hospital with a chief complaint of malaise, and received a diagnosis of agranulocytosis as indicated by a neutrophil count of 54/μL and was admitted to the hospital. Administration of filgrastim was started. |
| | | | | 2 days after discontinuation | Pyrexia started to be noted on the following day of admission, and febrile neutropenia developed, for which administration of meropenem hydrate was started. No infection focus was found, and the blood culture result was negative. |
| | | | | 3 days after discontinuation | The neutrophil count had decreased to 0/μL. After that, the neutrophil count gradually recovered. |
| | | | | 13 days after discontinuation | The neutrophil count remained below 100 for a while, but recovered to 2,414/μL. Treatment with filgrastim and meropenem hydrate was completed. |
| | | | | 15 days after discontinuation | The symptoms had resolved, and the patient was discharged from the hospital. |
| | | | | Date unknown | The patient was followed up, and no recurrence was noted. |

**Laboratory test values**

| Test item (unit) | Day 1 of administration | Day 21 of administration | 1 day after discontinuation | 3 days after discontinuation | 8 days after discontinuation | 13 days after discontinuation |
|---|---|---|---|---|---|---|
| White blood cell count (/μL) | 6,700 | 5,300 | 2,700 | - | - | 6,800 |
| Neutrophil count (/μL) | 4,730 | 3,060 | 54 | 0 | 84 | 2,414 |

Concomitant suspect drugs: None
Concomitant drugs: Monoammonium glycyrrhizinate/glycine/DL-methionine combination drug

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## 4 Nivolumab (genetical recombination)

| | |
|---|---|
| **Brand name (name of company)** | Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.) |
| **Therapeutic category** | Other antitumor agents |
| **Indications** | ○ Malignant melanoma<br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Neoadjuvant therapy for non-small cell lung cancer<br>○ Radically unresectable or metastatic renal cell carcinoma<br>○ Relapsed or refractory classical Hodgkin lymphoma<br>○ Recurrent or metastatic head and neck cancer<br>○ Unresectable, advanced or recurrent gastric cancer<br>○ Unresectable, advanced or recurrent malignant pleural mesothelioma<br>○ Malignant mesothelioma (excluding malignant pleural mesothelioma)<br>○ Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer<br>○ Radically unresectable, advanced or recurrent oesophageal carcinoma<br>○ Postoperative adjuvant therapy for oesophageal carcinoma<br>○ Carcinoma of unknown primary<br>○ Postoperative adjuvant therapy for urothelial carcinoma<br>○ Radically unresectable urothelial carcinoma<br>○ Radically unresectable, advanced or recurrent epithelial skin malignancies<br>○ Unresectable hepatocellular carcinoma |

**PRECAUTIONS (Revised language is underlined.)**

| | |
|---|---|
| **11. Clinically Significant Adverse Reactions** | Severe gastritis, oesophagitis<br>Severe gastritis or oesophagitis considered to be due to an immune reaction may occur. If any abnormalities are observed, appropriate measures including the administration of corticosteroids should be taken. |
| **Reference** | Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database<br>Cases involving oesophagitis reported in Japan:<br>6 patients (No patient mortalities)<br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 27,900<br>Japanese market launch: Opdivo I.V. Infusion 20 mg, 100 mg: September 2014<br>Opdivo I.V. Infusion 120 mg: November 2020<br>Opdivo I.V. Infusion 240 mg: November 2018 |

**Case summary**

| No. | Patient | | Daily dose/ Administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 1 | Male 50s | Unresectable, advanced or recurrent gastric cancer (metastases to bone) | Unknown Unknown | Immune-mediated oesophagitis<br>Medical history: Total gastrectomy, PS: 1 | |
| | | | | Around 13 years before administration | The patient underwent laparoscopic total gastrectomy for advanced gastric cancer. |
| | | | | Day 1 of administration | Treatment with nivolumab (dose unknown) + oxaliplatin + tegafur, gimeracil and oteracil potassium combination drug (SOX therapy) as first-line treatment for gastric cancer (HER2-negative) was started. |
| | | | | Around Month 3 of administration | After 5 doses of nivolumab + SOX therapy, the patient experienced pain precordial with swallowing. |
| | | | | Day 100 of administration | Based on upper gastrointestinal endoscopy (initial examination), reflux oesophagitis was diagnosed. |

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| | | | | | |
|---|---|---|---|---|---|
| | | | | Date unknown | As a treatment for reflux oesophagitis, administration of camostat mesilate (dose unknown) and a gastrointestinal mucosal protectant was started. |
| | | | | Day 112 of administration | As subjective symptoms were exacerbated and made oral intake difficult, the patient was urgently admitted to the hospital. Upper gastrointestinal endoscopy was performed again, which showed worsening of findings of oesophagitis mainly in the lower thoracic esophagus. On the basis of endoscopic findings and course during the treatment, immune-mediated oesophagitis was diagnosed, and prednisolone (dose unknown) was started. |
| | | | | Date unknown | Subjective symptoms gradually improved. |
| | | | | Day 123 of administration | Upper gastrointestinal endoscopy demonstrated improvement in the inflammatory findings. |
| | | | | Date unknown | The patient was able to resume oral intake and was discharged from the hospital. |
| | | | | Day 135 of administration | Upper gastrointestinal endoscopy was performed for follow-up. Not only subjective symptoms but also endoscopic findings demonstrated marked improvement in the inflammatory findings. Immune-mediated oesophagitis had resolved. |
| | Concomitant drugs: Oxaliplatin, tegafur, gimeracil and oteracil potassium combination drug | | | | |

**Case summary**

| No. | Patient | | Daily dose/ Administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 2 | Female 60s | Combination therapy for radically unresectable malignant melanoma (metastases to lymph nodes, stomach, liver, adrenals, bones and brain) | Unknown 2 courses every 4 weeks ↓ Discontinuation | Immune-mediated oesophagitis | |
| | | | | Day 1 of administration | For radically unresectable malignant melanoma (primary lesion: unknown, stage 4), treatment with nivolumab (dose unknown) and ipilimumab (genetical recombination) (dose unknown) was started. |
| | | | | Day 29 of administration | After the second dose, the patient became unable to eat due to chest pain with swallowing and was referred to the hospital. [Upper gastrointestinal endoscopy] Multiple ulcers with punched-out appearance were found throughout the esophagus. [Esophageal biopsy] Many CD4-positive T-lymphocytes and CD8 lymphocytes were observed. Metastasis of malignant melanoma and viral infection were considered unlikely. Based on these test results and the clinical course, oesophagitis (grade 3 or higher) as an immune-related adverse event was diagnosed. Treatment with nivolumab and ipilimumab (genetical recombination) was interrupted. |
| | | | | Day 58 of administration | The symptoms were improving after the treatment interruption but still hindered the patient from eating sufficiently. Intravenous administration of prednisolone 1 mg/kg/day was started. |
| | | | | Date unknown | The patient responded well to the treatment. After the symptoms resolved, tapering of prednisolone was started. Oesophagitis had resolved. |
| | Concomitant drugs: Ipilimumab (genetical recombination) | | | | |

## 5 Atezolizumab (genetical recombination)

| | |
|---|---|
| **Brand name (name of company)** | Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.) |
| **Therapeutic category** | Other antitumor agents |
| **Indications** | < Common to drug products ><br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Adjuvant treatment for PD-L1 positive non-small cell lung cancer<br>○ Extensive stage small cell lung cancer<br>○ Unresectable alveolar soft part sarcoma<br>○ Recurrent or refractory extranodal NK/T-cell lymphoma/nasal type<br>< Tecentriq for Intravenous Infusion 1200 mg ><br>○ Unresectable hepatocellular carcinoma<br>○ Unresectable thymic carcinoma<br>< Tecentriq for Intravenous Infusion 840 mg > |

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| | |
|---|---|
| | ○ PD-L1 positive, hormone receptor negative and HER2 negative inoperable or recurrent breast cancer |

**PRECAUTIONS (Revised language is underlined.)**

| | |
|---|---|
| **8. IMPORTANT PRECAUTIONS (newly added)** | Uveitis may occur. Whether ocular abnormalities occur should be examined periodically. In addition, patients should be instructed to immediately seek medical attention if any ocular abnormalities are observed. |
| **11. ADVERSE REACTIONS** | Uveitis |
| **11.1 Clinically Significant Adverse Reactions (newly added)** | |

**Reference**

Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database
Cases involving uveitis reported in Japan:
3 patients (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 18,920
Japanese market launch: Tecentriq for Intravenous Infusion 840 mg: November 2019
Tecentriq for Intravenous Infusion 1200 mg: April 2018

**Case summary**

| No. | Patient | | Daily dose/ Administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 1 | Female 70s | Non-small cell lung cancer (hypertension, dyslipidaemia [mild], aortic regurgitation, pancytopenia) | 1200 mg/dose 19 courses | Vogt-Koyanagi-Harada disease-like uveitis<br>[Disease stage (Stage)] 3<br>[PS at the start of administration] 2<br>[Metastatic lesion] Pleura and extrapulmonary region<br>[Medical history] Acute hepatitis, appendicitis<br>[History of surgery] Pulmonary resection | |
| | | | | Day 1 of administration | Administration of atezolizumab was started as the second-line and subsequent treatments. |
| | | | | Date unknown | The patient noticed visual acuity reduced in both eyes after the 19th dose of atezolizumab and visited the hospital. The event was not accompanied by extraocular symptoms. However, the patient was positive for HLA-DR4 and was found to have cytosis with predominance of mononuclear cells on cerebrospinal fluid test and then received a diagnosis of Vogt-Koyanagi-Harada disease-like uveitis (Grade-3).<br><br>[Test findings]<br>Visual acuity reduced (Uncorrected visual acuity: Right 0.02/left 0.06, Corrected visual acuity: Right 0.2/left 0.4).<br>Optical coherence tomography (OCT) revealed serous retinal detachment and choroidal thickening, and bilateral panuveitis (with inflammatory cell infiltration).<br>Cerebrospinal fluid test: Cytosis with predominance of mononuclear cells |
| | | | | Day 474 of administration (day of discontinuation) | Administration of atezolizumab was discontinued. |
| | | | | 23 days after discontinuation | Steroid pulse therapy was performed, which resulted in marked improvement in the findings. |
| | | | | 25 days after discontinuation | Steroid pulse therapy was completed. |
| | | | | 26 days after discontinuation | The treatment was switched to oral steroids. |
| | | | | 118 days after discontinuation | Vogt-Koyanagi-Harada disease-like uveitis was resolving. |
| | Concomitant drugs: None | | | | |

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# 4.

# Revisions of PRECAUTIONS (No. 372)

This section provides details of the revisions to the PRECAUTIONS and brand names of drugs that were subject to the revisions in accordance with the Notifications dated August 7, August 17, August 24, August 25, and August 28, 2026.

1 Other agents affecting nervous system and sensory organs

## Viltolarsen

| | |
|---|---|
| **Brand name** | Viltepso Injection 250 mg (Nippon Shinyaku Co., Ltd.) |
| **5. PRECAUTIONS CONCERNING INDICATIONS** | This product should be administered to patients for whom deletion of the dystrophin gene treatable by exon 53 skipping (e.g., deletion of exon 43-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52) has been confirmed by genetic testing. In addition, patients eligible for treatment with this product should be selected based on a thorough understanding of the contents of "17. CLINICAL STUDIES" section concerning dystrophin gene variants in patients enrolled in clinical trials. |
| **(newly added)** | Carefully decide whether to start and continue administration after thoroughly understanding the efficacy and safety of this drug and be thoroughly familiar with the contents of "17. CLINICAL STUDIES" section. In addition, the patient's condition should be carefully monitored after administration and the efficacy should be evaluated periodically to determine whether to continue administration. If no effect is observed, administration should be discontinued.<br>The efficacy and safety of this drug have not been established in patients on long-term mechanical ventilation or in patients with advanced mobility impairment. When administering this drug to these patients, the decision on whether to administer this drug should be made based on consideration of their remaining motor function and other factors. |

2 Other agents affecting central nervous system

## Donanemab (genetical recombination)

| | |
|---|---|
| **Brand name** | kisunla Intravenous Infusion 350 mg (Eli Lilly Japan K.K.) |
| **1. WARNINGS** | The incidence of ARIA was higher in apolipoprotein E allele 4 (APOEε4) homozygote carriers. Implementation of APOE genetic testing should be considered before starting treatment with this drug. Prior to the start of treatment with this drug, the incidence and risks of ARIA associated with the administration of this drug, tests required for management of the risks of ARIA, and measures to be taken when ARIA occurs should be explained to patients and their families/caregivers by providing sufficient information to them and their consent should be obtained. Patients should be instructed to immediately contact their physician if any abnormalities are observed. |
| **8. IMPORTANT PRECAUTIONS** | The frequencies of ARIA-E, ARIA-H, and the serious ARIA-E and ARIA-H are higher in patients who are APOEε4 (homozygote or heterozygote) carriers. Of note, the frequencies were highest in APOEε4 (homozygote) carriers, followed by APOEε4 (heterozygote) carriers and APOEε4 noncarriers. Implementation of APOE genetic testing should be considered before starting treatment with this drug in principle for management of risks of ARIA. Even if the testing was not |

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performed prior to the start of the treatment as a result of the consideration, implementation of the testing should be considered if it is deemed necessary during treatment with this drug. When performing the genetic testing, approved in vitro diagnostics should be used, and the significance of APOE genetic testing should be fully explained to patients and their families/caregivers with reference to the latest guidelines, etc., and their consent should be obtained. In addition, management of ARIA including MRI scanning specified in the 8.2.1 to 8.2.3 sections and the 11.1.2 section should be performed regardless of ApoEε4 carrier status. The percentage of APOEε4 homozygote carriers in a global phase III study (AACI Study) and an overseas phase III study (AACQ Study) of this drug involving patients with mild cognitive impairment or mild dementia due to Alzheimer's disease was 16.7% and 10.1%, respectively.

---

3 Other agents affecting central nervous system

## Lecanemab (genetical recombination)

| | |
|---|---|
| **Brand name** | Leqembi for Intravenous Infusion 200 mg, 500 mg (Eisai Co., Ltd.) |
| **1. WARNINGS** | The incidence of ARIA was higher in apolipoprotein E (ApoE) ε4 homozygote carriers. Implementation of APOE genetic testing should be considered before starting treatment with this drug. Prior to the start of treatment with this drug, the incidence and risks of ARIA associated with the administration of this drug, tests required for management of the risks of ARIA, and measures to be taken when ARIA occurs should be explained to patients and their families/caregivers by providing sufficient information to them and their consent should be obtained. Patients should be instructed to immediately contact their physician if any abnormalities are observed. |
| **8. IMPORTANT PRECAUTIONS** | The incidence and the imaging-assessed severity of ARIA and the incidence of symptomatic ARIA were higher in ApoEε4 homozygote carriers than in ApoEε4 heterozygote carriers or non-carriers. Implementation of APOE genetic testing should be considered before starting treatment with this drug in principle for management of risks of ARIA. Even if the testing was not performed prior to the start of the treatment as a result of the consideration, implementation of the testing should be considered if it is deemed necessary during treatment with this drug. When performing the genetic testing, approved in vitro diagnostics should be used, and the significance of APOE genetic testing should be fully explained to patients and their families/caregivers with reference to the latest guidelines, etc., and their consent should be obtained. In addition, management of ARIA including MRI scanning specified in Sections 8.1.1 to 8.1.3 and Section 11.1.2 should be performed regardless of ApoEε4 carrier status. The percentage of ApoEε4 homozygote carriers in patients with Alzheimer's disease is approximately 15%. |

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4 Other biological preparations

## Freeze-dried Bacillus Calmette-Guérin (BCG) for intravesical use (Japanese strain)

| | |
|---|---|
| **Brand name** | Immunobladder intravesical 80 mg, 40 mg (Japan BCG Laboratory) |
| **2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)** | Patients receiving anticancer therapy (such as cytotoxic chemotherapy or radiotherapy; however, excluding durvalumab (genetical recombination)) |
| **7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION (newly added)** | For the dosage and administration when used in combination with durvalumab (genetical recombination), refer to the electronic package insert for durvalumab (genetical recombination). This product should be administered only when the benefits are considered to outweigh the risks after patients have been |

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sufficiently informed of the risk of disseminated BCG infection.

**10. INTERACTIONS**

**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Immunosuppressants<br>Ciclosporin<br>Tacrolimus<br>Azathioprine,<br>etc.<br>Corticosteroids at immunosuppressive doses | Disseminated Bacillus Calmette-Guerin infection may occur. The effect of this drug may be reduced. | Immunosuppressive therapy not only decreases patients' immune response to this product but may also increase the risk of disseminated BCG infection. |
| Anticancer therapy (such as cytotoxic chemotherapy or radiotherapy; however, excluding durvalumab (genetical recombination)) | | |

5 Antipyretics, analgesics and anti-inflammatory agents, agents used for common cold, antitussives

## (1) Acetaminophen
## (2) Isopropylantipyrine/acetaminophen/allylisopropylacetylurea/anhydrous caffeine
## (3) Tramadol hydrochloride/acetaminophen
## (4) Salicylamide/acetaminophen/anhydrous caffeine/chlorpheniramine maleate
## (5) Salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate
## (6) Diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/bromovalerylurea

**Brand name**

(1) Calonal powder, Calonal tablets 200, 300, 500, Calonal Fine Gran. 20%, 50%, Calonal Syrup 2%, and the others (AYUMI Pharmaceutical Corporation, and the others), Alpiny Suppositories 50, 100, 200, and the others (Hisamitsu Pharmaceutical Co., Inc., and the others), Anhiba pediatric suppository 50 mg, 100 mg, 200 mg, and the others (Viatris Pharmaceuticals Japan G.K., and the others), Calonal Supp. 50 for Pediatric, Calonal Supp. 100, 200, 400, and the others (AYUMI Pharmaceutical Corporation, and the others), acelio Bag for Intravenous Injection 1000 mg (Terumo Corporation)
(2) SG Combination Granules (Shionogi Pharma Co., Ltd.)
(3) Tramcet Combination Tablets, and the others (Janssen Pharmaceutical K.K., and the others)
(4) Pelex combination granule, Pediatric Pelex combination granule (TAIHO Pharmaceutical Co., Ltd)

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(5) PL Combination Granules, and the others, PL Combination Granules for Infants (Shionogi Pharma Co., Ltd.)
(6) Coughcode-N Combination Tablets (Viatris Healthcare G.K.)

**9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS**
**9.1 Patients with Complication or History of Diseases, etc.**
**(newly added)**

Patients with a predisposition to accumulation of pyroglutamic acid due to serious renal impairment, liver impairment (excluding serious liver impairment), sepsis, malnutrition, etc.
Pyroglutamic acid excretion is inhibited or glutathione deficiency occurs in these patients. Administration of this drug may promote accumulation of pyroglutamic acid to cause high-anion gap metabolic acidosis.

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6 Psychotropic agents, other agents affecting digestive organs

## Olanzapine (oral dosage form)

**Brand name**

Zyprexa tablets 2.5 mg, 5 mg, 10 mg, Zyprexa Zydis tablets 2.5 mg, 5 mg, 10 mg, Zyprexa fine granule 1% (CHEPLAPHARM K.K.), OLANZAPINE OD Tablets 2.5 mg, "VTRS," 5 mg "VTRS," 10 mg "VTRS" (Viatris Healthcare G.K.), Olanzapine Tablets 1.25 mg "AMEL," 2.5 mg "AMEL," 5 mg "AMEL," 10 mg "AMEL," 20 mg "AMEL," Olanzapine OD Tablets 1.25 mg "AMEL," 2.5 mg "AMEL," 5 mg "AMEL," 10 mg "AMEL," Olanzapine Fine Granules 1% "AMEL" (Kyowa Pharmaceutical Industry Co., Ltd.), OLANZAPINE Tablets 2.5 mg "KYORIN," 5 mg "KYORIN," 10 mg "KYORIN," OLANZAPINE OD Tablets 2.5 mg "KYORIN," 5 mg "KYORIN," 10 mg "KYORIN," OLANZAPINE Fine Granules 1% "KYORIN" (KYORIN Rimedio Co., Ltd.), OLANZAPINE Tablets 2.5 mg [SAWAI], 5 mg [SAWAI], 10 mg [SAWAI], OLANZAPINE Fine Granules 1% [SAWAI] (Sawai Pharmaceutical Co., Ltd.), OLANZAPINE TABLETS 2.5 mg "DSEP", 5 mg "DSEP", 10 mg "DSEP", OLANZAPINE OD TABLETS 2.5 mg "DSEP", 5 mg "DSEP", 10 mg "DSEP", OLANZAPINE FINE GRANULES 1% "DSEP" (Daiichi Sankyo Espha Co., Ltd.), Olanzapine OD Tablets 2.5 mg "TAKATA," 5 mg "TAKATA," 10 mg "TAKATA," Olanzapine fine granules 1% "TAKATA" (TAKATA Pharmaceutical Co., Ltd.), OLANZAPINE TABLETS 2.5 mg "TOWA," 5 mg "TOWA," 10 mg "TOWA," OLANZAPINE OD TABLETS 2.5 mg "TOWA," 5 mg "TOWA," 10 mg "TOWA," OLANZAPINE FINE GRANULES 1% "TOWA" (Towa Pharmaceutical Co., Ltd.), Olanzapine OD Tablets 2.5 mg "Nichi-Iko," 5 mg "Nichi-Iko," 10 mg "NichiIko," Olanzapine Fine Granules 1% "Nichi-Iko" (Nichi-Iko Pharmaceutical Co., Ltd.), Olanzapine Tablets 2.5 mg "NIG," 5 mg "NIG," 10 mg "NIG," Olanzapine OD Tablets 2.5 mg "NIG," 5 mg "NIG," 10 mg "NIG," (Nichi-Iko Pharmaceutical Co., Ltd. Gifu Plant), Olanzapine Tablets 2.5 mg "NISSIN," 5 mg "NISSIN," 10 mg "NISSIN," Olanzapine Fine Granules 1% "NISSIN" (Nissin Pharmaceutical Co., Ltd.), Olanzapine Tablets 2.5 mg "Nipro," 5 mg "Nipro," 10 mg "Nipro," Olanzapine OD Tablets 2.5 mg "Nipro," 5 mg "Nipro," 10 mg "Nipro," Olanzapine Fine Granules 1% "Nipro," Olanzapine Tablets 2.5 mg "NP," 5 mg "NP," 10 mg "NP," Olanzapine OD Tablets 5 mg "NP," 10 mg "NP," Olanzapine Fine Granules 1% "NP" (Nipro Corporation), Olanzapine OD Tablets 2.5 mg "JG," 5 mg "JG," 10 mg "JG" (Nihon Generic Co., Ltd.), OLANZAPINE Tablets 2.5 mg "MEIJI," 5 mg "MEIJI," 10 mg "MEIJI," OLANZAPINE OD Tablets 2.5 mg "MEIJI," 5 mg "MEIJI," 10 mg "MEIJI," OLANZAPINE Fine granules 1% "MEIJI" (Meiji Seika Pharma Co., Ltd.), OLANZAPINE TABLETS 2.5 mg "YD," 5 mg "YD," 10 mg "YD" (Yoshindo Holdings Inc.)

**1. WARNINGS**
**(newly added)**

< Gastrointestinal symptoms (nausea and vomiting) associated with chemotherapy medicine (such as cisplatin) for cancer >
This drug should not be administered to patients with diabetes mellitus or a history of diabetes mellitus unless the potential therapeutic benefits are considered to

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outweigh the potential risks. Patients should be continuously monitored through such methods as frequent blood glucose monitoring each day before and during administration of this drug and continuous monitoring until blood glucose levels become stable after administration of this drug has ended, and this drug should be administered after establishing a system that enables an adequate response in emergencies throughout the administration period.

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**

< Schizophrenia and improvement of manic symptoms and depressive symptoms in bipolar disorder >
Patients with diabetes mellitus or a history of diabetes mellitus

**9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS**
**9.1 Patients with Complication or History of Diseases, etc. (newly added)**

< Gastrointestinal symptoms (nausea and vomiting) associated with chemotherapy medicine (such as cisplatin) for cancer >
Patients with diabetes mellitus or a history of diabetes mellitus
The following points should be noted. Administration of this drug may increase blood glucose levels and rapidly worsen the metabolic state. This drug should be administered after establishing a system that enables an adequate response in emergencies throughout the administration period.

- This drug should be administered only to patients with good glycaemic control. The necessity of this drug should be judged according to the patient's condition with reference to the latest guidelines of related academic societies, etc.
- The dose and duration of administration of this drug should be limited to the minimum necessary.
- Patients should be continuously monitored through such methods as frequent blood glucose monitoring each day before and during administration of this drug and continuous monitoring until blood glucose levels become stable after administration of this drug has ended.

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7 Other agents affecting digestive organs

## Domperidone

**Brand name**

Nauzelin Tablets 5, 10, Nauzelin OD Tablets 5, 10, Nauzelin Dry Syrup 1%, Nauzelin Suppository 10, 30, 60, and the others (Kyowa Kirin Co., Ltd., and the others)

**8. IMPORTANT PRECAUTIONS (newly added)**

Increased risks of fatal arrhythmias and sudden cardiac death have been suggested in Japanese and overseas epidemiological studies. Serious arrhythmias, including ventricular tachycardia and ventricular fibrillation, may occur. The following precautions should be observed:

- Use should be limited to the minimum necessary, and prolonged treatment without periodic reassessment should be avoided.
- Patients should be instructed to seek immediate medical attention if relevant symptoms occur.
- Patients should be closely monitored, and if relevant symptoms occur, cardiac function tests (electrocardiography, etc.) should be performed immediately.

**11. ADVERSE REACTIONS**

Serious arrhythmias

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

Serious arrhythmias, including ventricular tachycardia and ventricular fibrillation, may occur. If any abnormalities are observed, appropriate measures including discontinuation of this drug, resuscitative measures, and defibrillation should be taken.

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8 Other agents affecting digestive organs

## (1) Metoclopramide
## (2) Metoclopramide hydrochloride

**Brand name**

(1) Primperan Tablets 5, Primperan Syrup 0.1%, Primperan Fine Granules 2%, and

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the others. (Nichi-Iko Pharmaceutical Co., Ltd., and the others)
(2) Primperan Injection 10mg, and the others (Nichi-Iko Pharmaceutical Co., Ltd., and the others)

**8. IMPORTANT PRECAUTIONS (newly added)**

Increased risks of fatal arrhythmias have been suggested in Japanese epidemiological studies and those of sudden cardiac death have been suggested in Japanese and overseas epidemiological studies.
Serious arrhythmias, including ventricular tachycardia and ventricular fibrillation, may occur. The following precautions should be observed:

- Use should be limited to the minimum necessary, and prolonged treatment without periodic reassessment should be avoided.
- Patients should be instructed to seek immediate medical attention if relevant symptoms occur.
- Patients should be closely monitored, and if relevant symptoms occur, cardiac function tests (electrocardiography, etc.) should be performed immediately.

**11. ADVERSE REACTIONS**

Serious arrhythmias

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

Serious arrhythmias, including ventricular tachycardia and ventricular fibrillation, may occur. If any abnormalities are observed, appropriate measures including discontinuation of this drug, resuscitative measures, and defibrillation should be taken.

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9 Other hormone preparations

## Mitotane

**Brand name**

Opeprim (Yakult Honsha Co., Ltd.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**

Patients receiving spironolactone, pentobarbital, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate, darunavir ethanolate/cobicistat, darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate, doravirine, dolutegravir sodium/rilpivirine hydrochloride, bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate, rilpivirine, rilpivirine hydrochloride, rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate, ensitrelvir fumaric acid, and lenacapavir

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate<br>Darunavir ethanolate/cobicistat<br>Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate<br>Doravirine<br>Dolutegravir sodium/rilpivirine hydrochloride<br>Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate<br>Rilpivirine<br>Rilpivirine hydrochloride<br>Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate<br>Ensitrelvir fumaric acid<br>Lenacapavir | The blood concentrations of these drugs may decrease, leading to a reduction in their effects. | The hepatic cytochrome P450 (CYP3A4)-inducing activity of this drug is considered to promote the metabolism of these drugs. |

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10 Other antitumor agents

## (1) Atezolizumab (genetical recombination)
## (2) Avelumab (genetical recombination)
## (3) Durvalumab (genetical recombination)
## (4) Tremelimumab (genetical recombination)

| | |
|---|---|
| **Brand name** | (1) Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.)<br>(2) Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)<br>(3) Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)<br>(4) Imjudo Injection 25 mg, 300 mg (AstraZeneca K.K.) |
| **8. IMPORTANT PRECAUTIONS (newly added)** | Uveitis may occur. Whether ocular abnormalities occur should be examined periodically. In addition, patients should be instructed to immediately seek medical attention if any ocular abnormalities are observed. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | Uveitis |

11 Other antitumor agents

## Apalutamide

| | |
|---|---|
| **Brand name** | Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.) |
| **8. IMPORTANT PRECAUTIONS (newly added)** | Agranulocytosis, neutropenia, or leukopenia may occur. Patients should be carefully monitored through periodic blood tests, etc. during treatment with this drug. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | Agranulocytosis, neutropenia, leukopenia |

12 Other antitumor agents

## (1) Avelumab (genetical recombination)
## (2) Ipilimumab (genetical recombination)
## (3) Tislelizumab (genetical recombination)
## (4) Durvalumab (genetical recombination)
## (5) Tremelimumab (genetical recombination)
## (6) Retifanlimab (genetical recombination)

| | |
|---|---|
| **Brand name** | (1) Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)<br>(2) Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)<br>(3) Tevimbra I.V. Infusion 100 mg (BeOne Medicines Japan)<br>(4) Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)<br>(5) Imjudo Injection 25 mg, 300 mg (AstraZeneca K.K.)<br>(6) Zynyz for Intravenous Infusion 500 mg (Incyte Biosciences Japan G.K.) |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | Haemophagocytic lymphohistiocytosis |

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13 Other antitumor agents

## Ipilimumab (genetical recombination)

**Brand name**
Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)

**11. ADVERSE REACTIONS**
Severe oesophagitis

**11.1 Clinically Significant Adverse Reactions (newly added)**
Severe oesophagitis considered to be due to an immune reaction may occur. If any abnormalities are observed, appropriate measures including the administration of corticosteroids should be taken.

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14 Other antitumor agents

## Ivosidenib

**Brand name**
Tibsovo Tablets 250 mg (Nihon Servier Co., Ltd.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) (newly added)**
Patients receiving the following drugs:
elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate, darunavir ethanolate/cobicistat, darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate, doravirine, doravirine/islatravir hydrate, dolutegravir sodium/rilpivirine hydrochloride, bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate, rilpivirine, rilpivirine hydrochloride, rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate, lenacapavir sodium

**10. INTERACTIONS (newly added)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate<br>Darunavir ethanolate/cobicistat<br>Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate<br>Doravirine<br>Doravirine/islatravir hydrate<br>Dolutegravir sodium/rilpivirine hydrochloride<br>Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate<br>Rilpivirine<br>Rilpivirine hydrochloride<br>Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate<br>Lenacapavir sodium | The effects of these drugs may decrease, and resistance to these drugs may develop. | Induction of CYP3A by this drug may reduce the blood concentrations of these drugs. |

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15 Other antitumor agents

## Encorafenib

**Brand name**
Braftovi Capsules 50 mg, 75 mg (Ono Pharmaceutical Co., Ltd.)

**2. CONTRAINDICATIONS**
Patients receiving the following drugs:
elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate, darunavir ethanolate/cobicistat, darunavir ethanolate/cobicistat/emtricitabine/tenofovir

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**(This drug is contraindicated to the following patients.) (newly added)**

alafenamide fumarate, doravirine, doravirine/islatravir hydrate, dolutegravir sodium/rilpivirine hydrochloride, bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate, rilpivirine, rilpivirine hydrochloride, rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate, lenacapavir sodium

**10. INTERACTIONS (newly added)**

10.1 Contraindications for Co-administration (Do not co-administer with the following)

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate<br>Darunavir ethanolate/cobicistat<br>Darunavir ethanolate/cobicistat/ emtricitabine/tenofovir alafenamide fumarate<br>Doravirine<br>Doravirine/islatravir hydrate<br>Dolutegravir sodium/rilpivirine hydrochloride<br>Bictegravir sodium/emtricitabine/ tenofovir alafenamide fumarate<br>Rilpivirine<br>Rilpivirine hydrochloride<br>Rilpivirine hydrochloride/ emtricitabine/tenofovir alafenamide fumarate<br>Lenacapavir sodium | Since the blood concentrations of these drugs decrease, their effects may decrease, and resistance to these drugs may develop. | This drug induces CYP3A. |

16 Other antitumor agents

## Talaporfin sodium

**Brand name**

Laserphyrin for Injection 100 mg (Meiji Seika Pharma Co., Ltd.)

**8. IMPORTANT PRECAUTIONS**

< Local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy >

Patients should be fasted from the morning of the day of therapy with this drug and managed with intravenous fluids. Food intake may induce severe inflammation and tissue fragility, causing oesophageal perforation. Patients should be fasted until the day after laser irradiation and receive nutritional support with intravenous fluids. Endoscopy should be performed from the day after laser irradiation. If a haemorrhage, a deep ulcer, or an oesophageal perforation is observed at the site of laser irradiation, fasting and management with intravenous fluids should be continued.

**11. ADVERSE REACTIONS**

< Local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy >

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

Oesophageal stenosis, oesophageal perforation

Oesophageal stenosis or oesophageal perforation may occur after laser irradiation.

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17 Other antitumor agents

## Nivolumab (genetical recombination)

**Brand name**
Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)

**11.1 Clinically Significant Adverse Reactions**
Severe gastritis, oesophagitis
Severe gastritis or oesophagitis considered to be due to an immune reaction may occur. If any abnormalities are observed, appropriate measures including the administration of corticosteroids should be taken.

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18 Chinese medicines

## Kakkonto

**Brand name**
TSUMURA Kakkonto Extract Granules for Ethical Use (TSUMURA & CO.), Kracie Kakkonto Extract Fine Granules (Kracie, Ltd.), Kotaro Kakkonto Extract Fine Granules (Kotaro pharmaceutical Co., Ltd), SANWA Kakkonto Extract Fine Granules (Sanwa Shoyaku Co Ltd.), JUNKOU Kakkonto FC Extract Fine Granules for Ethical Use (Kowa Yakutsu Y.K.), TOYO kakkonto extract fine granules (Toyo-yakuko Co., Ltd), OHSUGI Kakkonto Extract Granules G (OHSUGI Pharmaceutical Co., Ltd.), JPS Kakkonto Extract Granules for Ethical Use (JPS Pharmaceutical CO., LTD.), Taikoseido Kakkonto Extract Granules (Taikoseido Pharmaceutical Co., Ltd.), Honzo kakkonto extract granules-M (Honzo Pharmaceutical Co., Ltd.), OHSUGI Kakkonto Extract T Tablets (OHSUGI Pharmaceutical Co., Ltd.), Kracie Kakkonto Extract Tablets T (Ominedo Pharmaceutical Industry Co., Ltd.)

**11. ADVERSE REACTIONS**
**11.1 Clinically Significant Adverse Reactions (newly added)**
Erythema multiforme

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19 Anti-virus agents

## Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate

**Brand name**
Genvoya Combination Tablets (Gilead Sciences K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving the following drugs: Carbamazepine, phenobarbital, phenytoin, fosphenytoin, rifampicin, apalutamide, food containing St. John's Wort, enzalutamide, encorafenib, ivosidenib, mitotane, dihydroergotamine mesilate, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, ergometrine maleate, methylergometrine maleate, asunaprevir, simvastatin, pimozide, sildenafil citrate (Revatio), vardenafil hydrochloride hydrate, tadalafil (Adcirca), blonanserin, azelnidipine, rivaroxaban, triazolam, midazolam, lomitapide mesilate, eplerenone, and telaprevir

**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Enzalutamide<br>Encorafenib<br>Ivosidenib<br>Mitotane | The blood concentrations of elvitegravir and cobicistat may significantly decrease. | Due to the CYP3A-inducing activity of these drugs. |

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20 Anti-virus agents

## Darunavir ethanolate/cobicistat

**Brand name**
Prezcobix Combination Tablets (Janssen Pharmaceutical K.K.)

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

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**

Patients receiving rifampicin, phenobarbital, phenytoin, fosphenytoin, carbamazepine, apalutamide, enzalutamide, ivosidenib, encorafenib, mitotane, food containing St. John's Wort, triazolam, midazolam, pimozide, simvastatin, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, ergometrine, methylergometrine, vardenafil, sildenafil (Revatio), tadalafil (Adcirca), blonanserin, azelnidipine, azelnidipine/olmesartan medoxomil, eplerenone, lurasidone, lomitapide, finerenone, voclosporin, ivabradine, venetoclax (during dose titration phase for relapsed or refractory chronic lymphocytic leukemia [including small lymphocytic lymphoma]), isavuconazonium sulfate, anamorelin hydrochloride, mavacamten, rivaroxaban, and ticagrelor

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Rifampicin<br>Phenobarbital<br>Phenytoin<br>Fosphenytoin<br>Carbamazepine<br>Apalutamide<br>Enzalutamide<br>Ivosidenib<br>Encorafenib<br>Mitotane | The blood concentrations of darunavir and cobicistat may decrease, leading to a reduction in the effect of this drug. | The CYP3A-inducing activity of these drugs promotes the metabolism of darunavir and cobicistat. |

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## 21 Anti-virus agents
## Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate

**Brand name**

Symtuza Combination Tablets (Janssen Pharmaceutical K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**

Patients receiving rifampicin, phenobarbital, phenytoin, fosphenytoin, carbamazepine, apalutamide, food containing St. John's Wort, enzalutamide, ivosidenib, encorafenib, mitotane, triazolam, midazolam, pimozide, simvastatin, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, ergometrine, methylergometrine, vardenafil, sildenafil (Revatio), tadalafil (Adcirca), blonanserin, azelnidipine, azelnidipine/olmesartan medoxomil, eplerenone, lurasidone, lomitapide, finerenone, voclosporin, ivabradine, venetoclax (during dose titration phase for relapsed or refractory chronic lymphocytic leukemia [including small lymphocytic lymphoma]), isavuconazonium sulfate, anamorelin hydrochloride, mavacamten, rivaroxaban, and ticagrelor

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Enzalutamide<br>Ivosidenib<br>Encorafenib<br>Mitotane | The blood concentrations of darunavir and cobicistat may decrease, leading to a reduction in the effect of this drug. | Due to the CYP3A-inducing activity of these drugs. |

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## 22 Anti-virus agents
## Doravirine

**Brand name**

Pifeltro Tablets 100 mg (MSD K.K.)

**2. CONTRAINDICATIONS**

Patients receiving carbamazepine, phenobarbital, phenytoin, fosphenytoin, enzalutamide, apalutamide, rifampicin, mitotane, ivosidenib, encorafenib, and food containing St. John's Wort

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**(This drug is contraindicated to the following patients.)**
**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Carbamazepine<br>Phenobarbital<br>Phenytoin<br>Fosphenytoin<br>Enzalutamide<br>Apalutamide<br>Rifampicin<br>Mitotane<br>Ivosidenib<br>Encorafenib<br>Food containing St. John's Wort | The plasma concentrations of this drug may decrease, leading to a reduction in the therapeutic effect. | The strong CYP3A4-inducing activity of these drugs and foods is expected to promote the metabolism of this drug. |

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23 Anti-virus agents

## Doravirine/islatravir hydrate

**Brand name**
Idvynso Combination Tablets (MSD K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving carbamazepine, phenobarbital, phenytoin, fosphenytoin, enzalutamide, apalutamide, rifampicin, mitotane, ivosidenib, encorafenib, food containing St. John's Wort, lamivudine, and emtricitabine

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Carbamazepine<br>Phenobarbital<br>Phenytoin<br>Fosphenytoin<br>Enzalutamide<br>Apalutamide<br>Rifampicin<br>Mitotane<br>Ivosidenib<br>Encorafenib<br>Food containing St. John's Wort | The plasma doravirine concentrations of this drug may decrease, leading to a reduction in the therapeutic effect. | The strong CYP3A4-inducing activity of these drugs and foods is expected to promote the metabolism of doravirine. |

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24 Anti-virus agents

## Dolutegravir sodium/rilpivirine hydrochloride

**Brand name**
Juluca Combination Tablets (Viiv Healthcare K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving rifampicin, carbamazepine, phenytoin, fosphenytoin sodium hydrate, phenobarbital, food containing St. John's Wort, apalutamide, enzalutamide, ivosidenib, encorafenib, mitotane, dexamethasone (systemic administration) (excluding single administration), and proton pump inhibitors (omeprazole, lansoprazole, rabeprazole sodium, esomeprazole magnesium hydrate, vonoprazan fumarate)

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|

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| | | |
|---|---|---|
| Apalutamide<br>Enzalutamide<br>Ivosidenib<br>Encorafenib<br>Mitotane | The blood concentrations of rilpivirine may decrease, leading to a reduction in the effect of this drug. | The CYP3A-inducing activity of these drugs promotes the metabolism of rilpivirine. |

25 Anti-virus agents

## Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate

**Brand name**
Biktarvy Combination Tablets (Gilead Sciences K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving the following drugs: Rifampicin, carbamazepine, phenobarbital, phenytoin, fosphenytoin, apalutamide, food containing St. John's Wort, enzalutamide, encorafenib, ivosidenib, and mitotane

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Enzalutamide<br>Encorafenib<br>Ivosidenib<br>Mitotane | Since the plasma concentration of bictegravir may decrease, the effect of this drug may decrease, and resistance to this drug may develop. | Due to the CYP3A-inducing activity of these drugs. |

26 Anti-virus agents

## Rilpivirine

**Brand name**
Rekambys Aqueous Suspension for IM Injection 600 mg, 900 mg (Janssen Pharmaceutical K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, fosphenytoin, apalutamide, enzalutamide, ivosidenib, encorafenib, mitotane, dexamethasone (systemic administration) (excluding single administration), and food containing St. John's Wort

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Apalutamide<br>Enzalutamide<br>Ivosidenib<br>Encorafenib<br>Mitotane | The blood concentration of this drug may decrease, leading to a reduction in the effects of this drug. | The CYP3A-inducing activity of these drugs promotes the metabolism of this drug. |

27 Anti-virus agents

## Rilpivirine hydrochloride

**Brand name**
Edurant Tablets 25 mg (Janssen Pharmaceutical K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving rifampicin, carbamazepine, phenobarbital, phenytoin, phenytoin/phenobarbital, fosphenytoin, apalutamide, enzalutamide, ivosidenib, encorafenib, mitotane, dexamethasone (systemic administration) (excluding single administration), food containing St. John's Wort, and proton pump inhibitors (omeprazole, lansoprazole, aspirin/lansoprazole, rabeprazole, esomeprazole, vonoprazan fumarate, aspirin/vonoprazan fumarate)

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|

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**(Do not co-administer with the following.)**

| | | |
|---|---|---|
| Apalutamide<br>Enzalutamide<br>Ivosidenib<br>Encorafenib<br>Mitotane | The blood concentration of this drug may decrease, leading to a reduction in the effects of this drug. | The CYP3A-inducing activity of these drugs promotes the metabolism of this drug. |

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## 28 Anti-virus agents
## Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate

**Brand name**
Odefsey Combination Tablets (Janssen Pharmaceutical K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, phenytoin/phenobarbital, fosphenytoin, apalutamide, food containing St. John's Wort, enzalutamide, ivosidenib, encorafenib, mitotane, dexamethasone (systemic administration) (excluding single administration), and proton pump inhibitors (omeprazole, lansoprazole, aspirin/lansoprazole, rabeprazole, esomeprazole, vonoprazan fumarate, aspirin/vonoprazan fumarate)

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Enzalutamide<br>Ivosidenib<br>Encorafenib<br>Mitotane | The blood concentrations of rilpivirine may decrease, leading to a reduction in the effect of this drug. | The CYP3A-inducing activity of these drugs promotes the metabolism of rilpivirine. |

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## 29 Anti-virus agents
## Lenacapavir sodium

**Brand name**
Sunlenca Tablets 300 mg, Sunlenca Subcutaneous Injection 463.5 mg (Gilead Sciences K.K.)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**
Patients receiving rifampicin, phenytoin, phenytoin/phenobarbital, fosphenytoin sodium hydrate, carbamazepine, apalutamide, enzalutamide, mitotane, encorafenib, ivosidenib, food containing St. John's Wort, lomitapide mesilate, methylergometrine maleate, and ergotamine tartrate/anhydrous caffeine/isopropylantipyrine

**10. INTERACTIONS**
**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Rifampicin<br>Phenytoin<br>Phenytoin/ phenobarbital<br>Fosphenytoin sodium hydrate<br>Carbamazepine<br>Apalutamide<br>Enzalutamide<br>Mitotane<br>Encorafenib<br>Ivosidenib | Since the plasma concentrations of lenacapavir may decrease, the effect of this drug may decrease, and resistance to this drug may develop. | The strong CYP3A-, P-gp-, or UGT1A1-inducing activity of these drugs may decrease the plasma concentration of this drug. |

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## 30 Cold medicines (excluding preparations consisting of crude drugs only)
## Preparations containing Kakkonto (OTC drugs)

**Brand name**
Tsumura-Kampo Kakkonto Extract Granules A (TSUMURA & CO.), PRECOL ace granulated powder (TAMURA PHARMACEUTICAL CO., LTD.), other OTC drugs

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**CONSULTATION**

If the following symptoms are observed after taking this drug, they may be adverse reactions. In such cases, immediately discontinue the use of this drug and consult a physician, pharmacist, or registered salesclerk, presenting them with this document

The following serious symptoms may rarely occur. In such cases, immediately seek medical attention.

**8. IMPORTANT PRECAUTIONS**

| Name of symptom | Symptoms |
|---|---|
| Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis * | Symptoms such as high fever, red eyes, eye mucus, inflamed lips, sore throat, rash and redness affecting an extensive area of the skin, blisters appearing on the reddened skin, small rash (small pustule) appearing on reddened skin *, general malaise *, and loss of appetite * may persist or worsen suddenly. |

*Only preparations containing acetaminophen

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## 31 Preparations containing Kakkonto (preparations containing earthworm extract or vitamins combined with Kakkonto extract) (OTC drugs)

**Brand name**

Tsumura-Kampo Kakkonto Extract Granules A (TSUMURA & CO.), PRECOL ace granulated powder (TAMURA PHARMACEUTICAL CO., LTD.), other OTC drugs

**CONSULTATION**

If the following symptoms are observed after taking this drug, they may be adverse reactions. In such cases, immediately discontinue the use of this drug and consult a physician, pharmacist, or registered salesclerk, presenting them with this document

The following serious symptoms may rarely occur. In such cases, immediately seek medical attention.

**(newly added)**

| Name of symptom | Symptoms |
|---|---|
| Erythema multiforme | Symptoms such as extensive reddening of the skin, blisters appearing on reddened skin, high fever, and sore throat may persist or suddenly worsen. |

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## 32 Chinese medicines
## Kakkonto (OTC Chinese medicines)

**Brand name**

Tsumura-Kampo Kakkonto Extract Granules A (TSUMURA & CO.), PRECOL ace granulated powder (TAMURA PHARMACEUTICAL CO., LTD.), other OTC drugs

**CONSULTATION**

If the following symptoms are observed after taking this drug, they may be adverse reactions. In such cases, immediately discontinue the use of this drug and consult a physician, pharmacist, or registered salesclerk, presenting them with this document

The following serious symptoms may rarely occur. In such cases, immediately seek medical attention.

**(newly added)**

| Name of symptom | Symptoms |
|---|---|
| Erythema multiforme | Symptoms such as extensive reddening of the skin, blisters appearing on reddened skin, high fever, and sore throat may persist or suddenly worsen. |

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## 33 Other antitumor agents
## Tucatinib ethanolate

**Brand name**

Tukysa Tablets 50 mg, 150 mg (Pfizer Japan Inc.)

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**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**

Patients receiving the following drugs: Venetoclax (chronic lymphocytic leukaemia (including small lymphocytic lymphoma) and relapsed or refractory mantle cell lymphoma during the dose escalation phase), anamorelin hydrochloride, voclosporin, ivabradine hydrochloride, quinidine sulfate hydrate, ticagrelor, mavacamten, rivaroxaban, azelnidipine, olmesartan edoxomil/azelnidipine, eplerenone, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, simvastatin, tadalafil (Adcirca), macitentan/tadalafil, finerenone, lomitapide mesilate, suvorexant, daridorexant hydrochloride, triazolam, blonanserin, vornorexant hydrate, lurasidone hydrochloride, vardenafil hydrochloride hydrate, methylergometrine maleate, lonafarnib, ibrutinib, palovarotene

**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Anamorelin hydrochloride<br>Voclosporin<br>Ivabradine hydrochloride<br>Quinidine sulfate hydrate<br>Ticagrelor<br>Mavacamten<br>Azelnidipine<br>Olmesartan medoxomil/azelnidipine<br>Eplerenone<br>Ergotamine tartrate/anhydrous caffeine/isopropylantipyrine<br>Simvastatin<br>Tadalafil (Adcirca)<br>Macitentan/tadalafil<br>Finerenone<br>Lomitapide mesilate<br>Suvorexant<br>Daridorexant hydrochloride<br>Triazolam<br>Blonanserin<br>Vornorexant hydrate<br>Lurasidone hydrochloride<br>Vardenafil hydrochloride hydrate<br>Methylergometrine maleate<br>Lonafarnib<br>Ibrutinib<br>Palovarotene | The adverse reactions associated with these drugs may be enhanced. | Because this drug strongly inhibits CYP3A, blood concentrations of these drugs may increase. |

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34 Agents affecting metabolism, n.e.c. (not elsewhere classified)

## Palovarotene

**Brand name**

Sohonos Capsules 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg (IPSEN Co., Ltd)

**2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**

Patients receiving strong CYP3A inhibitors (itraconazole, preparations containing ritonavir, preparations containing clarithromycin, posaconazole, voriconazole, ensitrelvir fumaric acid, preparations containing cobicistat, ceritinib, preparations containing darunavir ethanolate, lonafarnib, tucatinib ethanolate)

**10.1 Contraindications for Co-administration (Do not co-administer with the following.)**

| Drugs | Signs, symptoms, and treatment | Mechanism/risk factors |
|---|---|---|
| Strong CYP3A inhibitors<br>Itraconazole<br>Preparations containing ritonavir | Blood concentrations of this drug may increase, which may enhance adverse reactions. | Because this drug is metabolized primarily by CYP3A, inhibition of its metabolism results in |

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| | | |
|---|---|---|
| Preparations containing clarithromycin<br>Posaconazole<br>Voriconazole<br>Ensitrelvir fumaric acid<br>Preparations containing cobicistat<br>Ceritinib<br>Preparations containing darunavir ethanolate<br>Lonafarnib<br>Tucatinib ethanolate | | increased blood concentrations of this drug. |

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# 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 adverse drug reactions (ADRs) 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 July 31, 2026)
◎: Products for which EPPV was initiated after July 1, 2026

| | Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiation |
|---|---|---|---|
| ◎ | Risovalisib mesilate hydrate<br>Haizexin tablets 10 mg | Haihe Biopharma Co., Ltd. | July 28, 2026 |
| ◎ | Nerandomilast<br>Jascayd Tablets 9mg, 18mg | Nippon Boehringer Ingelheim Co., Ltd. | July 15, 2026 |
| ◎ | Palovarotene<br>Sohonos Capsules 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg | IPSEN Co., Ltd | July 7, 2026 |
| | Tafasitamab (genetical recombination) *1<br>Minjuvi for intravenous infusion 200 mg | Incyte Biosciences Japan G.K. | June 19, 2026 |
| | Ivosidenib *2<br>Tibsovo Tablets 250 mg | NIHON SERVIER CO., LTD | June 19, 2026 |
| | Incobotulinumtoxin A *3<br>Xeomin 50 units for injection, 100 units, 200 units | Teijin Pharma Limited | June 19, 2026 |
| | Lomitapide mesilate<br>Juxtapid Capsules 5 mg, 10 mg, 20 mg | Recordati Rare Diseases Japan K.K. | June 19, 2026 |
| | Semaglutide (genetical recombination) *4<br>Wegovy Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD, 1.7 mg SD, 2.4 mg SD, Wegovy Subcutaneous Injection 0.25 mg pen 1.0 MD, 0.5 mg pen 2.0 MD, 1.0 mg pen 4.0 MD, 1.7 mg pen 6.8 MD, 2.4 mg pen 9.6 MD | Novo Nordisk Pharma Ltd. | June 19, 2026 |
| | Fedratinib hydrochloride hydrate<br>Inrebic capsules 100 mg | Recordati Rare Diseases Japan K.K. | June 1, 2026 |
| | Gadoquatrane hydrate<br>Ambelvist iv injection 2 mL, Ambelvist iv injection syringes 5 mL, 7.5 mL, 10 mL | Bayer Yakuhin, Ltd. | May 26, 2026 |

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| Nonproprietary name<br>Brand name | | Name of the MAH | Date of EPPV initiation |
|---|---|---|---|
| | Triheptanoin<br>Dojolvi oral liquid 100% | Ultragenyx Japan K.K. | May 21, 2026 |
| | Tirzepatide [*5]<br>Zepbound Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos | Eli Lilly Japan K.K. | May 18, 2026 |
| | Benralizumab (genetical recombination) [*6]<br>Fasenra Subcutaneous Injection 30 mg Syringe, Fasenra Subcutaneous Injection 30 mg Pen | AstraZeneca K.K. | May 18, 2026 |
| | Deucravacitinib [*7]<br>Sotyktu tablets 6 mg | Bristol-Myers Squibb K.K. | May 18, 2026 |
| | Oxymetazoline hydrochloride [*8]<br>Upneeq Mini ophthalmic solution 0.1% | Santen Pharmaceutical Co., Ltd. | May 15, 2026 |
| | Freeze-dried live attenuated measles and rubella combined vaccine<br>MearubikII Subcutaneous Injection | The Research Foundation for Microbial Diseases of Osaka University | May 8, 2026 |
| | [1] [2] Human milk/calcium glycerophosphate/calcium gluconate hydrate/calcium chloride hydrate/anhydrous citric acid sodium/potassium citrate/magnesium monohydrogen phosphate/ zinc sulfate hydrate/sodium chloride/copper sulfate [3] Human milk<br>[1] PreemieFort Enteral Solution 6, [2] 8, [3] PreemieFort Enteral Solution CF | Clinigen K.K. | April 28, 2026 |
| | Tucatinib ethanolate<br>Tukysa Tablets 50 mg, 150 mg | Pfizer Japan Inc. | April 21, 2026 |
| | Atogepant hydrate<br>Aquipta tablets 10 mg, 30 mg, 60 mg | AbbVie GK | April 17, 2026 |
| | Doravirine/islatravir hydrate<br>Idvynso Combination Tablets | MSD K.K. | April 15, 2026 |
| | Depemokimab (genetical recombination)<br>Exdensur solution for s.c. injection 100 mg pen, Exdensur solution for s.c. injection 100 mg syringe | GlaxoSmithKline K.K. | April 15, 2026 |
| | Glycerol phenylbutyrate<br>Ravicti Oral Liquid 1.1g/mL | OrphanPacific, Inc. | April 15, 2026 |
| | Motugivatrep<br>Avarept Ophthalmic Suspension 0.3% | Senju Pharmaceutical Co.,Ltd. | April 6, 2026 |
| | Vorasidenib citric acid hydrate<br>Voranigo Tablets 10 mg, 40 mg | NIHON SERVIER CO., LTD | March 30, 2026 |
| | Luseogliflozin hydrate<br>Lusefi OD film 2.5mg, Lusefi tablets 2.5mg, 5mg | Taisho Pharmaceutical Co., Ltd. | March 23, 2026 |
| | Linzagolix choline<br>Yselty Tablets 100mg | KISSEI PHARMACEUTICAL CO., LTD. | March 19, 2026 |

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| Nonproprietary name / Brand name | | Name of the MAH | Date of EPPV initiation |
|---|---|---|---|
| | Zuranolone<br>Zurzuvae Capsules 30mg | Shionogi & Co., Ltd. | March 19, 2026 |
| | Sebetralstat<br>Ekterly Tablets 300mg | KalVista Pharmaceuticals Ltd. | March 18, 2026 |
| | Tafasitamab (genetical recombination)<br>Minjuvi for intravenous infusion 200 mg | Incyte Biosciences Japan G.K. | March 18, 2026 |
| | Tagraxofusp (genetical recombination)<br>Elzonris I.V. Injection 1000 μg | Nippon Shinyaku Co., Ltd. | March 18, 2026 |
| | Retifanlimab (genetical recombination)<br>Zynyz for Intravenous Infusion 500mg | Incyte Biosciences Japan G.K. | March 18, 2026 |
| | Sepiapterin<br>Sephience Granules 250 mg, 1000 mg | PTC Therapeutics K.K. | March 18, 2026 |
| | Amivantamab (genetical recombination)/vorhyaluronidase alfa (genetical recombination)<br>Rybrofaz Combination Subcutaneous Injection | Janssen Pharmaceutical K.K. | March 18, 2026 |
| | Mosunetuzumab (genetical recombination)<br>Lunsumio for Subcutaneous Injection 5 mg, 45 mg | CHUGAI PHARMACEUTICAL CO., LTD. | March 18, 2026 |
| | Belantamab mafodotin (genetical recombination)<br>Blenrep for I.V. infusion 100 mg | GlaxoSmithKline K.K. | March 18, 2026 |
| | Vonicog alfa (genetical recombination)<br>Vonvendi Intravenous 1300 | Takeda Pharmaceutical Company Limited. | February 19, 2026 |
| | Tezepelumab (genetical recombination) *9<br>Tezspire Subcutaneous Injection 210mg Syringe, Tezspire Subcutaneous Injection 210mg Pen | AstraZeneca K.K. | February 19, 2026 |
| | Adrenaline<br>neffy nasal spray 1mg, 2mg | Alfresa Pharma Corporation | February 12, 2026 |
| | Cantharidin<br>Ycanth topical solution 0.71% | TORII PHARMACEUTICAL CO., LTD. | February 9, 2026 |

*1 Relapsed or refractory diffuse large B-cell lymphoma

*2 Unresectable biliary tract cancer with IDH1 gene mutation positive exacerbated after cancer chemotherapy

*3 Cervical dystonia and blepharospasm

*4 Metabolic dysfunction-associated steatohepatitis without hepatic cirrhosis (only for patients with moderate-severe fibrosis)

*5 Moderate or more severe obstructive sleep apnoea syndrome, for only patients with BMI of ≥ 27 kg/m2

*6 Eosinophilia

*7 Psoriatic arthritis in patients who have not responded sufficiently to conventional therapies

*8 Acquired blepharoptosis

*9 Chronic rhinosinusitis with nasal polyps (for use only in patients who have not responded sufficiently to conventional treatments)

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