Pharmaceuticals and Medical Devices Safety Information

No. 428 April 2026

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Pharmaceutical Safety Division,
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Pharmaceuticals and Medical Devices Safety Information

No. 428 April 2026

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

[Outline of Information]

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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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Abbreviations

EGFR	Epidermal Growth Factor Receptor
MAH	Marketing Authorization Holder
PSB/PSD	Pharmaceutical Safety Bureau/ Pharmaceutical Safety Division
PSB/PED	Pharmaceutical Safety Bureau/ Pharmaceutical Evaluation Division
PSB/MDED	Pharmaceutical Safety Bureau/ Medical Devices Evaluation Division
VTE	Venous Thromboembolism

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1

Precautions for antiepileptic drugs concerning driving a car, etc.

1. Introduction

Carbamazepine, sodium valproate, lamotrigine, lacosamide, and levetiracetam (hereinafter referred to as "5 antiepileptic drugs") may cause adverse reactions affecting the central nervous system, such as somnolence, and decreased attention, concentration, and reflex motor capacity, and therefore a precautionary description indicating that patients should not engage in hazardous machine operations such as driving a car during treatment has been included in the "Important Precautions" section in "PRECAUTIONS" for these drugs.

Recently, the Japan Epilepsy Society requested a revision of the description of the package inserts of the 5 oral antiepileptic drugs so that patients taking these drugs will be allowed to drive a car, etc., and in response to this request, based on the discussion in the 10th Subcommittee on Drug Safety Committee on Drug Safety Pharmaceutical Affairs in FY 2025 held on January 28, 2026 (hereinafter referred to as the "Subcommittee on Drug Safety"), the Ministry of Health, Labour and Welfare instructed revision of "PRECAUTIONS" on March 17, 2026.

This document introduces the points to be noted by physicians and patients in the case where patients taking these 5 antiepileptic drugs drive a car, etc.

2. Details of the revision of package inserts of the 5 antiepileptic drugs

On the basis of the request from the Japan Epilepsy Society and comprehensively considering the following situations in Japan and overseas, in the Subcommittee on Drug Safety, it was accepted to revise the package inserts of the 5 antiepileptic drugs (oral dosage forms) so that physicians can judge the appropriateness of performing hazardous machine operations such as driving a car depending on the condition of individual patients, based on the points to consider provided by the Japan Epilepsy Society, instead of having the patient refrain from driving a car, etc. uniformly during treatment when the indications are related to various types of seizure associated with epilepsy. For specific sections of "PRECAUTION" to be revised for each ingredient, see "4. Revision of PRECAUTIONS (No. 368) (P. 18 to 20)".

- For 21 events[1] that are expected to affect the ability to drive a car or are related to accidents, there has been no major change over time in the trend of the number of cases of adverse reactions reported to the Pharmaceuticals and Medical Devices Agency (PMDA) for the past 5 years and no particular safety concerns have been identified.
- For patients with epilepsy, physicians judge the appropriateness of driving a car for each patient based on the patient's symptoms, medication compliance status, adverse reactions, etc. in accordance with the provisions of the Road Traffic Act. In reality, patients with epilepsy are driving a car during treatment with antiepileptic drugs. However, judging from the status of adverse reaction reporting, it is considered that there is no problem if physicians make individual judgments based on the patient's condition.
- The Japan Epilepsy Society has presented a request for revision of the package insert as well as "Point to consider when people who have epilepsy and are taking antiepileptic drugs drive a car or perform hazardous machine operation" (hereinafter referred to as "points to consider provided by the Society"), in which points of view on what types of patient should be judged to be able to drive a car based on patients' symptoms, medication compliance status, and adverse reactions, etc. are presented as "What should be noted by physicians" and the guidance to patients is presented as "What should be noted by people who take antiepileptic drugs".

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- In the published literature (Neuropsychopharmacol Rep 2024; 44(4):682-687), it is suggested that the 5 antiepileptic drugs may affect driving skills and special attention is thus required in the early phase after treatment initiation, but the influences will diminish with continued use.
- Among European or US labeling of the 5 antiepileptic drugs, there is no labeling that uniformly prohibits patients from driving a car during treatment.

*Details of revision of package insert

Example) Carbamazepine
< Before revision >
As symptoms such as somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur, caution patients not to engage in hazardous machine operations such as driving a car during treatment.
< After revision >
Somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur. The appropriateness of performing hazardous machine operations such as driving a car should be carefully determined by a physician based on a full understanding of the points to consider provided by relevant academic societies. Patients should be appropriately instructed that, if they perform hazardous machine operations, they should be very careful when performing such operations. Patients should also be instructed that, if they experience somnolence, etc., they should not engage in hazardous machine operations such as driving a car.

The relevant revision is limited to oral dosage forms of the 5 antiepileptic drugs. Package inserts of injections are not subject to the revision because injections are to be used when oral drugs cannot be taken temporarily or in patients with status epilepticus. In addition, it should be noted that if these drugs are used for indications other than epilepsy-related conditions, the description indicating that patients should not engage in driving a car, etc. during treatment will continue to be maintained.

3. Points to be noted by physicians and patients

At the Subcommittee on Drug Safety, it was indicated that, while revision of the package inserts of 5 antiepileptic drugs (oral dosage forms) has been determined to be acceptable, this determination presupposes that the contents of the points to consider provided by the Society will be appropriately disseminated and followed in the medical practice settings.

Following this indication, the Ministry of Health, Labour and Welfare instructed the marketing authorization holders of 5 antiepileptic drugs to prepare materials for information provision to healthcare professionals and patients, including the contents of the points to consider provided by the Society in order to disseminate the points to consider provided by the Society in the medical practice settings, etc.

Physicians should carefully determine the appropriateness of performing hazardous machine operations such as driving a car based on a full understanding of the points to consider provided by the Society and give patients appropriate instructions. It should be noted that pharmacists are also required to understand, when providing medication instructions to patients, that the antiepileptic drugs are drugs to be taken based on the said points to consider provided by the Society.

*"Point to consider when people who have epilepsy and are taking antiepileptic drugs drive a car or perform hazardous machine operation" (The Japan Epilepsy Society, prepared on March 17, 2026)

a. What should be noted by physicians
1. Physicians should confirm that epilepsy in a patient has been appropriately diagnosed and treated with standard treatment. Specifically, the latest guidelines of the Japanese Society of

Neurology and the Japan Epilepsy Society should be used as a reference.

2. Physicians should check whether the epileptic seizure in a patient is well controlled so that it does not impair the ability to drive a car. The criteria for assessing seizure control shall be those specified in the Road Traffic Act and its subordinate laws and regulations.

3. Physicians should instruct a patient not to drive a car, etc. when factors inducing epileptic seizure in individual patients such as stress, lack of sleep, pyrexia, and fatigue occur.

4. Physicians should comply with appropriate dosage and administration for each drug. In addition, physicians should instruct a patient to comply with the dosage and administration of the drug, and check whether the patient complies with the medication instructions.

5. The use of antiepileptic drugs may cause adverse reactions such as dizziness, sleepiness, and ataxia that may affect the ability to drive a car, etc. Physicians should instruct a patient not to drive a car if the patient has these symptoms.

6. Physicians should note that adverse reactions may occur due to interactions between drugs depending on the combination of concomitant drugs.

7. In a patient who underwent necessary checks and received instructions based on the above items and has been already driving a car, etc., switching from other drugs or dose changes may cause recurrence of seizure or adverse reactions that may affect the ability to drive a car, and therefore, physicians should set an adequate observation period and instruct the patient not to drive a car, etc. during the observation period. The observation period to confirm the absence of recurrence of seizure shall be about 6 months after the prescription change, and the observation period to monitor adverse reactions that may affect the ability to drive a car, etc. shall be about 1 month after the prescription change.

8. For a patient who underwent necessary checks and received instructions based on the above items and has been already driving a car, etc., physicians should examine the patient on an outpatient basis at least once every 3 months to check whether or not there is any problem with driving a car, etc. as well as the above items, and give necessary instructions.

b. What should be noted by people who take antiepileptic drugs

1. When patients who have received a diagnosis of epilepsy and are treated with antiepileptic drugs desire to drive a car, etc. it should be confirmed by a physician that their seizure has been well controlled and they do not have adverse reactions that impair the ability to drive a car, etc. and they should be allowed by the physician to drive a car, etc.

2. If individual factors inducing epileptic seizure such as stress, lack of sleep, pyrexia, and fatigue cannot be avoided, the patient should not perform operations such as driving a car.

3. Patients should take drugs as prescribed by a physician. In addition, the patients must comply with the instructions given by a physician or pharmacist when taking the drug.

4. The use of antiepileptic drugs may cause adverse reactions such as dizziness, sleepiness, and ataxia that may affect the ability to drive a car, etc. Patients must not perform operations such as driving a car when these subjective symptoms occur. If the above conditions occur while driving a car, stop driving promptly.

5. When patients receive prescription or purchase over-the-counter drugs for diseases or symptoms other than epilepsy, the patients should ask a physician or a pharmacist about their influence on the effects and adverse reactions of the prescribed antiepileptic drugs.

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4. Conclusion

In accordance with this revision of "PRECAUTIONS", the description is to be revised so that driving a car, etc., which had been prohibited during treatment, will be allowed for the 5 antiepileptic drugs (oral dosage forms). However, this revision does not uniformly allow all patients who are receiving the treatment to drive a car, etc. This revision allows physicians to judge the appropriateness of performing hazardous machine operations such as driving a car, etc. according to the condition of individual patients, based on the points to consider provided by the Society when these drugs are used for various types of seizure associated with epilepsy. Thus, it is important for physicians to make a careful judgment on the appropriateness of driving a car, etc. and for physicians and pharmacists to give appropriate instructions to patients. When giving instructions, physicians should instruct a patient to pay attention to the status of occurrence of adverse reactions and the physical condition in daily life and not to drive a car, etc., when the patient notices any symptoms such as sleepiness, poor physical condition, etc. Healthcare professionals are encouraged to understand the purpose of this revision and to continue to cooperate in ensuring the proper use of these drugs.

[References]

• The 10th Subcommittee on Drug Safety Committee on Drug Safety Pharmaceutical Affairs in FY 2025 (held on January 28, 2026)
https://www.mhlw.go.jp/stf/newpage_69439.html (only in Japanese)
• Revision of "PRECAUTIONS" (PSB/PSD Notification No. 0317-1 dated March 17, 2026)
https://www.mhlw.go.jp/content/11125000/001673821.pdf (only in Japanese)
• Provision of information on precautions for antiepileptic drugs concerning driving a car, etc. (PSB/PSD Administrative Notice dated March 17, 2026)
https://www.mhlw.go.jp/content/11120000/001675763.pdf (only in Japanese)
• "Point to consider when people who have epilepsy and are taking antiepileptic drugs drive a car or perform hazardous machine operation" (The Japan Epilepsy Society, March 17, 2026)
https://jes-jp.org/pdf/20260317_info.pdf (only in Japanese)

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2

Points to consider in taking safety measures when Notification on concomitant drugs are applied

1. Introduction

Amivantamab (Genetical Recombination) (hereinafter referred to as "amivantamab") has been marketed for the indications of EGFR exon 20 insertion mutation-positive unresectable advanced/recurrent non-small cell lung cancer and EGFR mutation-positive unresectable advanced/recurrent non-small cell lung cancer since November 2024. Lazertinib mesilate hydrate (hereinafter referred to as "lazertinib") has been marketed for the indication of EGFR mutation-positive unresectable advanced/recurrent non-small cell lung cancer since November 2025.

In the electronically formatted package inserts (hereinafter referred to as "electronic package insert") of amivantamab and lazertinib, a precautionary statement to the effect that when these drugs are co-administered, apixaban is used in combination to prevent onset of venous thromboembolism (hereinafter referred to as "VTE") has been described. Therefore, these 3 drugs shall be administered in combination.

Recently, a description on renal function in the electronic package insert of apixaban was confirmed in the post-marketing drug use-results survey. As precautions concerning renal function are stated for each indication, apixaban is contraindicated in patients with renal failure (CLcr < 15 mL/min) when used for the approved indications. However, the precautions concerning administration to patients with renal failure in the combination therapy with the above 3 drugs were not clearly stated in the descriptions in the electronic package insert.

As a result of a review of how to provide precautions based on these situations, it was determined appropriate to clearly state in the electronic package insert of apixaban that apixaban should not be administered to patients with renal failure when co-administered with amivantamab and lazertinib. Based on this determination, the Ministry of Health, Labour and Welfare issued a notification instructing revision of the "PRECAUTIONS" on March 6, 2026. This article introduces the details of the review, etc.

2. Background and details of the revision

With regard to administration of apixaban when amivantamab and lazertinib are co-administered, the usage of apixaban for the purpose of prophylaxis of VTE has been described only in the electronic package inserts of amivantamab and lazertinib without obtaining approval for this usage as an additional indication for apixaban, a concomitant drug, based on a notification “Handling of Approval Applications, etc. for Drugs, Medical Devices, and Regenerative Medical Products which are Used in Combination with Other Drugs (PSB/PED Notification No. 0531-1, PSB/MDED Notification No. 0531-3, and PSB/PSD Notification No. 0531-1, dated May 31, 2024)” issued by the Ministry of Health, Labour and Welfare in May 2024 (hereinafter referred to as “Notification on concomitant drugs”). On the other hand, in the electronic package insert of apixaban, attention to the administration to patients with renal impairment has been called for in each indication as a general precaution concerning the approved indications, but precautions concerning administration to these patients in the relevant combination therapy have not been clearly provided.

In general, when multiple drugs are concomitantly used, the package insert of each drug should be referred to. For drugs for which obtaining an approval for additional indications is considered unnecessary in accordance with Notification on concomitant drugs, the indication is not

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described in the package insert, but the package insert should be checked on the assumption that the drugs are used for the relevant indications. For this reason, in the case where the appropriateness of administration should be judged according to renal function as in the present case concerning apixaban, the judgment should be made by paying due attention to the description of precaution in the electronic package insert of apixaban in addition to amivantamab and Lazertinib, even if the drug is used for an indication not described the section of indications in the package insert of apixaban based on Notification on concomitant drugs.

In terms of the proper use of drugs, for drugs that require attention when used in combination therapy, it was considered that the precautions concerning the concomitant drugs should be described more specifically to improve understandability in medical practice settings even if the handling of the concomitant drugs is based on Notification on concomitant drugs.

In the revision of "PRECAUTIONS" instructed on March 6, 2026, in the electronic package insert of apixaban, the description to the effect that administration to patients with renal failure is contraindicated when co-administered with amivantamab and lazertinib was added, and the precaution concerning administration to patients with renal failure was also added to the electronic package inserts of amivantamab and lazertinib.

3. Description of precautions based on Notification on concomitant drugs

Notification on concomitant drugs specifies the handling of concomitant drugs used in treatment with drugs, medical devices, and regenerative medical products (hereinafter referred to as "principal drugs, etc.") as follows: For concomitant drugs that are expected to be used in combination with principal drugs, etc. in addition to premedications or rescue drugs, application for approval can be made by describing usage of the concomitant drug in the electronic package insert of the principal drugs, etc. without obtaining an approval for the additional indication for the concomitant drug.

The conventional handling had required application for approval of concomitant drugs if the usage of the concomitant drugs is not included in the scope of approval of the concomitant drugs. With Notification on concomitant drugs, necessary combination therapy will be promptly provided to the medical practice settings.

Even if the application for approval of the concomitant drugs is not required, the usage of the concomitant drugs will be described in the electronic package insert of the principal drugs, etc. However, as in the present case, how to provide precautions will differ depending on the drugs used in the combination therapy, and therefore it will be necessary to describe precautions so that appropriate attention will be called in each use.

[Recent Major Response Examples]

Date of Revision	Primary Drug(s)	Concomitant Drug(s)
March 23,2026	Darolutamide	Goserelin acetate
February 19, 2026	Tucatinib ethanol adduct	Capecitabine
May 19, 2025	Pembrolizumab (genetical recombination)	Combination therapy with pemetrexed sodium hemipentahydrate and carboplatin
March 27, 2025	Combination therapy with amivantamab (genetical recombination) and lazertinib mesylate hydrate	Apixaban

4. Closing remark

Notification on concomitant drugs has made it unnecessary to obtain an approval for additional indications for concomitant drugs that satisfy the specified conditions. However, it is

important, for proper use, to make an appropriate judgment after checking the package inserts of both principal drugs and concomitant drugs to perform a cross check of the information such as contraindications, appropriateness of administration according to renal function or hepatic function, dose adjustment, interactions, risk of adverse events, etc. Healthcare professionals are continuously requested to carefully check the electronic package inserts for a careful decision on administration of drugs in order to ensure proper use of the drugs and patient safety.

[References]
• Handling of Approval Applications, etc. for Drugs, Medical Devices, and Regenerative Medical Products which are Used in Combination with Other Drugs (PSB/PED Notification No. 0531-1, PSB/MDED Notification No. 0531-3, and PSB/PSD Notification No. 0531-1, dated May 31, 2024)
• Revision of PRECAUTIONS (PSB/PSD Notification No. 0306-1 dated March 6, 2026)

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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 March 17 ,2026, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Olaparib

Brand name (name of company)	Lynparza Tablets 100 mg, 150 mg (AstraZeneca K.K.)
Therapeutic category	Other antitumor agents
Indications	< Lynparza Tablets 100 mg, 150 mg > ○ Maintenance treatment of recurrent ovarian cancer responding to platinum-based chemotherapy ○ Maintenance treatment of BRCA mutation-positive ovarian cancer after first-line chemotherapy ○ Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination) ○ Treatment of inoperable or recurrent BRCA mutation-positive HER2-negative breast cancer previously treated with chemotherapy ○ Adjuvant pharmacotherapy for BRCA mutation-positive HER2-negative breast cancer with a high risk of recurrence ○ Treatment of BRCA mutation-positive metastatic castration-resistant prostate cancer ○ Maintenance treatment of incurable, unresectable BRCA mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs ○ Maintenance treatment of advanced or recurrent endometrial cancer with proficient mismatch repair (pMMR) in patients who have received chemotherapy including treatment with durvalumab (genetical recombination)

PRECAUTIONS (Revised language is underlined.)

8. IMPORTANT PRECAUTIONS (newly added)	Hepatic impairment may occur. Liver function tests should be performed prior to and periodically during administration of this drug, and patients should be carefully monitored for their condition.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Hepatic impairment

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Reference information

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 Hepatic impairment reported in Japan:3
(No patient mortalities)

* Cases meeting both of the following conditions were retrieved from those collected in the PMDA's database for adverse drug reactions, etc. reports: • Cases that fell under MedDRA ver. 27.0 SMQ (narrow) "Hepatitis, non-infectious," "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," or "Liver-related investigations, signs and symptoms" • Cases in which the hepatic function test values (either of ALT, AST, ALP, γ-GTP, or T-Bil) at the time of onset of the event and after discontinuation of olaparib were available

Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 66,000
Japanese market launch:
①Lynparza Tablets 100 mg, 150 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/ 50s	Recurrent ovarian cancer (none)	300 mg × 2 times for 49 days ↓ Discontinuation ↓ 300 mg × 2 times for 15 days ↓ Discontinuation	**Acute hepatitis, liver disorder** Medical history, allergy history: None	
				2 years and 2 months before administration	Ovarian cancer was diagnosed.
				3 days before administration	AST: 12. ALT: 11.
				Day 1 of administration	The patient started receiving administration of olaparib 300 mg twice daily as maintenance therapy for platinum-sensitive recurrent ovarian cancer.
				Day 41 of administration	AST: 87. ALT: 198. Liver disorder (non-serious) occurred.
				Day 48 of administration (day of discontinuation)	AST and ALT had increased to 96 and 251, respectively. Administration of olaparib was discontinued. The patient was placed under observation.
				14 days after discontinuation (day 1 of readministration)	AST and ALT had improved to 32 and 61, respectively. Liver disorder (non-serious) resolved. Administration of olaparib was resumed at 300 mg twice daily.
				Day 14 of readministration (day of discontinuation of readministration)	AST and ALT had increased to 1,018 and 1,718, respectively. As acute hepatitis (serious) was diagnosed, readministration of olaparib was discontinued. The patient was placed under observation.

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				1 day after discontinuation of readministration	The patient was admitted to the department of gastroenterological medicine for detailed examination and treatment. Based on the detailed examination, viral liver disorder was considered unlikely. After that, the liver disorder spontaneously improved without treatment.
				6 days after discontinuation of readministration	The patient was discharged from the hospital. She was followed up on an outpatient basis thereafter.
				42 days after discontinuation of readministration	AST and ALT had recovered to 17 and 16, respectively. The liver disorder and acute hepatitis resolved.
				70 days after discontinuation of readministration	Blood test results had all normalized.
				133 days after discontinuation of readministration	No relapse of the liver disorder was noted. No recurrence of ovarian cancer was noted.
				On an unknown date	Olaparib was not administered. The patient continued to be followed up.

Laboratory test values

	3 days before administration	Day 13 of administration	Day 27 of administration	Day 41 of administration	Day 48 of administration (day of discontinuation)	14 days after discontinuation (day 1 of readministration)
T-Bil (mg/dL)	0.3	0.4	0.2	0.4	0.4	0.3
AST(GOT) (IU/L)	12	10	12	87	96	32
ALT(GPT) (IU/L)	11	10	15	198	251	61
LDH (IU/L)	156	145	142	223	215	168
ALP (IU/L)	302	248	246	298	344	296
γ-GTP (IU/L)	45	28	29	83	96	58

	Day 14 of readministration (day of discontinuation of readministration)	1 day after discontinuation of readministration	2 days after discontinuation of readministration	5 days after discontinuation of readministration	14 days after discontinuation of readministration	42 days after discontinuation of readministration	70 days after discontinuation of readministration
T-Bil (mg/dL)	2.2	1.9	1.7	1.2	0.9	0.5	0.4
AST (GOT) (IU/L)	1018	986	767	375	58	17	15
ALT (GPT) (IU/L)	1718	1691	1444	980	152	16	17
LDH (IU/L)	453	461	394	257	178	—	—
ALP (IU/L)	800	790	729	701	427	—	—
γ-GTP (IU/L)	360	354	336	374	218	57	31

Concomitant drugs: None

4

Revisions of PRECAUTIONS (No. 368)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated February 24, 25, March 6, and 17 2026.

1 Gout preparations
Colchicine

Brand name

Colchicine Tablets 0.5 mg "Takata" (TAKATA Pharmaceutical Co., Ltd.)

1. WARNINGS (newly added)

Cases of serious toxic symptoms (gastrointestinal disorder, blood disorder, renal disorder, liver disorder, etc.) that resulted in death have been reported in patients who received this drug at high doses exceeding the daily dose of this drug of 1.5 mg and in patients with severe renal impairment. Administration of doses higher than 1.5 mg/day or administration to patients with severe renal impairment should be avoided unless clinically warranted. In addition, if any symptoms such as nausea/vomiting, abdominal pain, diarrhoea, burning sensation in the pharynx/stomach/skin, haematuria, oliguria, muscle weakness, etc. occur, patients should be instructed to seek medical attention immediately.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION <Common to all indications>

Since the frequency of occurrence of gastrointestinal disorders, such as diarrhoea, etc. increases as the dose increases, the following matters should be noted. Cases of serious toxic symptoms (gastrointestinal disorder, blood disorder, renal disorder, liver disorder, etc.) that occurred after administration at high doses exceeding the daily dose of 1.5 mg and resulted in death have been reported.

- When this drug is used for the relief of a gout attack, administration at high doses exceeding 1.5 mg/day should be avoided unless clinically warranted. For the one-time dose, daily dose, and administration duration, the latest Japanese guideline should be used as a reference.
- This drug should not be administered at a dose exceeding the approved dosage when used for the prophylaxis of gout attack or the treatment of familial mediterranean fever.

Acute toxic symptoms may occur within several hours after administration when this drug is administered at a high dose or misused.

<Relief of gout attac >

Starting medication earlier after the onset of a gout attack is more effective. In addition, administration of this drug should be discontinued as soon as the pain improves.

<Prophylaxis of gout attack>

Long-term prophylactic administration for gout attack is not recommended because it may cause serious adverse reactions such as blood disorder, genital disorder, liver/renal disorder, alopecia, etc. and is of limited usefulness.

This drug should preferably be taken as soon as possible when an

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	antecedent sign occurring 3 to 4 hours before the attack is detected.
8. IMPORTANT PRECAUTIONS (newly added)	Symptoms of colchicine poisoning may occur in patients who have received high-dose administration or in patients with renal impairment. If any symptoms such as nausea/vomiting, abdominal pain, diarrhoea, burning sensation in the pharynx/stomach/skin, haematuria, oliguria, muscle weakness, etc. occur, patients should be instructed to seek medical attention immediately.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.2 Patients with Renal Impairment (newly added)	Patients with severe renal impairment who are not receiving any of the concomitant drugs described in 9.2.1 Administration of this drug should be avoided unless clinically warranted. When this drug is administered, care should be taken by starting at a very low dose and limiting the administration duration to the minimum necessary, etc. Cases of serious toxic symptoms that resulted in death have been reported in patients with severe renal impairment. Patients with renal impairment who are not receiving any of the concomitant drugs described in 9.2.1 (excluding patients with severe renal impairment) When this drug is administered, care should be taken by starting at a very low dose and limiting the administration duration to the minimum necessary, etc. Plasma concentration of this drug may increase and serious adverse reactions may occur early.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Symptoms of colchicine poisoning Symptoms of colchicine poisoning may occur as a result of increased blood concentration of this drug in patients who received this drug at high doses or in patients with renal impairment, etc., even if the doses are within the range of the approved dosage and administration. If toxic symptoms such as gastrointestinal disorder, blood disorder, renal disorder, liver disorder, etc. are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Measures: Fluid replacement for dehydration, correction of electrolytes, symptomatic treatment for cytopenia, infection, and coagulation abnormalities, and management of blood pressure and respiratory conditions should be performed. This drug is not eliminated by forced diuresis or haemodialysis.

2 Mixed biological preparations
Adsorbed Diphtheria-Purified Pertussis-Tetanus Combined Vaccine

Brand name	Tribik (Tanabe Pharma Corporation)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women	Pregnant women or women who may be pregnant should be vaccinated only if the potential benefits of vaccination are considered to outweigh the potential risks. It has been reported that vaccination with this product did not increase the incidences of pregnancy complications or fetal abnormalities and was demonstrated to increase anti-pertussis toxin (PT) antibody titers and anti-pertussis FHA antibody titers, etc. in umbilical blood.

3 Anticoagulants
Apixaban

Brand name	Eliquis tablets 2.5 mg, 5 mg (Bristol-Myers Squibb K.K.)

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2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	<Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, prevention of venous thromboembolism associated with the concomitant use of amivantamab (genetical recombination) and lazertinib> Patients with Renal Failure (creatinine clearance (CLcr) < 15 mL/min)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.2 Patients with Renal Impairment**	<Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, prevention of venous thromboembolism associated with the concomitant use of amivantamab (genetical recombination) and lazertinib> Patients with renal failure (CLcr < 15 mL/min) Do not administer this drug. No clinical study to assess the efficacy or safety in patients with renal failure (CLcr < 15 mL/min) has been conducted. Patients with renal disorder (CLcr 15-50 mL/min) The risk of bleeding may increase.

4 Other antitumor agents

[1] Amivantamab (genetical recombination)
[2] Amivantamab (genetical recombination)/vorhyaluronidase alfa (genetical recombination)

Brand name	[1] Rybrevant Intravenous Infusion 350 mg (Janssen Pharmaceutical K.K.) [2] Rybrofaz Combination Subcutaneous Injection (Janssen Pharmaceutical K.K.)
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	When administering this drug in combination with lazertinib, administer oral apixaban 2.5 mg twice daily to prevent venous thromboembolism for the first 4 months of treatment. Pay attention to the risk of bleeding by referring to the electronic package insert of apixaban. Since apixaban cannot be administered in patients with renal failure (creatinine clearance (CLcr) < 15 mL/min), treatment options other than the concomitant use of amivantamab (genetical recombination) and lazertinib should be considered.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.2 Patients with Renal Impairment (newly added)**	<*EGFR* mutation-positive unresectable advanced or recurrent non-small cell lung cancer> Patients with renal failure (CLcr < 15 mL/min) Since apixaban cannot be administered, the concomitant use with lazertinib should be avoided, and other treatment options should be considered.

5 Other antitumor agents

Lazertinib mesilate hydrate

Brand name	Lazcluze Tablets 80 mg, 240 mg (Janssen Pharmaceutical K.K.)
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	When administering this drug in combination with amivantamab (genetical recombination), administer oral apixaban 2.5 mg twice daily to prevent venous thromboembolism for the first 4 months of

	treatment. Pay attention to the risk of bleeding by referring to the electronic package insert of apixaban. Since apixaban cannot be administered in patients with renal failure (creatinine clearance (CLcr) < 15 mL/min), treatment options other than the concomitant use of amivantamab (genetical recombination) and lazertinib should be considered.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	
9.2 Patients with Renal Impairment (newly added)	Patients with renal failure (CLcr < 15 mL/min) Since apixaban cannot be administered, other treatment options should be considered.

6 Hypnotics and sedatives, antianxietics

Triazolam

Brand name

Halcion Tablets 0.125 mg, 0.25 mg (Pfizer Japan Inc.), and others

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

Patients receiving the following drugs: Itraconazole, posaconazole, fluconazole, fosfluconazole, voriconazole, miconazole, HIV protease inhibitors (atazanavir sulfate, darunavir ethanolate, fosamprenavir calcium hydrate, ritonavir, lopinavir/ritonavir), nirmatrelvir/ritonavir, ensitrelvir fumaric acid, preparations containing cobicistat, efavirenz, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Ceritinib	The blood concentration of this drug may rise. The effects may be enhanced, and the duration of effects may be prolonged.	Since this drug and the drugs listed on the left-hand side are metabolized by the same enzyme (CYP3A4), the metabolism of this drug is inhibited.

7 Antiepileptics、psychotropic agents

Carbamazepine

Brand name

Tegretol Tablets 100 mg, 200 mg, Tegretol Fine Granules 50%, and the others (Sun Pharma Japan Limited), and the others

8. IMPORTANT PRECAUTIONS
<Common to all indications>

(deleted)

(newly added)

<Psychomotor seizure, mental disorder associated with epileptic personality or epilepsy, epileptic convulsive seizure: tonic-clonic seizure

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	(generalized convulsive seizure, grand mal)> Somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur. The appropriateness of performing hazardous machine operations such as driving a car should be carefully determined by a physician based on a full understanding of the points to consider provided by relevant academic societies. Patients should be appropriately instructed that, if they perform hazardous machine operations, they should be very careful when performing such operations. Patients should also be instructed that, if they experience somnolence, etc., they should not engage in hazardous machine operations such as driving a car.
(newly added)	< Mania, manic state in manic depressive illness, excitement in schizophrenia, and trigeminal neuralgia > As symptoms such as somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur, caution patients not to engage in hazardous machine operations such as driving a car during treatment.

8 Antiepileptics, psychotropic agents

Sodium valproate

Brand name	Depakene Tablets 100 mg, 200 mg, Depakene R Tablets 100mg, 200 mg, Depakene Fine Granules 20%, 40%, Depakene Syrup 5%, and the others (Nichi-Iko Gifu Plant Co., Ltd.), and the others Selenica-R Granules 40%, Selenica-R Tab. 200 mg, 400 mg, and the others (Kowa Co., Ltd.), and the others
8. IMPORTANT PRECAUTIONS <Common to all indications>	(deleted)
(newly added)	<Treatment of various types of epilepsy and personality or behaviour disorder associated with epilepsy> Somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur. The appropriateness of performing hazardous machine operations such as driving a car should be carefully determined by a physician based on a full understanding of the points to consider provided by relevant academic societies. Patients should be appropriately instructed that, if they perform hazardous machine operations, they should be very careful when performing such operations. Patients should also be instructed that, if they experience somnolence, etc., they should not engage in hazardous machine operations such as driving a car.
(newly added)	<Treatment of mania, manic state in manic depressive illness, prevention of migraine attacks> As symptoms such as somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur, caution patients not to engage in hazardous machine operations such as driving a car during treatment.

9 Antiepileptics

Lacosamide (oral dosage form)

Brand name	Vimpat Tablets 50 mg, 100 mg, Vimpat Dry Syrup 10%, and the others (UCB Japan Co. Ltd.), and the others
8. IMPORTANT PRECAUTIONS	Dizziness, vision blurred, somnolence, and decreased attention/concentration/reflex motor capacity, etc. may occur. The appropriateness of performing hazardous machine operations such as driving a car should be carefully determined by a physician based on a full understanding of the points to consider provided by relevant academic societies. Patients should be appropriately instructed that, if they perform hazardous machine operations, they should be very careful when performing such operations. Patients should also be instructed that, if they experience somnolence, etc., they should not engage in hazardous machine operations such as driving a car.

10 Antiepileptics, psychotropic agents

Lamotrigine

Brand name	Lamictal Tablets 2 mg, 5 mg for Pediatric, Lamictal Tablets 25 mg, 100 mg, (GlaxoSmithKline K.K.), and the others
8. IMPORTANT PRECAUTIONS <Common to all indications>	(deleted)
(newly added)	<Treatment of various types of epilepsy> Somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur. The appropriateness of performing hazardous machine operations such as driving a car should be carefully determined by a physician based on a full understanding of the points to consider provided by relevant academic societies. Patients should be appropriately instructed that, if they perform hazardous machine operations, they should be very careful when performing such operations. Patients should also be instructed that, if they experience somnolence, etc., they should not engage in hazardous machine operations such as driving a car.
(newly added)	<Suppression of recurrent/relapsed mood episodes in patients with bipolar disorde > As symptoms such as somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur, caution patients not to engage in hazardous machine operations such as driving a car during treatment.

11 Antiepileptics

Levetiracetam (oral dosage form)

Brand name	E Keppra Tablets 250 mg, 500 mg, E Keppra Dry syrup 50%, and the others (UCB Japan Co. Ltd.), and the others
8. IMPORTANT PRECAUTIONS	Somnolence and decreased attention/concentration/reflex motor capacity, etc. may occur. The appropriateness of performing hazardous machine operations such as driving a car should be carefully determined by a physician based on a full understanding of the points to consider provided by relevant academic societies. Patients should be appropriately instructed that, if they perform hazardous machine operations, they should be very careful when performing such operations. Patients should also be instructed that, if they experience somnolence, etc., they should not engage in

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hazardous machine operations such as driving a car.

12 Antipyretics, analgesics and anti-inflammatory agents
Ergotamine tartrate/anhydrous caffeine/isopropylantipyrine

Brand name
Cleamine Combination Tablets A1.0, Cleamine Combination Tablets S0.5 (Nichi-iko Pharmaceutical Co.,Ltd)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving the following drugs: HIV protease inhibitors (preparations containing ritonavir, fosamprenavir, atazanavir, darunavir), efavirenz, preparations containing cobicistat, macrolide antibiotics (erythromycin, josamycin, clarithromycin, roxithromycin), azole antifungal agents (itraconazole, miconazole, fluconazole, fosfluconazole, voriconazole, posaconazole), letermovir, ensitrelvir, lenacapavir, lonafarnib, ceritinib, 5-HT $_{1B/1D}$ receptor agonists (sumatriptan, zolmitriptan, eletriptan, rizatriptan, naratriptan), ergot alkaloids (ergometrine, methylergometrine)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
HIV protease inhibitors Preparations containing ritonavir, fosamprenavir, atazanavir, darunavir Efavirenz Preparations containing cobicistat Macrolide antibiotics Erythromycin, josamycin, clarithromycin, roxithromycin Azole antifungal agents Itraconazole, miconazole, fluconazole, fosfluconazole, voriconazole, posaconazole Letermovir Ensitrelvir Lenacapavi Lonafarnib Ceritinib	The blood concentration of ergotamine may increase, which may cause serious adverse reactions such as angiospasm.	The metabolism of ergotamine is suppressed due to CYP3A4 inhibition by these drugs.

13 Psychotropic agents
Blonanserin (oral dosage form)

Brand name
Lonasen Tablets 2 mg, 4 mg, 8 mg, Lonasen Powders 2% (Sumitomo Pharma Co.,Ltd.), and the others

2. CONTRAINDICATIONS (This drug is
Patients receiving the following drugs: Itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injectable dosage

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contraindicated to the following patients.)

forms), fluconazole, fosfluconazole, posaconazole, preparations containing ritonavir, darunavir, atazanavir, fosamprenavir, ensitrelvir, preparations containing cobicistat, lonafarnib, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Drugs that strongly inhibit CYP3A4 Itraconazole Voriconazole Miconazole (oral dosage form, oral preparation, injectable dosage forms) Fluconazole Fosfluconazole Posaconazole Preparations containing ritonavir Darunavir Atazanavir Fosamprenavir Ensitrelvir Preparations containing cobicistat Lonafarnib Ceritinib	The blood concentration of this drug may increase, and the effects may be enhanced.	Oral clearance may decrease since these drugs inhibit CYP3A4, the major metabolic enzyme of this drug. It has been reported overseas that the AUC and Cmax of this drug increased 17-fold and 13-fold, respectively, when co-administered with ketoconazole (oral dosage form; not marketed in Japan).

14 Psychotropic agents
Blonanserin (patches)

Brand name

Lonasen Tapes 20 mg, 30 mg, 40 mg (Sumitomo Pharma Co.,Ltd.), and the others

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

Patients receiving the following drugs: Itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injectable dosage forms), fluconazole, fosfluconazole, posaconazole, preparations containing ritonavir, darunavir, atazanavir, fosamprenavir, ensitrelvir, preparations containing cobicistat, lonafarnib, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Drugs that strongly inhibit CYP3A4 Itraconazole Voriconazole Miconazole (oral dosage form, oral preparation, injectable dosage forms) Fluconazole Fosfluconazole Posaconazole Preparations containing ritonavir	The blood concentration of this drug may increase, and the effects may be enhanced.	The clearance may decrease since these drugs inhibit CYP3A4, the major metabolic enzyme of this drug.

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Darunavir Atazanavir Fosamprenavir Ensitrelvir Preparations containing cobicistat Lonafarnib Ceritinib		

15 Psychotropic agents

Lurasidone hydrochloride

Brand name Latuda tablets 20 mg, 40 mg, 60 mg, 80 mg (Sumitomo Pharma Co.,Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving drugs that strongly inhibit CYP3A4 (itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injectable dosage forms), fluconazole, fosfluconazole, posaconazole, preparations containing ritonavir, darunavir, atazanavir, fosamprenavir, ensitrelvir, preparations containing cobicistat, clarithromycin, lonafarnib, ceritinib)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Drugs that strongly inhibit CYP3A4 Itraconazole Voriconazole Miconazole (oral dosage form, oral preparation, injectable dosage forms) Fluconazole Fosfluconazole Posaconazole Preparations containing ritonavir Darunavir Atazanavir Fosamprenavir Ensitrelvir Preparations containing cobicistat Clarithromycin Lonafarnib Ceritinib	The blood concentration of this drug may increase, and the effects may be enhanced.	The metabolism of this drug is suppressed, leading to an increase in the blood concentration of this drug.

16 Other agents affecting central nervous system

Suvorexant

Brand name Belsomra Tablets 10 mg, 15 mg, 20 mg (MSD K.K.)

2. CONTRAINDICATIONS (This drug is Patients receiving the following drugs: Itraconazole, posaconazole, voriconazole, clarithromycin, vonoprazan/amoxicillin/clarithromycin, rabeprazole/amoxicillin/clarithromycin, ritonavir, nirmatrelvir/ritonavir,

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

ensitrelvir, ceritinib

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Itraconazole Posaconazole Voriconazole Clarithromycin Vonoprazan/amoxicillin/clarithromycin Rabeprazole/amoxicillin/clarithromycin Ritonavir Nirmatrelvir/ritonavir Ensitrelvir Ceritinib	These drugs may markedly enhance the effects of this drug.	These drugs strongly inhibit CYP3A, a metabolic enzyme of suvorexant, and markedly increase the plasma concentration of suvorexant.

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17 Antiarrhythmic agents

Quinidine sulfate hydrate

Brand name

Quinidine Sulfate Powder, Quinidine Sulfate Tablets 100 mg (Viatris Pharmaceuticals Japan Inc.)

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

Patients receiving the following drugs: Amiodarone hydrochloride (injection), vardenafil hydrochloride hydrate, eliglustat tartrate, siponimod fumaric acid, fingolimod hydrochloride, toremifene citrate, ceritinib, voriconazole, posaconazole, moxifloxacin hydrochloride, lascufloxacin hydrochloride (injection), ritonavir, nirmatrelvir/ritonavir, ensitrelvir fumaric acid, itraconazole, fluconazole, fosfluconazole, miconazole, mefloquine hydrochloride

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Ceritinib	QT prolonged, etc. may occur.	The blood concentration of this drug is expected to increase because of inhibited metabolism of this drug due to inhibition of the hepatic drug metabolizing enzyme (CYP3A4) by the drugs listed on the left.

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18 Antihypertensives

Azelnidipine

Brand name

Calblock Tablets 8 mg, 16 mg (Daiichi Sankyo Company, Limited), and the others

2. CONTRAINDICATIONS (This drug is

Patients receiving the following drugs: Itraconazole, miconazole (oral dosage form, injections, agents for oral use), fluconazole,

contraindicated to the following patients.)

fosfluconazole, voriconazole, posaconazole, HIV protease inhibitors (preparations containing ritonavir, atazanavir sulfate, fosamprenavir calcium hydrate, preparations containing darunavir), preparations containing cobicistat, nirmatrelvir/ritonavir, ensitrelvir fumaric acid, clarithromycin, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Clarithromycin Ceritinib	The effects of azelnidipine may be enhanced.	It is considered that these drugs inhibit CYP3A4 and that the clearance of azelnidipine is decreased.

19 Antihypertensives
Eplerenone

Brand name

Selara Tablets 25 mg, 50 mg, 100 mg (Viatris Pharmaceuticals Inc.), and the others

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

Patients receiving the following drugs: Itraconazole, voriconazole, posaconazole, preparations containing ritonavir, preparations containing cobicistat, ceritinib, and ensitrelvir fumaric acid

10. INTERACTIONS
10.1 Contraindications for Co-administration (Do not co-administer with the following.) <Common to all indications>

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Itraconazole Voriconazole Posaconazole Preparations containing ritonavir Preparations containing cobicistat Ceritinib Ensitrelvir fumaric acid	The plasma concentration of eplerenone may increase, and an increase in serum potassium levels may be induced.	The metabolism of eplerenone is suppressed by strong CYP3A4 inhibitor.

20 Antihypertensives
Olmesartan medoxomil/azelnidipine

Brand name

Rezaltas Combination Tablets LD, HD (Daiichi Sankyo Co., Ltd.)

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

Patients receiving the following drugs: Itraconazole, miconazole (oral dosage form, injections, agents for oral use), fluconazole, fosfluconazole, voriconazole, posaconazole, HIV protease inhibitors (preparations containing ritonavir, atazanavir sulfate, fosamprenavir calcium hydrate, preparations containing darunavir), preparations containing cobicistat, nirmatrelvir/ritonavir, ensitrelvir fumaric acid, clarithromycin, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Clarithromycin Ceritinib	The effects of azelnidipine may be enhanced.	It is considered that these drugs inhibit CYP3A4 and that the

		clearance of azelnidipine is decreased.

21 Agents for hyperlipidemias

Simvastatin

Brand name Lipovas Tablets 5, 10, 20 (Organon K.K.), and the others

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving itraconazole, miconazole, posaconazole, atazanavir, saquinavir mesylate, preparations containing cobicistat, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Atazanavir Saquinavir mesylate Preparations containing cobicistat Ceritinib	Serious adverse reactions such as myopathy, including rhabdomyolysis, may occur.	These drugs inhibit CYP3A4, thereby suppressing the metabolism of this drug.

22 Agents for hyperlipidemias

Lomitapide mesilate

Brand name Juxtapid Capsules 5 mg, 10 mg, 20 mg (Recordati Rare Diseases Japan K.K.)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Strong CYP3A inhibitors Clarithromycin Indinavir Itraconazole Nelfinavir Saquinavir Telaprevir Voriconazole Preparations containing ritonavir Preparations containing cobicistat Ceritinib	The blood concentration of this drug may increase markedly.	The metabolism of this drug is suppressed due to CYP3A inhibition by these drugs.

23 Other cardiovascular agents

Ivabradine Hydrochloride

Brand name Coralan Tablets 2.5 mg, 5 mg, 7.5 mg (Ono Pharmaceutical Co., Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving the following drugs: Preparations containing ritonavir, josamycin, itraconazole, clarithromycin, preparations containing cobicistat, voriconazole, ensitrelvir fumaric acid, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Preparations containing ritonavir Josamycin Itraconazole Clarithromycin Preparations containing cobicistat Voriconazole Ensitrelvir fumaric acid Ceritinib	Excessive bradycardia may occur.	CYP3A-mediated metabolism of this drug is strongly inhibited, leading to an increase in the blood concentration of this drug.

24 Other cardiovascular agents

Tadalafil (pulmonary arterial hypertension)

Brand name
Adcirca Tablets 20 mg (Nippon Shinyaku Co., Ltd.), and others

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving drugs that strongly inhibit cytochrome P450 3A4 (CYP3A4) (itraconazole, preparations containing ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, preparations containing darunavir, clarithromycin, telaprevir, preparations containing cobicistat, ensitrelvir, ceritinib)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Drugs that strongly inhibit CYP3A4 Itraconazole Preparations containing ritonavir Atazanavir Indinavir Nelfinavir Saquinavir Preparations containing darunavir Clarithromycin Telaprevir Preparations containing cobicistat Ensitrelvir Ceritinib	It has been reported that co-administration with ketoconazole (400 mg/day: oral dosage form, not marketed in Japan), which has a strong inhibitory effect on CYP3A4, increases the AUC and Cmax of this drug (20 mg) by 312% and 22%, respectively. In addition, it has been reported that co-administration with ritonavir (200 mg twice daily) increases the AUC of this drug (20 mg) by 124%.	These drugs are expected to severely reduce the clearance of this drug by strongly inhibiting CYP3A4, leading to an increase in the plasma concentration of this drug. Patients receiving these drugs have been excluded from clinical studies.

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25 Other cardiovascular agents

Finerenone

Brand name Kerendia tablets 10 mg, 20 mg (Bayer Yakuhin, Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving the following drugs: Itraconazole, posaconazole, voriconazole, preparations containing ritonavir, darunavir, fosamprenavir, preparations containing cobicistat, clarithromycin, ensitrelvir, lonafarnib, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Itraconazole Posaconazole Voriconazole Preparations containing ritonavir Darunavir Fosamprenavir Preparations containing cobicistat Clarithromycin Ensitrelvir Lonafarnib Ceritinib	The blood concentration of finerenone may markedly increase.	The clearance of finerenone is decreased by the potent inhibition of CYP3A.

26 Other cardiovascular agents

Macitentan/tadalafil

Brand name Yuvanci Combination Tablets (Janssen Pharmaceutical K.K.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving a strong CYP3A4 inhibitor (itraconazole, preparations containing ritonavir, atazanavir, preparations containing darunavir, clarithromycin, preparations containing cobicistat, ensitrelvir, ceritinib)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Strong CYP3A4 inhibitors Itraconazole Preparations containing ritonavir Atazanavir Preparations containing darunavir Clarithromycin Preparations containing cobicistat Ensitrelvir Ceritinib	The blood concentrations of macitentan and tadalafil may increase, which may make adverse reactions to this drug more likely to occur.	Strong CYP3A4 inhibition increases exposure to macitentan and tadalafil.

27 Oxytocics

Methylergometrine maleate

Brand name Martan M Tablets 0.125 mg, Partan M Injection 0.2 mg (Mochida Pharmaceutical Co., Ltd.), Methylergometrine Tablets 0.125 mg "Aska",

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Methylergometrine Injection 0.2 mg "Aska" (Aska Pharmaceutical Co., Ltd.), and others

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

Patients receiving the following drugs: HIV protease inhibitors (preparations containing ritonavir, atazanavir sulfate, fosamprenavir calcium hydrate, preparations containing darunavir ethanolate), efavirenz, azole antifungal agents (itraconazole, voriconazole, posaconazole), preparations containing cobicistat, nirmatrelvir/ritonavir, letermovir, ensitrelvir fumaric acid, lenacapavir sodium, 5-HT1B/1D receptor agonists (sumatriptan, zolmitriptan, eletriptan hydrobromide, rizatriptan benzoate, naratriptan hydrochloride), ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
HIV protease inhibitors Preparations containing ritonavir Atazanavir sulfate Fosamprenavir calcium hydrate Preparations containing darunavir ethanolate Efavirenz Azole antifungal agents Itraconazole Voriconazole Posaconazole Preparations containing cobicistat Nirmatrelvir/ritonavir Letermovir Ensitrelvir fumaric acid Lenacapavir sodium Ceritinib	The blood concentration of this drug may increase, which may cause serious adverse reactions such as angiospasm.	The metabolism of this drug may be suppressed by CYP3A4 inhibition due to these drugs.

28 Other agents for uro-genital and anal organ
Vardenafil hydrochloride hydrate

Brand name

Vardenafil Tablets 5 mg "FCI", 10 mg "FCI", 20 mg "FCI" (Fuji Chemical Industries Co., Ltd.), and others

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

Patients receiving the following drugs: Riociguat, CYP3A4 inhibitors (ritonavir, atazanavir, fosamprenavir, lopinavir/ritonavir, nirmatrelvir/ritonavir, preparations containing darunavir, ketoconazole (excluding topical formulations), itraconazole, ensitrelvir, preparations containing cobicistat, ceritinib)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Ceritinib	The plasma concentration of vardenafil hydrochloride hydrate may increase.	The clearance of vardenafil hydrochloride hydrate is decreased by the inhibition of CYP3A4.

29 Other agents relating to blood and body fluids

Ticagrelor

Brand name Brilinta tablets 60 mg, 90 mg (AstraZeneca K.K.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving a strong CYP3A inhibitor (itraconazole, voriconazole, clarithromycin, ritonavir, preparations containing cobicistat, ensitrelvir fumaric acid, ceritinib)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Strong CYP3A inhibitors Itraconazole Voriconazole Clarithromycin Ritonavir Preparations containing cobicistat Ensitrelvir fumaric acid Ceritinib	The platelet aggregation inhibition by this drug may be enhanced.	These drugs are expected to inhibit the metabolism of this drug by strongly inhibiting CYP3A, leading to a marked increase in plasma concentrations of this drug.

30 Gout preparations

Colchicine

Brand name Colchicine Tablets 0.5 mg "Takata" (TAKATA Pharmaceutical Co., Ltd.)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Drugs that strongly inhibit the hepatic metabolizing enzyme CYP3A4 (When administered to patients with hepatic or renal disorder) Atazanavir Preparations containing clarithromycin Itraconazole Preparations containing ritonavir	The effect of this drug may be enhanced. This drug is not co-administered with these drugs.	Inhibition of the hepatic metabolizing enzyme CYP3A4 may increase the blood concentration of this drug.

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Preparations containing darunavir Preparations containing cobicistat Ensitrelvir Lonafarnib Ceritinib, etc.		

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

Anamorelin hydrochloride

Brand name Adlumiz Tablets 50 mg (Ono Pharmaceutical Co., Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving the following drugs: Clarithromycin, itraconazole, voriconazole, preparations containing ritonavir, preparations containing cobicistat, ensitrelvir fumaric acid, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Clarithromycin Itraconazole Voriconazole Preparations containing ritonavir Preparations containing cobicistat Ensitrelvir fumaric acid Ceritinib	The blood concentration of this drug may increase, which may lead to an increased occurrence of adverse reactions.	The metabolism of this drug is suppressed due to strong CYP3A4 inhibition by these drugs.

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

Tacrolimus hydrate (oral and injectable dosage forms)

Brand name Prograf Capsules 0.5 mg, 1 mg, 5 mg, Prograf Granules 0.2 mg, 1 mg, Prograf Injection 2 mg, 5 mg, Graceptor Capsules 0.5 mg, 1 mg, 5 mg (Astellas Pharma Inc.), and the others

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
9.5 Pregnant Women

Taking into account the following reports, pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks.

<Common to all indications>

Teratogenic effects and fetal toxicity have been reported in animal studies in rabbits.

Placental transfer in humans has been reported.

Premature birth and effects on infants (low birth weight, congenital anomalies, hyperkalaemia, renal impairment) have been reported in women who received this drug during pregnancy.

<Liver and kidney transplant>

In an overseas cohort study on 2,905 cases of pregnancy in liver and kidney transplant recipients which were available from the database of Transplant Pregnancy Registry International, the following results were reported from prospectively-reported cases.

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・Major malformations were observed in 6/297 livebirths (2.0%) in the tacrolimus group and in 1/53 livebirths (1.9%) Note 2) in the non-tacrolimus-containing regimen group Note 1).
・Minor malformations were observed in 12/297 livebirths (4.0%) in the tacrolimus group and not observed in the non-tacrolimus-containing regimen group Note 2).
・Spontaneous abortions were observed in 33/335 cases (9.9%) in the tacrolimus group and in 3/56 cases (5.4%) in the non-tacrolimus-containing regimen group Note 2).
・Pre-eclampsia was observed in 84/226 cases (37.2%) in the tacrolimus group and in 7/37 cases (18.9%) in the non-tacrolimus-containing regimen group among kidney transplant recipients.
・Early pre-term birth was observed in 156/352 livebirths (44.3%) in the tacrolimus group and in 25/59 livebirths (42.4%) in the non-tacrolimus-containing regimen group.
・A normal birth weight for gestational age was reported in 289/352 livebirths (82.1%) in the tacrolimus group and in 40/59 livebirths (67.8%) in the non-tacrolimus-containing regimen group.

Note 1) Patients who received treatment with regimens containing one or more of the following: azathioprine, cyclosporine, everolimus, mycophenolic acid, prednisone, and sirolimus.

Note 2) The analysis results obtained after excluding patients who had mycophenolic acid exposure during the period from 6 weeks prior to pregnancy through childbirth

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33 Other antitumor agents

Apalutamide

Brand name

Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.)

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

Patients receiving nirmatrelvir/ritonavir, ensitrelvir fumaric acid, lenacapavir sodium, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate, darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate, bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate, rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate, darunavir ethanolate/cobicistat, doravirine, dolutegravir sodium/rilpivirine hydrochloride, rilpivirine, or rilpivirine hydrochloride

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Lenacapavir sodium Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate Rilpivirine hydrochloride/emtricitabine/tenofovir	Since the blood concentration of these drugs decreases, their effects may decrease, and resistance to these drugs may develop.	Apalutamide induces CYP3A and P-gp.

alafenamide fumarate		

(newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Darunavir ethanolate/cobicistat Doravirine Dolutegravir sodium/rilpivirine hydrochloride Rilpivirine Rilpivirine hydrochloride	Since the blood concentration of these drugs decreases, their effects may decrease, and resistance to these drugs may develop.	Apalutamide induces CYP3A.

34 Other antitumor agents

Ibrutinib

Brand name Imbruvica Capsules 140 mg (Janssen Pharmaceutical K.K.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving the following drugs: Ketoconazole, itraconazole, clarithromycin, ensitrelvir fumaric acid, ceritinib

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Ketoconazole (oral dosage form; not marketed in Japan) Itraconazole Clarithromycin Ensitrelvir fumaric acid Ceritinib	The blood concentration of this drug may rise, and adverse reactions may be enhanced.	The metabolism of this drug is suppressed due to CYP3A inhibition by these drugs.

35 Other antitumor agents

Enzalutamide

Brand name Xtandi Tablets 40 mg, 80 mg (Astellas Pharma Inc.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving doravirine, ensitrelvir fumaric acid, lenacapavir sodium, nirmatrelvir/ritonavir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate, darunavir ethanolate/cobicistat, darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate, dolutegravir sodium/rilpivirine hydrochloride, bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate, rilpivirine, rilpivirine hydrochloride, or rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Doravirine Ensitrelvir fumaric acid Lenacapavir sodium Nirmatrelvir/ritonavir Elvitegravir/cobicistat/ emtricitabine/tenofovir	The effects of these antiviral drugs may be attenuated by coadministration with enzalutamide.	The CYP3A4-inducing activity of enzalutamide may lead to a decrease in the blood

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alafenamide fumarate Darunavir ethanolate/cobicistat Darunavir ethanolate/cobicistat/ emtricitabine/tenofovir alafenamide fumarate Dolutegravir sodium/rilpivirine hydrochloride Bictegravir sodium/emtricitabine/ tenofovir alafenamide fumarate Rilpivirine Rilpivirine hydrochloride Rilpivirine hydrochloride/ emtricitabine/tenofovir alafenamide fumarate		concentration of these antiviral drugs.

36 Other antitumor agents

Olaparib

Brand name	Lynparza Tablets 100 mg, 150 mg (AstraZeneca K.K.)
8. IMPORTANT PRECAUTIONS (newly added)	Hepatic impairment may occur. Liver function tests should be performed prior to and periodically during administration of this drug, and patients should be carefully monitored for their condition.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Hepatic impairment

37 Other antitumor agents

Ceritinib

Brand name	Zykadia tablets 150 mg (Novartis Pharma K.K.)
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	Patients receiving the following drugs: Venetoclax (relapsed or refractory chronic lymphocytic leukaemia (including small lymphocytic lymphoma) and relapsed or refractory mantle cell lymphoma during the dose escalation phase), anamorelin hydrochloride, ivabradine hydrochloride, quinidine sulfate hydrate, ticagrelor, azelnidipine, olmesartan medoxomil/azelnidipine, eplerenone, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, simvastatin, tadalafil (Adcirca), macitentan/tadalafil, finerenone, lomitapide mesilate, suvorexant, triazolam, blonanserin, lurasidone hydrochloride, vardenafil hydrochloride hydrate, methylergometrine maleate, ibrutinib
(newly added) 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC	Patients with hepatic or renal impairment receiving colchicine

BACKGROUNDS

9.2 Patients with Renal Impairment (newly added)

Patients with renal impairment receiving colchicine
This drug should not be administered. The blood concentration of colchicine may increase.

9.3 Patients with Hepatic Impairment (newly added)

Patients with hepatic impairment receiving colchicine This drug should not be administered. The blood concentration of colchicine may increase.
Patients with severe hepatic impairment (excluding patients receiving colchicine)

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Anamorelin hydrochloride Ivabradine hydrochloride Quinidine sulfate hydrate Ticagrelor Azelnidipine Olmesartan medoxomil/azelnidipine Eplerenone Ergotamine tartrate/anhydrous caffeine/isopropylantipyrine Simvastatin Tadalafil (Adcirca) Macitentan/tadalafil Finerenone Lomitapide mesilate Suvorexant Triazolam Blonanserin Lurasidone hydrochloride Vardenafil hydrochloride hydrate Methylergometrine maleate Lonafarnib Ibrutinib	Adverse reactions to these drugs may be enhanced.	Strong CYP3A inhibition by ceritinib may suppress the metabolism of these drugs, leading to an increase in the blood concentration of these drugs.

38 Antibiotic preparations acting mainly on gram-positive bacteria and mycoplasma

Clarithromycin

Brand name

Klaricid Tablets 200 mg, Klaricid Tablets 50 mg for Pediatric Use (Nippon Chemiphar Co., Ltd.), Clarith tablets 200, Clarith tablets 50 for pediatric, Clarith dry syrup 10% for pediatric (Taisho Pharmaceutical Co., Ltd.), and others

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

Patients receiving pimozide, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, suvorexant, daridorexant hydrochloride, vornorexant hydrate, lomitapide mesilate, tadalafil (Adcirca), ticagrelor, ibrutinib, ivabradine hydrochloride, venetoclax (relapsed or refractory chronic lymphocytic leukaemia [including small lymphocytic lymphoma] and relapsed or refractory mantle cell lymphoma during the dose escalation phase), lurasidone

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hydrochloride, anamorelin hydrochloride, finerenone, isavuconazonium sulfate, voclosporin, mavacamten, azelnidipine, or olmesartan medoxomil/azelnidipine

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Azelnidipine Olmesartan medoxomil/azelnidipine	The blood concentration of azelnidipine may increase, and its effects may be enhanced.	The CYP3A inhibitory activity of clarithromycin may suppress the metabolism of these drugs, leading to an increase in their blood concentration.

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39 Other antibiotic preparations

Vonoprazan fumarate/amoxicillin hydrate/clarithromycin

Brand name
Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving atazanavir sulfate, rilpivirine hydrochloride, pimozide, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, suvorexant, daridorexant hydrochloride, vornorexant hydrate, lomitapide mesilate, tadalafil (Adcirca), ticagrelor, ibrutinib, ivabradine hydrochloride, venetoclax (relapsed or refractory chronic lymphocytic leukaemia [including small lymphocytic lymphoma] and relapsed or refractory mantle cell lymphoma during the dose escalation phase), lurasidone hydrochloride, anamorelin hydrochloride, finerenone, isavuconazonium sulfate, voclosporin, mavacamten, azelnidipine, or olmesartan medoxomil/azelnidipine

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Azelnidipine Olmesartan medoxomil/azelnidipine	The blood concentration of azelnidipine may increase, and its effects may be enhanced.	The CYP3A inhibitory activity of clarithromycin may suppress the metabolism of these drugs, leading to an increase in their blood concentration.

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40 Other antibiotic preparations

Rabeprazole sodium/amoxicillin hydrate/clarithromycin

Brand name
Rabecure Pack 400, 800 (Eisai Co., Ltd.)

2.CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving rilpivirine hydrochloride, pimozide, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, suvorexant, daridorexant hydrochloride, vornorexant hydrate, lomitapide mesilate, tadalafil (Adcirca), ticagrelor, ibrutinib, ivabradine hydrochloride, venetoclax (relapsed or refractory chronic lymphocytic leukaemia [including small lymphocytic lymphoma] and relapsed or

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refractory mantle cell lymphoma during the dose escalation phase), lurasidone hydrochloride, anamorelin hydrochloride, finerenone, isavuconazonium sulfate, voclosporin, mavacamten, azelnidipine, or olmesartan medoxomil/azelnidipine

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

<Clarithromycin>

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Azelnidipine Olmesartan medoxomil/azelnidipine	The blood concentration of azelnidipine may increase, and its effects may be enhanced.	The CYP3A inhibitory activity of clarithromycin may suppress the metabolism of these drugs, leading to an increase in their blood concentration.

41 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, 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, telaprevir

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Carbamazepine Phenobarbital Phenytoin Fosphenytoin Rifampicin Apalutamide Food containing St. John's Wort	The blood concentration of elvitegravir and cobicistat may significantly decrease. The blood concentration of tenofovir alafenamide may also decrease.	It is considered that these drugs induce CYP3A and P-gp.

(newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Enzalutamide	The blood concentration of elvitegravir and cobicistat may significantly decrease.	It is considered that enzalutamide induces CYP3A.
Eplerenone	The blood	It is considered

	concentration of eplerenone may increase, and an increase in serum potassium levels may be induced.	that cobicistat inhibits CYP3A.

42 Anti-virus agents
Darunavir ethanolate/cobicistat

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

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

Patients receiving rifampicin, phenobarbital, phenytoin, fosphenytoin, carbamazepine, apalutamide, enzalutamide, 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 (relapsed or refractory chronic lymphocytic leukaemia [including small lymphocytic lymphoma] during the dose escalation phase), isavuconazonium sulfate, anamorelin hydrochloride, mavacamten, rivaroxaban, or 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 Phenobarbital Phenytoin Fosphenytoin Carbamazepine Apalutamide Enzalutamide	The blood concentration of darunavir and cobicistat may decrease, leading to attenuation of the effects of darunavir ethanolate/cobicistat.	The CYP3A-inducing activity of these drugs promotes the metabolism of darunavir and cobicistat.

(newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Eplerenone	The blood concentration of eplerenone may increase, and an increase in serum potassium levels may be induced.	The CYP3A inhibitory activity of darunavir and cobicistat suppresses the metabolism of eplerenone.

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

Brand name Symtuza Combination Tablets (Janssen Pharmaceutical K.K.)

2. CONTRAINDICATIONS (This drug is

Patients receiving rifampicin, phenobarbital, phenytoin, fosphenytoin, carbamazepine, apalutamide, food containing St. John's Wort, enzalutamide, triazolam, midazolam, pimozide, simvastatin,

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contraindicated to the following patients.)

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 (relapsed or refractory chronic lymphocytic leukaemia [including small lymphocytic lymphoma] during the dose escalation phase), isavuconazonium sulfate, anamorelin hydrochloride, mavacamten, rivaroxaban, or 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 Phenobarbital Phenytoin Fosphenytoin Carbamazepine Apalutamide	The blood concentration of darunavir, cobicistat, and tenofovir alafenamide may decrease, leading to attenuation of the effects of this drug.	It is considered that these drugs induce CYP3A and P-glycoprotein.

(newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Enzalutamide	The blood concentration of darunavir and cobicistat may decrease, leading to attenuation of the effects of this drug.	It is considered that enzalutamide induces CYP3A.
Eplerenone	The blood concentration of eplerenone may increase, and an increase in serum potassium levels may be induced.	The CYP3A inhibitory activity of darunavir and cobicistat suppresses the metabolism of eplerenone.

44 Anti-virus agents
Doravirine

Brand name

Pifeltro Tablets 100 mg (MSD K.K.)

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

Patients receiving carbamazepine, phenobarbital, phenytoin, fosphenytoin, enzalutamide, apalutamide, rifampicin, mitotane, or 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
Carbamazepine Phenobarbital Phenytoin Fosphenytoin Enzalutamide Apalutamide	The plasma concentration of doravirine may decrease, leading to attenuation of the therapeutic effects.	The strong CYP3A4-inducing effects of these drugs and foods are expected to promote the

Rifampicin Mitotane Food containing St. John's Wort		metabolism of doravirine.

45 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, dexamethasone (systemic administration) (excluding single administration), or 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.) (newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Apalutamide Enzalutamide	The blood concentration of rilpivirine may decrease, leading to attenuation of the effects of dolutegravir sodium/rilpivirine hydrochloride.	The CYP3A-inducing activity of these drugs promotes the metabolism of rilpivirine.

46 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

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Carbamazepine Phenobarbital Phenytoin Fosphenytoin Apalutamide Food containing St. John's Wort	Since the plasma concentration of bictegravir and tenofovir alafenamide decreases, the effects of this drug may be attenuated, and resistance to this drug may occur.	It is considered that these drugs induce CYP3A and P-gp.

(newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Enzalutamide	Since the plasma concentration of bictegravir decreases, the effects of this drug	It is considered that enzalutamide induces CYP3A.

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	may be attenuated, and resistance to this drug may occur.	

47 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, dexamethasone (systemic administration) (excluding single administration), or food containing St. John's Wort

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Apalutamide Enzalutamide	The blood concentration of rilpivirine may decrease, leading to attenuation of the effects of rilpivirine.	The CYP3A-inducing activity of these drugs promotes the metabolism of rilpivirine.

48 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, dexamethasone (systemic administration) (excluding single administration), food containing St. John's Wort, or 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.) (newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Apalutamide Enzalutamide	The blood concentration of rilpivirine hydrochloride may decrease, leading to attenuation of the effects of rilpivirine.	The CYP3A-inducing activity of these drugs promotes the metabolism of rilpivirine hydrochloride.

49 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,dexamethasone (systemic administration) (excluding single administration), or 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.) (newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Apalutamide	The blood concentration of rilpivirine and tenofovir alafenamide may decrease, leading to attenuation of the effects of this drug.	The CYP3A-inducing activity of apalutamide promotes the metabolism of rilpivirine. The P-glycoprotein-inducing activity of apalutamide may decrease the plasma concentration of tenofovir alafenamide.
Enzalutamide	The blood concentration of rilpivirine may decrease, leading to attenuation of the effects of this drug.	The CYP3A-inducing activity of enzalutamide promotes the metabolism of rilpivirine.

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 February 28, 2026)
◎: Products for which EPPV was initiated after February 1, 2026

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiation
◎	Vonicog Alfa（genetical recombination） Vonvendi Intravenous 1300	Takeda Pharmaceutical Company Limited	February 19, 2026
◎	Tezepelumab (genetical recombination)[*1] Tezspire Subcutaneous Injection 210 mg Syringe, 210 mg Pen	AstraZeneca K.K.	February 19, 2026
◎	Adrenaline Neffy nasal spray 1 mg, 2 mg	Alfresa Pharma Corporation	February 12, 2026
◎	Cantharidin Ycanth topical solution 0.71%	Torii Pharmaceutical Co., Ltd.	February 9, 2026
	Diazepam Spydia Nasal Spray 5 mg, 7.5 mg, 10 mg	Aculys Pharma, Inc.	December 24, 2025
	Finerenone*[2] Kerendia tablets 10 mg, 20 mg	Bayer Yakuhin, Ltd.	December 22, 2025
	Odevixibat hydrate Bylvay Granules 200 μg, 600 μg	IPSEN Co., Ltd	December 18, 2025
	Rimegepant sulfate hydrate Nurtec OD Tablets 75 mg	Pfizer Japan Inc.	December 16, 2025
	Midazolam Dormicum syrup 2 mg/mL	Maruishi Pharmaceutical Co., Ltd.	November 27, 2025
	Avacincaptad pegol sodium Izervay for intravitreal injection 20 mg/mL	Astellas Pharma Inc.	November 27, 2025
	Vornorexant hydrate Vorzzz tablets 2.5 mg, 5 mg, 10 mg	Taisho Pharmaceutical Co., Ltd.	November 27, 2025
	Chenodeoxycholic Acid[*3] Fujichenon granular tablets 125	Fujimoto Pharmaceutical Corporation	November 21, 2025

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Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiation
	Bempedoic Acid Nexletol tablets 180 mg	Otsuka Pharmaceutical Co., Ltd.	November 21, 2025
	Repotrectinib[*4] Augtyro capsules 40 mg, 160 mg	Bristol-Myers Squibb K.K.	November 20, 2025
	Inebilizumab (genetical recombination)[*5] Uplizna for intravenous infusion 100 mg	Tanabe Pharma Corporation	November 20, 2025
	Gallium (^{68}Ga) gozetotide Locametz kit	Novartis Pharma K.K.	November 12, 2025
	Lutetium (177Lu) vipivotide tetraxetan Pluvicto injection	Novartis Pharma K.K.	November 12, 2025
	Taletrectinib adipate Ibtrozi capsules 200 mg	Nippon Kayaku Co., Ltd.	November 12, 2025
	Zongertinib Hernexeos tablets 60 mg	Nippon Boehringer Ingelheim Co., Ltd.	November 12 2025
	Nusinersen Sodium Spinraza intrathecal injection 28 mg, 50 mg	Biogen Japan Ltd.	November 12, 2025
	Selumetinib sulfate Koselugo granules 5 mg, 7.5 mg	Alexion Pharma Godo Kaisha	November 12, 2025
	Nipocalimab (genetical recombination) Imaavy intravenous infusion 1200 mg	Janssen Pharmaceutical K.K.	November 12, 2025
	Palopegteriparatide Yorvipath subcutaneous injection 168 μg pen, 294 μg pen, 420 μg pen	Teijin Pharma Limited	November 6, 2025
	Gallium (^{68}Ga) chloride GalliaPharm ^{68}Ge/^{68}Ga generator	Eckert & Ziegler Radiopharma GmbH (Oversee products designated MAH) Novartis Pharma K.K.	November 5, 2025
	Remimazolam besilate[*6] Anerem 20 mg for I.V. injection	Mundipharma K.K.	November 4, 2025
	Pneumococcal 21-valent Conjugate Vaccine (joint component of nontoxic diphtheria toxin derivatives) Capvaxive for intramuscular injection syringes	MSD K.K.	October 29, 2025
	Sepetaprost Setaneo ophthalmic solution 0.002%	Santen Pharmaceutical Co., Ltd.	October 23, 2025
	Coronavirus (SARS-CoV-2) RNA Vaccine DAICHIRONA INTRAMUSCULAR INJECTION	Daiichi Sankyo Co., Ltd.	September 19, 2025
	Etrasimod L-Arginine Velsipity Tablets 2 mg	Pfizer Japan Inc.	September 12, 2025

*1 Chronic rhinosinusitis with nasal polyps (limited to patients for whom existing treatments are ineffective)

*2 Chronic cardiac failure, only limited to patients receiving standard treatment for chronic heart failure

*3 Cerebrotendinous xanthomatosis

*4 NTRK fusion gene-positive advanced or recurrent solid tumor

*5 Suppression of relapse in IgG4-related diseases

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*6 Sedation during gastrointestinal endoscopy

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