Pharmaceuticals and Medical Devices Safety Information

No. 394

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 394

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

[Outline of Information]

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 medical and pharmaceutical providers.

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

Please utilize the Report Reception Site for reporting.
(This service is only available in Japanese.)
https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADR	Adverse drug reaction
CSF	Cerebral spinal fluid
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
NIHS	National Institute of Health Sciences
NSCLC	Non-small cell lung cancer
PMDA	Pharmaceuticals and Medical Devices Agency
PCR	Polymerase chain reaction
PS	Performance status
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis

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Genome Research on Drug-induced Interstitial Lung Disease

1. Introduction

The onset of adverse drug reactions unrelated to the intended pharmacological action tends to be generally difficult to predict and often requires medical treatment. However, it has been reported since around 2004 that the onset of some such adverse drug reactions may be predicted based on the associated genomic information. The Ministry of Health, Labour and Welfare (MHLW) and the National Institute of Health Sciences (NIHS) have been conducting research to collect and analyze genomic samples and clinical information of patients who have developed adverse drug reactions of skin disorders (Stevens-Johnson syndrome, also known as oculomucocutaneous syndrome [SJS], toxic epidermal necrolysis [TEN]), rhabdomyolysis (muscle disorder), and interstitial lung disease, in order to use genomic information for establishing predictive and preventive safety measures against the adverse drug reactions. As of the end of March 2022, 346 cases of skin disorder, 265 cases of rhabdomyolysis (muscle disorder), and 287 cases of interstitial lung disease were collected. The results of the analysis on SJS/TEN were reported in Pharmaceuticals and Medical Devices Safety Information No. 372[1)] and those of rhabdomyolysis (muscle disorder) in No. 361,[2)] respectively. This section presents the current status and results of the research on drug-induced interstitial lung disease.

2. Drug-induced Interstitial Lung Disease

The diagnostic criteria for drug-induced lung disease released from the committee of the Japanese Respiratory Society include 1) history of ingestion of a drug that is known to induce lung injury, 2) the clinical manifestations have been reported to be induced by a drug, 3) other causes of the clinical manifestations could be ruled out, 4) improvement of the clinical manifestations after drug discontinuation, and 5) exacerbation of the clinical manifestations after resuming drug administration.[3,4)] Therefore, there is no specific diagnostic method, and the diagnosis is comprehensively made mainly by a respiratory specialist based on physical examination, imaging findings, laboratory tests including Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D), differential diagnosis from infectious diseases, etc. Some drugs were reported to induce this reaction more frequently in Japan than overseas: The reported incidence was ≥ 100-fold for leflunomide, ≥ 50-fold for bleomycin, ≥ 10-fold for gefitinib and bortezomib, and ≥ 5-fold for erlotinib.[3,4)]

Drug-induced interstitial lung disease is clinically manifested as dyspnoea and cough (particularly dry cough) due to inflammation of the alveolar walls and fibrosis of the interstitium.[5)] Specifically in interstitial pneumonia, chest CT, particularly high-resolution CT, is useful for diagnosis, which shows various images reflecting pathological conditions of the lung, such as ground-glass opacities and their distribution. For example, patients may have a pattern of diffuse alveolar damage, organizing pneumonia, or nonspecific interstitial pneumonia. It is possible that multiple patterns are noted in a patient, or different patterns are observed with the same causative drug. The pathogenetic mechanisms of drug-induced interstitial lung disease are not well understood but are typically considered to be direct cytotoxic effects of drugs and immune-mediated pulmonary injuries. The onset is dose-dependent by the former mechanism, and amiodarone and bleomycin are known as representative drugs with this mechanism.

In FY 2016 and FY 2017, the most commonly reported suspected drugs associated with drug-induced interstitial lung disease were antineoplastic agents including nivolumab (genetical recombination) and pembrolizumab (genetical recombination), immune checkpoint inhibitors; everolimus and temsirolimus, mTOR inhibitors; tyrosine kinase inhibitors including gefitinib and erlotinib hydrochloride; and others such as nanoparticle albumin-bound paclitaxel, docetaxel hydrate, and gemcitabine hydrochloride.[5)] In addition, amiodarone hydrochloride (antiarrhythmic

drug) and apixaban (anticoagulant) have been reported as well. By therapeutic class, antirheumatic drugs, antipyretic analgesic anti-inflammatory drugs, and antihypertensive drugs have been associated.[3-6] The time from the start of treatment to the onset of symptoms was most commonly within 3 months.[6] Drugs with the highest number of cases receiving payments for relief benefits between FY 2013 and FY 2017 under the Relief System for Sufferers from Adverse Drug Reactions (antineoplastic agents, etc. are not covered) were Kampo medicines, followed by antipyretic analgesic anti-inflammatory drugs, drugs classified as miscellaneous metabolism agents, and then peptic ulcer drugs.[5] Kampo medicine-induced interstitial lung disease was addressed in the Pharmaceuticals and Medical Devices Safety Information in 1998.[7] A literature review from 1996 to 2015 revealed that shosaikoto was associated with the greatest number of reports on this adverse drug reaction, followed by saireito, seishinrenshiin, and then bofutsushosan.[8]

The treatment begins with the withdrawal of the suspected drug. Steroids are administered to moderate-grade patients with hypoxemia, and high-dose steroids, such as methylprednisolone pulse therapy, are used in patients with severe respiratory failure.[3-6]

3. Genome Research on Drug-induced interstitial lung disease

Pre-existing interstitial lung disease is a known risk factor for drug-induced interstitial lung disease. Other known risk factors include old age, male sex, and smoking. The fact that this disease is more often reported in the Japanese population suggests that some genetic factors may be associated with its pathogenesis.[3-5]

3.1 Research results on gefitinib

Many cases of interstitial lung disease were initially reported in patients with non-small cell lung cancer (NSCLC) who were treated with gefitinib after the launch in 2002. A nested case-control study within a cohort indicated that gefitinib has a significantly increased risk of interstitial lung disease compared with other anticancer drugs. Additional risk factors include a WHO performance status ≥ 2, smoking, and pre-existing interstitial lung disease.[9] A genome-wide association study was also performed in Japanese patients with NSCLC to find the association of approximately 500 000 genetic polymorphisms with gefitinib-induced interstitial lung disease:[10] The top 67 genetic polymorphisms with the lowest p-values were selected in a case-control study of 52 and 139 NSCLC patients with and without interstitial lung disease, respectively. Subsequently, this potential association was further investigated using 28 and 55 NSCLC patients with and without disease, respectively. Results showed no statistically significant association of these polymorphisms with the disease after multiplicity adjustment.

3.2 Analytical results from the NIHS

In collaboration with Shinshu University, the NIHS performed genetic analyses to investigate the association between *HLA* alleles and the development of drug-induced interstitial lung disease in the Japanese population.[11] First, for an exploratory group, they conducted a case-control study using samples collected at the NIHS from 177 patients clinically diagnosed with drug-induced interstitial lung disease and 3 002 healthy adult controls to identify *HLA* alleles with significant differences in frequency among *HLA-A, -B, -C, and -DRB1* genes. As a result, they found a significant association of *HLA-DRB1*04:05* with the disease ($p = 0.043$ after multiplicity adjustment using the number of *DRB1* alleles detected). This association was confirmed (not adjusted for multiplicity) in a validation group including 55 patients with drug-induced interstitial lung disease and 201 healthy adult controls (both collected at Shinshu University). This association was still observed in the analysis of a patient subgroup excluding those with rheumatoid arthritis, for which this *HLA* allele is a known risk factor. This *HLA* allele was associated with interstitial lung disease induced by chemical drugs ($p = 1.7 \times 10^{-4}$), but not by therapeutic proteins. Allele frequency information from various countries revealed that, similar to that in Papua New Guinea and the Philippines, the frequency of *HLA-DRB1*04:05* was much higher in Japan (carrier frequency of 0.253) than in the US and European countries. This high carrier frequency of the *HLA* allele may be an explanatory factor of the high incidence of drug-induced interstitial lung disease in the Japanese population. A larger number of cases will be needed to perform drug-specific analyses in the future.

4. Closing Remarks

Regarding drug-induced interstitial lung disease, there are very few published reports on the genetic analysis even in the Japanese population, in which the incidence is relatively high. Collecting a larger number of cases to perform genomic analyses and to obtain fundamental information for clinical application will lead to “safety measures that predict and prevent adverse drug reactions.” As described above, the NIHS is conducting genome research with the cooperation of the Federation of Pharmaceutical Manufacturers’ Associations of Japan, the PMDA, marketing authorization holders, healthcare professionals, and patients. The target adverse drug reactions of this research are potentially fatal ones, although the incidences of all the 3 types of adverse drug reactions are low. The reported genetic factors associated with their onsets vary among countries and regions. Therefore, collecting information on cases of these adverse drug reactions in Japanese is considered essential to obtain results useful for the prediction of their onsets.

For further development of “safety measures that predict and prevent adverse drug reactions” through the accumulation of knowledge, healthcare professionals are requested to provide information on cases of interstitial lung disease, rhabdomyolysis, or skin disorders (SJS and TEN) occurring after the use of pharmaceutical products to the PMDA or the MAHs of the suspected product. We would also appreciate your continuous cooperation on this research, especially contacting the NIHS on the onset of cases.[12)]

<References>

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2
Revision of Precautions for Zolpidem Tartrate, Zopiclone, Eszopiclone, Triazolam

1. Introduction

Zolpidem tartrate, zopiclone, eszopiclone, and triazolam are ultrashort-acting benzodiazepine receptor agonists. Zolpidem tartrate is a drug indicated for “insomnia (except for insomnia associated with schizophrenia and manic depressive),” zopiclone and triazolam for “insomnia, anesthetic premedication,” and eszopiclone for “insomnia.” The marketing of zolpidem tartrate was initiated in December 2000, zopiclone in June 1989, eszopiclone in April 2012, and triazolam in April 1983.

Regarding the package inserts for zolpidem tartrate, zopiclone, and triazolam, the Precautions for hypnotic agent-induced parasomnia, etc. were revised overall in the US. Considering the details of the revisions in the US and adverse drug reactions reported in Japan, the revision to alert the occurrence of parasomnia was made in the WARNING section, etc. in June 2007 to call further attention. Regarding eszopiclone, there has been an alert for parasomnia in the WARNING section, etc. since the time of approval in January 2012.

Recently, the MHLW considered it necessary to take further safety measures to patients with a history of parasomnia induced by these drugs for the treatment of insomnia, and the MHLW instructed the marketing authorization holders (MAHs) to revise the Precautions. The details are described in this section.

2. Background

The U.S. FDA has taken the following measures with regard to non-benzodiazepine drugs:

・To contraindicate their use in patients with a history of complex sleep behavior

・To alert patients to the risk of serious self/other-injuries, including death, due to complex sleep behaviors.

In response to the decision, the MAHs in Japan have also requested a consultation for contraindicating their use in patients with a history of parasomnia.

Regarding these consultations on revision, the necessity of revision of the electronic package inserts in Japan of ultrashort-acting benzodiazepine receptor agonists indicated for insomnia was discussed, considering overseas measures and adverse drug reactions reported in Japan.

3. Details of the review

As a result of investigating the published literature on the pharmacological mechanisms of parasomnia and cases involving parasomnia reported in Japan, the MHLW instructed the MAHs of zolpidem tartrate, zopiclone, and triazolam to revise the Precautions to contraindicate their use in “patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug” in July 2022 from the viewpoints shown below.

- In patients with a history of drug-induced parasomnia, the risk of recurrence cannot be excluded, and it is difficult to predict serious self/other-injuries or accidents that may occur secondary to adverse drug reactions. In addition, patients are considered to be unconscious and will not exercise intentional control when adverse drug reactions occur.
- There is no certainty in reducing the dose of the drugs or controlling adverse drug reactions when they occur. Discontinuation of the suspected drugs is currently considered the best way to avoid the recurrence of parasomnia.
- Cases involving parasomnia have been reported in Japan.
- It has been reported that parasomnia tends to occur due to their pharmacological properties such as half-life.

Regarding eszopiclone, considering that no cases involving parasomnia have been reported

in Japan, the MHLW instructed the MAHs of eszopiclone to add an alert in the “Careful Administration” section (“PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS” section when the Precautions are based on the New instructions) to consider discontinuation of administration to “patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug.”

4. Closing remark

Healthcare professionals are requested to pay sufficient attention to the following (1) to (4).

(1) When zolpidem tartrate, zopiclone, eszopiclone, or triazolam are prescribed or dispensed, please ask patients and their families or other caregivers whether the patients have experienced abnormal behavior as a symptom of parasomnia (e.g., whether or not other people pointed out any abnormal behavior, or there were any changes in the situations such as scattered things after awakening) after they used these drugs in the past.

Examples of abnormal behavior as a symptom of parasomnia
-Walk around indoors or outdoors　-Drive a car
-Make or eat a meal　-Make a phone call
-Behave violently or call out, etc.
*Most of the abnormal behaviors occur after the use of the drug without being fully awake, and those behaviors are not remembered the next day.

(2) If zolpidem tartrate, zopiclone, or triazolam are used, and abnormal behavior as a symptom of parasomnia is observed, please discontinue the use of the drug.
(3) If eszopiclone is used and abnormal behavior as a symptom of parasomnia is observed, please consider discontinuation of the use.
(4) Please explain to patients who use zolpidem tartrate, zopiclone, eszopiclone, or triazolam that abnormal behavior may lead to serious self/other-injuries, accidents, etc., as well as instruct the patients to contact their physicians, etc. immediately when parasomnia occurs.

Healthcare professionals are requested to understand the gist of the revision this time and to carefully check the electronic package inserts for a careful decision. Continued cooperation by healthcare professionals for proper use would be appreciated.

[References]
Pharmaceuticals and Medical Devices Safety Information No.238
https://www.pmda.go.jp/files/000153046.pdf
Revision of Precautions (PSEHB/PSD Notification No. 0720-1 dated July 20, 2022)
https://www.pmda.go.jp/files/000247531.pdf (in Japanese)
English translation by PMDA (July 20, 2022)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated July 20, 2022, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Durvalumab (genetical recombination)

Brand name (name of company)	Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)
Therapeutic category	Other antitumor agents
Indications	Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy Extensive stage small cell lung cancer

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Encephalitis
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period Cases involving encephalitis: 5 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 5 262 Japanese market launch: August 2018

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 60s	Small cell lung cancer (metastases to pancreas and adrenals)	1 500 mg (once every 3 weeks)	Autoimmune Encephalitis Medical history: Gastric ulcer Others: Ex-tobacco user	
				Day 1 of administration (Day of termination)	PS: 0, The treatment of durvalumab with carboplatin and etoposide was initiated (the last day of administration of durvalumab).
				19 days after termination (Date of onset)	The patient's fever persisted (grade 4 autoimmune encephalitis occurred).
				21 days after termination	The patient was hospitalized because pyrexia and general debility persisted despite the introduction of amoxicillin

					hydrate/clavulanate potassium (fever of unknown origin). Test values at the time of hospitalization: White blood cell (WBC) 3 250/mm^3; neutrophils 65.2%; hemoglobin 12.0 g/dL; platelet count $31.0\times10^4/mm^3$; C-reactive protein 5.19 mg/dL. Coagulation and hepatic/renal function were normal. The tumor marker values were lower than before the treatment (NSE 7.5 ng/mL and Pro-GRP 229 pg/mL). Urine/sputum/blood culture was negative. Assessment by chest and abdominal computed tomography (CT) image showed a partial response according to the Immune-Related Response Evaluation Criteria in solid tumor (irRECIST). However, no findings related to inflammation such as pneumonia, hepatitis, colitis, and pyelonephritis which cause pyrexia were shown. Vegetations were not observed on echocardiography, and doubts arose about the diagnosis of endocarditis. Transthoracic or transesophageal echocardiography was not performed. Endocrine testing such as T3, T4, TSH, ACTH, and cortisol was normal.
				Date unknown	After admission to the hospital, the patient was treated with levofloxacin hydrate, cefepime dihydrochloride hydrate, and itraconazole. However, pyrexia persisted.
				22 days after termination	Brain MRI was normal.
				26 days after termination	Headache also appeared.
				29 days after termination	The patient presented with disturbed orientation, memory impairment, and eating disorder. Somnolence developed, and she was not able to answer well to even easy questions. As a result, she was diagnosed with encephalitis. Headache and dizziness appeared, but the patient had no feeling of queasy or vomiting. No abnormality was found in the brain MRI with gadolinium contrast medium. Results of the cerebrospinal fluid tests Xanthochromia: Negative, Appearance: Clear, Cell count: 9 cells/mm^3, Protein: 83 mg/dL, Glucose: 68 mg/dL. No malignant cells were observed in cerebral spinal fluid (CSF). Spinal fluid culture was negative.
				30 days after termination	Electroencephalography (EEG) found diffuse slow wave (4 to 7 Hz). A modest increase in cell count and increase in the amount of protein were observed in CSF. The patient was diagnosed with encephalitis related to durvalumab. No seizure was observed. EEG: A slow wave was found in the entire brain. The patient was diagnosed with autoimmune encephalitis due to immune checkpoint inhibitors by these tests. Steroid pulse therapy (methylprednisolone (mPSL) 1g)) was conducted.
				31 days after termination	The patient was administered with mPSL at a dose of 1 g.
				32 days after termination	The patient was administered with mPSL at a dose of 1 g. All the symptoms improved immediately.

				33 days after termination	The steroid pulse therapy was dramatically effective. The patient was orally administered with 50 mg of prednisolone (PSL). Herpes encephalitis was suspected, and administration of acyclovir was started at 500 mg×3 times/day (until 39 days after termination).
				35 days after termination	The dose of PSL was reduced to 40 mg.
				38 days after termination	The dose of PSL was reduced to 35 mg.
				41 days after termination	The dose of PSL was reduced to 30 mg.
				44 days after termination	The dose of PSL was reduced to 25 mg. As the symptoms of autoimmune encephalitis resolved, the patient was discharged from the hospital.
				Date unknown	The dose of PSL was reduced to 20 mg.
				57 days after termination	By the co-administration with PSL 15 mg, the administration of carboplatin + etoposide could be resumed.
				Date unknown	After the 2nd course of carboplatin + etoposide, mild headache appeared; however, CSF tests improved (cell count 5 cells/mm^3, protein level 28 mg/dL). No malignant cells were observed, and the spinal fluid culture was negative. The polymerase chain reaction (PCR) result was negative for herpes simplex virus (HSV). As a result, the dose of steroid was increased to 25 mg, then, it was gradually reduced.

Laboratory test value

	1 day before administration	21 days after termination	37 days after termination
WBC(/mm^3)	6 510	3 250	11 960
CRP (mg/dL)	0.13	5.19	0.10

Suspected concomitant drugs: Carboplatin, etoposide

2 Avelumab (genetical recombination)

Brand name (name of company)	Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)
Therapeutic category	Other antitumor agents
Indications	Unresectable Merkel cell carcinoma Radically unresectable or metastatic renal cell carcinoma Maintenance treatment of radically unresectable urothelial carcinoma following chemotherapy

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Encephalitis
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period Cases involving encephalitis: 1 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 950 Japanese market launch: November 2017

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 60s	Bladder cancer (metastases to lymph nodes, increased creatinine)	10 mg/kg 3 courses at 2-week intervals	**Meningoencephalitis**	
				1 month before administration	Chemotherapy (gemcitabine + cisplatin for 4 cycles) was completed as prior treatment.
				Day 1 of administration	Administration of avelumab was initiated.
				28 days after administration (Day of termination)	The final dose of avelumab was administered (the 3rd dose).
				7 days after termination	The patient had symptoms of encephalitis. He visited the department of neurology. There was a finding of meningoencephalitis (grade 3). Cerebrospinal fluid lactic acid and adenosine deaminase (ADA) were noted. Administration of avelumab was terminated. The PCR test was also negative for mycobacterium tuberculosis, but antituberculosis drugs, etc. (aciclovir 500 mg/day and ceftriaxone sodium 4 g/day for 2 days starting on this day; rifampicin 450 mg/day, isoniazid 300 mg/day, pyrazinamide 1.5 g/day and pyridoxal 10 mg/day for approximately 1 month, ethambutol 1000 mg/day for 15 days and ampicillin 8 g/day for 5 days starting on the next day) were administered for the treatment of meningoencephalitis.
				Date unknown	Cerebrospinal fluid finding was resolving thereafter.
				19 days after termination	Urinary tract infection developed. Administration of levofloxacin was started the next day.

				21 days after termination	Ceftriaxone sodium 2 g/day for 6 days and 1 g/day for 1 day were administered for the treatment of meningoencephalitis.
				25 days after termination	The patient developed fever.
				27 days after termination	Urinary tract infection resolved.
				40 days after termination	Hepatic impairment developed. Steroid therapy (prednisolone 50 mg/day, 40 mg/day, 30 mg/day and 25 mg/day for 4 days, respectively, and 20 mg/day for 7 days, then reduced to 15 mg/day) was initiated 7 days later.
				50 days after termination	Hepatic impairment resolved.
				72 days after termination	Meningoencephalitis resolved.
	Concomitant drugs: Acetaminophen, diphenhydramine				

4
Revision of Precautions (No.334)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated July 8, July 20, 2022.

1 Vaccines
Recombinant COVID-19 (SARS-CoV-2) vaccine (Nuvaxovid Intramuscular Injection)

Brand name	Nuvaxovid Intramuscular Injection (Takeda Pharmaceutical Company Limited.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Cases of myocarditis, pericarditis have been reported. Vaccine recipients or their caregivers should be instructed in advance to seek medical attention immediately if they experience or notice any symptoms that could suggest myocarditis or pericarditis (such as chest pain, palpitation, oedema, dyspnoea, and tachypnoea).

2 Hypnotics and sedatives, antianxietics
Eszopiclone

Brand name	Lunesta Tablets 1 mg, 2 mg, 3 mg (Eisai Co., Ltd.), and the others
[Under Old instructions]	
Careful Administration (newly added)	Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug [Parasomnia leading to serious self/other-injuries, accidents, etc. may occur. Discontinuation of this drug should be considered.]
Adverse Reactions Clinically Significant Adverse Reactions	Psychiatric symptom, disturbed consciousness: Psychiatric symptoms or disturbed consciousness such as nightmare (abnormal dreams), depressed level of consciousness, excitement (agitation), confusion (confusional state), hallucination, aggression, delirium, and abnormal behavior may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued. Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.): Transient anterograde amnesia (failure to remember events during nocturnal awakening, etc.), twilight state, and parasomnia (somnambulism, etc.) may occur. Careful administration of this drug is required, such as starting with a low dose. With respect to zopiclone preparations, there have been reports of patients driving a car, eating, etc. without being fully awake and not remembering the events. If any abnormalities are observed, administration of this drug should be discontinued.
[Under New instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug Discontinuation of this drug should be considered. Parasomnia leading to serious self/other-injuries, accidents, etc. may occur.

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Psychiatric symptom, disturbed consciousness Nightmare (abnormal dreams), depressed level of consciousness, excitement (agitation), confusion (confusional state), hallucination, aggression, delirium, and abnormal behavior, etc. may occur. Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.) Careful administration of this drug is required, such as starting with a low dose. There have been reports of patients driving, eating, etc. without being fully awake and not remembering the events.

3 Hypnotics and sedatives, antianxietics

Zopiclone

Brand name	Amoban Tablet 7.5, 10 (Sanofi K.K.), and the others
[Under Old instructions]	
Contraindications	Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug [Parasomnia leading to serious self/other-injuries, accidents, etc. may occur.]
Adverse Reactions	Psychiatric symptom, disturbed consciousness:
Clinically Significant Adverse Reactions	Psychiatric symptoms or disturbed consciousness such as hallucination, delirium, confusion, nightmare, irritability, aggression, and abnormal behavior may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued. Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.): Transient anterograde amnesia (failure to remember events during nocturnal awakening, etc.), twilight state, and parasomnia (somnambulism, etc.) may occur. Careful administration of this drug is required, such as starting with a low dose. There have been reports of patients driving, eating, etc. without being fully awake and not remembering the events. If any abnormalities are observed, administration of this drug should be discontinued.
[Under New instructions]	
2. CONTRAINDICATIONS (newly added)	Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug [Parasomnia leading to serious self/other-injuries, accidents, etc. may occur.]
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Psychiatric symptom, disturbed consciousness Hallucination, delirium, confusion, nightmare, irritability, aggression, abnormal behavior, etc. may occur. Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.) Careful administration of this drug is required, such as starting with a low dose. There have been reports of patients driving, eating, etc. without being fully awake and not remembering the events.

4 Hypnotics and sedatives, antianxietics

Zolpidem tartrate

Brand name	Myslee Tablets 5 mg, 10 mg (Astellas Pharma Inc.), and the others
[Under Old instructions]	
Contraindications	Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug [Parasomnia leading to serious self/other-injuries, accidents, etc. may occur.]
Adverse Reactions	Psychiatric symptom, disturbed consciousness:

Clinically Significant Adverse Reactions	Psychiatric symptoms or disturbed consciousness such as delirium, confusion, hallucination, excitement, disinhibition, and depressed level of consciousness may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued. Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.): Transient anterograde amnesia (failure to remember events before falling asleep or during nocturnal awakening after taking this drug), twilight state, and parasomnia (somnambulism, etc.) may occur. Patients should be put to bed immediately after taking this drug, and caution should be exercised to not wake them up while asleep. There have been reports of patients driving, eating, etc. without being fully awake and not remembering the events. In addition, there have also been reports of serious self/other-injuries, accidents, etc. including death. If any abnormalities are observed, administration of this drug should be discontinued.
[Under New instructions]	
2. CONTRAINDICATIONS (newly added)	Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug [Parasomnia leading to serious self/other-injuries, accidents, etc. may occur.]
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Psychiatric symptom, disturbed consciousness Psychiatric symptoms or disturbed consciousness such as delirium, confusion, hallucination, excitement, disinhibition, and depressed level of consciousness may occur. Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.) Patients should be put to bed immediately after taking this drug, and caution should be exercised to not wake them up while asleep. There have been reports of patients driving, eating, etc. without being fully awake and not remembering the events. In addition, there have also been reports of serious self/other-injuries, accidents, etc. including death.

5 Hypnotics and sedatives, antianxietics

Triazolam

Brand name	Halcion Tablets 0.125 mg, 0.25 mg (Pfizer Japan Inc.), and the others
[Under Old instructions]	
Contraindications	Patients receiving the following drugs: Itraconazole, posaconazole, fluconazole, fosfluconazole, voriconazole, miconazole, HIV protease inhibitors (indinavir, ritonavir, etc.), efavirenz, telaprevir
(newly added)	Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug [Parasomnia leading to serious self/other-injuries, accidents, etc. may occur.]

Interactions Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Itraconazole, posaconazole, fluconazole, fosfluconazole, voriconazole, miconazole, HIV protease inhibitors (indinavir, ritonavir,	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.

	etc.), efavirenz, telaprevir		

Adverse Reactions Clinically Significant Adverse Reactions

Psychiatric symptom:
Psychiatric symptoms such as stimulated excitement, confusion, aggression, hallucination, delusion, and agitation may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued.

Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.):
Transient anterograde amnesia (failure to remember events during nocturnal awakening), twilight state, and parasomnia (somnambulism, etc.) may occur. Careful administration of this drug is required, such as starting with a low dose. There have been reports of patients driving, eating, etc. without being fully awake and not remembering the events. If any abnormalities are observed, administration of this drug should be discontinued.

[Under New instructions]

2. CONTRAINDICATIONS

Patients receiving the following drugs: Itraconazole, posaconazole, fluconazole, fosfluconazole, voriconazole, miconazole, HIV protease inhibitors (indinavir, ritonavir, etc.), efavirenz, telaprevir

(newly added)

Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug [Parasomnia leading to serious self/other-injuries, accidents, etc. may occur.]

10. INTERACTIONS
10.1 Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Itraconazole, posaconazole, fluconazole, fosfluconazole, voriconazole, miconazole, HIV protease inhibitors (indinavir, ritonavir , etc.), efavirenz, telaprevir	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.

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions

Psychiatric symptom
Psychiatric symptoms such as stimulated excitement, confusion, aggression, hallucination, delusion, and agitation may occur.

Transient anterograde amnesia, twilight state, parasomnia (somnambulism, etc.)
Careful administration of this drug is required, such as starting with a low dose. There have been reports of patients driving, eating, etc. without being fully awake and not remembering the events.

6 Other antitumor agents
[1] Avelumab (genetical recombination)
[2] Durvalumab (genetical recombination)

Brand name

[1] Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)
[2] Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)

[Under New instructions]

11. ADVERSE REACTIONS

Encephalitis

11.1 Clinically Significant Adverse Reactions (newly added)

7 Other antitumor agents

Bortezomib

Brand name Velcade Injection 3 mg (Janssen Pharmaceutical K.K.), and the others

[Under Old instructions]

Adverse Reactions Clinically Significant Adverse Reactions Guillain-Barré syndrome, demyelinating polyneuropathy: Guillain-Barré syndrome, demyelinating polyneuropathy may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

[Under New instructions]

11. ADVERSE REACTIONS

11.1 Clinically Significant Adverse Reactions (newly added) Guillain-Barré syndrome, demyelinating polyneuropathy

8 Antibiotic preparations acting mainly on mold

Posaconazole

Brand name Noxafil Tablets 100 mg, Noxafil for Intravenous Infusion 300 mg (MSD K.K.)

[Under New instructions]

2. CONTRAINDICATIONS Patients receiving ergotamine tartrate/anhydrous caffeine/ isopropylantipyrine, dihydroergotamine, methylergometrine, ergometrine, simvastatin, atorvastatin, pimozide, quinidine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], suvorexant, lurasidone hydrochloride, blonanserin, or triazolam

10. INTERACTIONS
10.1 Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Triazolam	The effects of triazolam may be enhanced, and the duration of effects may be prolonged.	The blood concentration of triazolam is expected to rise due to inhibition of CYP3A4 by co-administration with posaconazole.

9 X-ray contrast agents

[1] Iopamidol
[2] Iohexol

Brand name [1] Iopamiron injection 150, and the others, Iopamiron injection 300, and the others, Iopamiron injection 370, and the others, Iopamiron injection 300 syringes, and the others, Iopamiron injection 370 syringes, and the others (Bayer Yakuhin Ltd.), and the others
[2] Omnipaque 140 Injection 50 mL, 220 mL, and the others, Omnipaque 240 Injection 20 mL, 50 mL, 100 mL, and the others, Omnipaque 300 Injection 20 mL, 50 mL, 100 mL, 150 mL, and the

	others, Omnipaque 350 Injection 20 mL, 50 mL, 100 mL, and the others, Omnipaque 180 Injection 10 mL, and the others, Omnipaque 240 Injection 10 mL, and the others, Omnipaque 300 Injection 10 mL, and the others, Omnipaque 240 Injection Syringe 100 mL, and the others, Omnipaque 300 Injection Syringe 50 mL, 80 mL, 100 mL, 110 mL, 125 mL, 150 mL, and the others, Omnipaque 350 Injection Syringe 45 mL, 70 mL, 100 mL, and the others (GE Healthcare Pharma Co., Ltd.), and the others
[Under Old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Acute coronary syndrome accompanying allergic reaction: Acute coronary syndrome accompanying allergic reaction may occur. Patients should be carefully monitored, and appropriate measures should be taken as necessary.
[Under New instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions <Common to all indications> (newly added)	Acute coronary syndrome accompanying allergic reaction

10 X-ray contrast agents

Iomeprol

Brand name	Iomeron 300 injection 20 mL, 50 mL, 100 mL, Iomeron 350 injection 20 mL, 50 mL, 100 mL, Iomeron 400 injection 50 mL, 100 mL, Iomeron 300 syringe 50 mL, 75 mL, 100 mL, Iomeron 350 syringe 50 mL, 75 mL, 100 mL, 135 mL (Bracco-Eisai Co.,Ltd.)
[Under New instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions <Common to all indications> (newly added)	Acute coronary syndrome accompanying allergic reaction

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 June 30, 2022)
◎: Products for which EPPV was initiated after June 1, 2022

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	[1] [2] Cabotegravir, [3] Cabotegravir sodium, [4] [5] Rilpivirine / [1] Vocabria Aqueous Suspension for IM Injection 400 mg, [2] Vocabria Aqueous Suspension for IM Injection 600 mg, [3] Vocabria Tablets 30 mg, [4] Rekambys Aqueous Suspension for IM Injection 600 mg, [5] Rekambys Aqueous Suspension for IM Injection 900 mg	[1] [2] [3] ViiV Healthcare K.K. [1] [2] Janssen Pharmaceutical K.K.	June 27, 2022
◎	Emicizumab (genetical recombination) *1 / Hemlibra for Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	June 20, 2022
◎	Daptomycin / Cubicin IV 350 mg	MSD K.K.	June 20, 2022
◎	Brolucizumab (genetical recombination) *2 / Beovu kit for intravitreal injection 120 mg/mL	Novartis Pharma K.K.	June 20, 2022
◎	Rituximab (genetical recombination) *3 / Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	June 20, 2022
◎	Lasmiditan succinate / Reyvow tablets 50 mg, 100 mg	Eli Lilly Japan K.K.	June 8, 2022
◎	Avacopan / Tavneos Capsules 10 mg	Kissei Pharmaceutical Co., Ltd.	June 7, 2022
◎	Olipudase alfa (genetical recombination) / Xenpozyme for I.V. Infusion 20 mg	Sanofi K.K.	June 3, 2022
◎	Finerenone / Kerendia tablets 10 mg, 20 mg	Bayer Yakuhin Ltd.	June 2, 2022
◎	Valbenazine tosilate / Dysval Capsules 40 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2022
◎	Difamilast / Moizerto ointment 0.3%, 1%	Otsuka Pharmaceutical Co., Ltd.	June 1, 2022
	Carotegrast methyl	EA Pharma Co., Ltd.	May 30,

Nonproprietary name Brand name		Name of the MAH	Date of EPPV initiate
	Carogra Tablets 120 mg		2022
	Fosnetupitant chloride hydrochloride Arokaris I.V. infusion 235 mg	TAIHO Pharmaceutical Co., Ltd.	May 30, 2022
	Tolvaptan sodium phosphate Samtasu for I.V. infusion 8 mg, 16 mg	Otsuka Pharmaceutical Co., Ltd.	May 30, 2022
	Lanadelumab (genetical recombination) Takhzyro subcutaneous injection 300 mg syringes	Takeda Pharmaceutical Company Limited.	May 30, 2022
	Metronidazole[*4] Rozex Gel 0.75%	Maruho Co., Ltd.	May 26, 2022
	Asciminib hydrochloride Scemblix tablets 20 mg, 40 mg	Novartis Pharma K.K.	May 25, 2022
	Faricimab (genetical recombination) Vabysmo solution for Intravitreal Injection 120 mg/mL	Chugai Pharmaceutical Co., Ltd.	May 25, 2022
	Andexanet alfa (genetical recombination) Ondexxya for Intravenous Injection 200 mg	Alexion Pharma Godo Kaisha	May 25, 2022
	Glycopyrronium tosilate hydrate Rapifort Wipes 2.5%	Maruho Co., Ltd.	May 23, 2022
	Recombinant COVID-19 (SARS-CoV-2) vaccine Nuvaxovid Intramuscular Injection	Takeda Pharmaceutical Company Limited.	May 10, 2022
	Efgartigimod Alfa (genetical recombination) Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	May 9, 2022
	Somatrogon (genetical recombination) Ngenla Inj. 24 mg Pens, 60 mg Pens	Pfizer Japan Inc.	April 27, 2022
	Gefapixant citrate Lyfnua Tablets 45 mg	MSD K.K.	April 21, 2022
	Sotorasib Lumakras Tablets 120 mg	Amgen K.K.	April 20, 2022
	Clazosentan sodium Pivlaz I.V. Infusion liquid 150 mg	Idorsia Pharmaceuticals Japan Ltd.	April 20, 2022
	Bimekizumab (genetical recombination) Bimzelx Syringe for S.C injection 160 mg, Bimzelx Autoinjector for S.C injection 160 mg	UCB Japan Co. Ltd.	April 20, 2022
	Filgotinib maleate[*5] Jyseleca Tablets 100 mg, 200 mg	Gilead Sciences K.K.	March 28, 2022
	Selpercatinib[*6] Retevmo Capsules 40 mg, 80 mg	Eli Lilly Japan K.K.	February 25, 2022
	Pegfilgrastim (genetical recombination)[*7] G-Lasta Subcutaneous Injection 3.6 mg	Kyowa Kirin Co., Ltd.	February 25, 2022
	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 5 to 11 years old	Pfizer Japan Inc.	February 22, 2022
	Nirmatrelvir/ritonavir	Pfizer Japan Inc.	February 14,

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Paxlovid Pack		2022
	Tocilizumab (genetical recombination) *8 Actemra for Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	January 21, 2022
	3-Iodobenzylguanidine (^{131}I) Raiatt MIBG-I 131 Injection	FUJIFILM Toyama Chemical Co., Ltd.	January 18, 2022

*1 Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with acquired hemophilia A

*2 Diabetic macular oedema

*3 Prevention of recurrence of neuromyelitis optica spectrum disorder (including neuromyelitis optica)

*4 Rosacea

*5 Treatment and maintenance therapy for moderately to severely active ulcerative colitis (limited to patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapies)

*6 Radically unresectable RET fusion-positive thyroid cancer, radically unresectable RET-mutant medullary thyroid cancer

*7 Mobilization of haematopoietic stem cells into peripheral blood for allogeneic blood stem cell transplantation

*8 SARS-CoV-2 pneumonia (limited to patients requiring oxygen intervention)