Pharmaceuticals and Medical Devices Safety Information

No. 404 September 2023

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

Available information is listed here

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

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

Register here

Published by
Ministry of Health, Labour and Welfare

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This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 404 September 2023

Ministry of Health, Labour and Welfare
Pharmaceutical Safety 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 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 only available in Japanese.)

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

Abbreviations

ADR	Adverse Drug Reaction
EPPV	Early Post-marketing Phase Vigilance
GERD	Gastrooesophageal Reflux Disease
HOT	Home Oxygen Therapy
JIMGA	Japan Industrial and Medical Gases Association
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
NDB	National Database of Health Insurance Claims and Specific Health Checkups of Japan
PFSB	Pharmaceuticals and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SD	Safety Division

1
Fire Accidents During Home Oxygen Therapy

1. Introduction

Home oxygen therapy (HOT) is utilized in a wide variety of ways, including home oxygenation therapy for patients with severe chronic respiratory failure due to various causes, patients with pulmonary hypertension, or patients with chronic heart failure who are discharged from hospital in stable condition or awaiting surgery, or patients with severe cluster headaches who all inhale oxygen on their own at home; oxygen therapy given at home to patients with cyanotic congenital heart disease during an attack. According to the 8th NDB* Open Data, approximately 1.68 million cases of HOT instruction and management fees and approximately 3.97 million cases of oxygen suppliers necessary for oxygen administration at home are assessed annually[1].

* National Database of Health Insurance Claims and Specific Health Checkups of Japan.

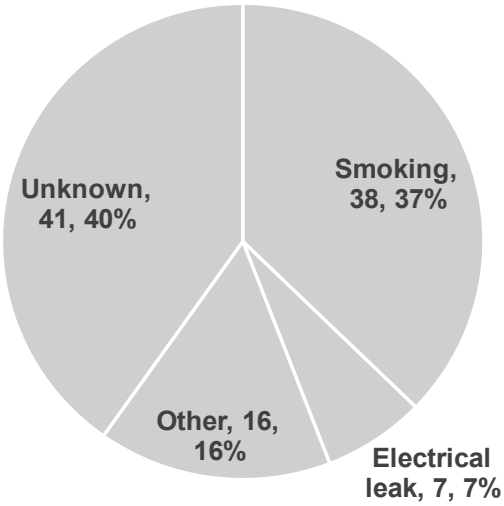
While it is widely used in this way, 102 cases of serious injury or death due to fire accidents during HOT were reported in Japan in the 20-year period from 2003 to May 2023. Among the causes of the fires in these 102 cases including those based on speculation, there are many cases where a causal relationship with the sources of fire, such as cigarettes and gas stoves, cannot be ruled out. Of note, there have been no cases of fires directly caused by oxygen suppliers themselves.

Cases of serious health damage (Counted by Medical Gases Division, Japan Industrial and Medical Gases Association [as of the end of May 2023])

Classfication by Causes of Fire Accidents

＊Unknown includes incidents in which the location where the fire started is unknown.

＊Oxygen suppliers themselves have never caused fire.



＊Other includes stoves, incense sticks, kitchen, candles, etc.

（Classification of all 102 fire accidents by cause）

Excerpted from https://www.jimga.or.jp/files/page/hot/oyakudachi/HHN_jiko.pdf

[1] The 8th NDB Open Data (according to C151 HOT instruction and management fees, C157 oxygen cylinder premium, C158 oxygen concentrator premium, and C159 liquid oxygen unit premium)

Oxygen is a combustion-enhancing gas. For this reason, it is cautioned in the package inserts and the user's manual for oxygen suppliers used for HOT that any sources of fire should not be placed within 2 meters of an oxygen supplier. In addition, various precautions have been issued including leaflets and videos for handling of fire during HOT, which have been prepared and distributed by the Japan Industrial and Medical Gases Association (hereinafter referred to as “JIMGA”). Furthermore, it has been requested that medical institutions be informed and instructed through the PMDA Medical Safety Information No. 4 “Precautions Against Smoking and Use of Fire in Long-term Oxygen Therapy (LTOT)” issued in June 2008 and the “Handling of Fire During Home Oxygen Therapy (Precautions and Request for Information Dissemination)” issued by the MHLW in January 2010.

However, fatal fire accidents caused by mishandling of fire have still occurred repeatedly during the use of oxygen suppliers. Accordingly, healthcare professionals, patients, and their caregivers are advised again to take precautions.

2. Items to be explained to patients under HOT and their caregivers

Please explain to patients undergoing HOT and their caregivers that following precautions against handling of fire should be taken with sufficient understanding when using the oxygen suppliers.

1) While using an oxygen supplier, sources of fire including cigarettes near an oxygen supplier may cause items such as cannulas and clothing to ignite, resulting in severe burn injuries or home fires.
2) Smoking is strictly prohibited while using an oxygen supplier.
3) Any sources of fire (cigarettes, heaters, gas stoves, candles, incense sticks, matches, lighters, etc.) should not be placed within 2 meters of an oxygen supplier when it is in use.
4) Do not place sources of fire within 5 meters from the liquid oxygen unit when transferring and filling liquid oxygen from an installed device (parent container) to a portable device (child container).
5) Oxygen will not cause fire on items such as cannulas and clothing or cause home fires when properly used in accordance with the package insert with appropriate precautions against fire. Patients are advised to inhale oxygen as directed by a physician without undue fear.

According to the JIMGA survey, it is reported that, among the cases of fire accidents, the duration of using oxygen suppliers is mostly less than 6 months or over 4 years from the start of use, which is when patients become used to using the device. For this reason, please provide detailed explanations, especially in the initial period of introduction of HOT, and continue to provide explanations after the introduction.

3. Others

Among oxygen suppliers, oxygen concentrators are required to be marketed in accordance with “JIS T 7209: 2018 Medical electrical equipment - Particular requirements for basic safety and essential performance of oxygen concentrator equipment” from February 1, 2021. This standard specifies additional requirements regarding fire prevention and the items related to reduction of the risk of a fire by using accessories. It mandates that oxygen outlet connector be equipped with a means to prevent flames from passing through the relevant connector to the inside[2]. However, this standard is intended to prevent flames from reaching the inside of a device and does not completely prevent a fire. Therefore, healthcare professionals are requested to explain what is described in 2. above to patients undergoing HOT and their caregivers, and to continue to cooperate for the proper use of oxygen suppliers.

[References]
Please refer to the web page of the MHLW for information on handling of fire during HOT.

[2] JIS T 7209: 2018 Medical electrical equipment - Particular requirements for basic safety and essential performance of oxygen concentrator equipment (from 201.11.2.101 and 201.102.3)

Precautions Regarding Handling of Fire During Home Oxygen Therapy
https://www.mhlw.go.jp/stf/houdou/2r98520000003m15_1.html (only in Japanese)

The above webpage also contains the following links.

- Medical Safety Information No. 4 of the Pharmaceuticals and Medical Devices Agency "Precautions Against Smoking and Use of Fire in Long-term Oxygen Therapy (LTOT)"
  https://www.pmda.go.jp/files/000144705.pdf (in Japanese)
  https://www.pmda.go.jp/files/000153519.pdf (in English)

- Joint Notification by the Directors of General Affairs Division and Guidance of Medical Service Division, Health Policy Bureau, and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated January 15, 2010, "Handling of Fire During Home Oxygen Therapy (Precautions and Request for Information Dissemination)"
  https://www.mhlw.go.jp/content/11125000/2r98520000003m9w.pdf (only in Japanese)

- Website of the Japan Industrial and Medical Gases Association
  https://www.jimga.or.jp/hot/ (only in Japanese)
  *Videos of "Precautions for handling of portable oxygen cylinder" and "Precautions Regarding Handling of Fire during HOT" are also available.

2
Amendment of the Guidance for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications

1. Introduction

To prevent the occurrence of hazards in public health and hygiene associated with the use of drugs, medical devices, and regenerative medical products (hereinafter referred to as “drugs, etc.”), it is important that post-marketing reports of adverse reactions/malfunctions, etc. be collected and reviewed in order to promptly provide feedback about necessary information to medical institutions.

Under Article 68-9, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960), when marketing authorization holders (MAHs) of drugs, etc. learn of the occurrence or spread of hazards in health and hygiene suspected to be caused by using the drugs, etc. that they have manufactured and marketed, they must take necessary measures including recall, discontinuing selling, and information provision to prevent such hazards. In addition to the notifications of Revisions of PRECAUTIONS, information has been provided to healthcare professionals through Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter), which provide emergent and important safety information about drugs, etc., or Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter), which provide information that does not require emergent communications but should be promptly provided to alert them.

The methods, etc. for providing information to healthcare professionals through Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications have been described in “The Guidance for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications” (PFSB/SD Notification No. 1031-1 by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated October 31, 2014, hereinafter referred to as the “previous notification”), which was amended by the PSEHB/PSD Notification No.0515-1 issued by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW on May 15, 2020. Given the increasing need to obtain information electronically at medical institutions, etc. in recent years, the operation was partially amended. This section will introduce the details of the amendment.

2. Background

Regarding the information provision of Dear Healthcare Professional Letters of Emergent Safety Communications and Dear Healthcare Professional Letters of Rapid Safety Communications to the medical institutions, the former has been directly provided in principle. The latter has been provided via fax, e-mail, direct mail, etc. in addition to direct distribution.

In recent years, the method of information provision/collection of drugs, etc. has been shifting from face-to-face visits to non-face-to-face visits/contactless visits due to the COVID-19 epidemics. Taking this situation into consideration, the previous notification was set to be partially amended to improve the speed and comprehensiveness of information provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications.

3. Contents of amendment

The main contents of the amendment are as follows:

•For Dear Healthcare Professional Letters of Emergent Safety Communications, in addition

to the conventional direct distribution, it was made possible to provide information through electronic means such as fax, e-mail, and direct mail as with information provision of Dear Healthcare Professional Letters of Rapid Safety Communications to improve the speed and comprehensiveness of the information.

- It was decided to provide more detailed information via face-to-face visits, online interviews, telephone calls, etc. as necessary for Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications and revised information on precautions, etc.

In addition, "Questions and Answers (Qs & As) on the Guidance for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications" and "Amendment of Q&A on Post-marketing Reports on Adverse Drug Reactions, etc. and Clinical Trial Reports on Adverse Drug Reactions, etc. Conforming to Implementation Guide of E2B (R3)" were amended to reflect this partial amendment.

These amendments came into effect on August 10, 2023.

4. Request for healthcare professionals

When especially important safety information such as Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications is obtained, healthcare professionals are requested to understand the information and share it promptly among healthcare professional staff members in their institutions.

Information related to revision of package inserts including Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications is promptly distributed to PMDA medi-navi subscribers via e-mail. Although the number of PMDA medi-navi subscribers at medical institutions, pharmacies, etc. has been increasing, there are still some medical institutions, etc. with no subscribers. Healthcare professionals are encouraged to register with PMDA medi-navi to obtain the latest safety information promptly and properly and to take necessary safety measures in a timely manner.

[References]

- Partial Amendment of the Guidance for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications
https://www.mhlw.go.jp/content/11120000/001133360.pdf (only in Japanese)

- Questions and Answers (Qs & As) on The Guidance for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications
https://www.mhlw.go.jp/content/11120000/001133389.pdf (only in Japanese)

- Amendment of Q&A on Post-marketing Reports on Adverse Drug Reactions, etc. and Clinical Trial Reports on Adverse Drug Reactions, etc. Conforming to Implementation Guide of E2B (R3)
https://www.mhlw.go.jp/content/11120000/001133391.pdf (only in Japanese)

- Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter) and Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter)
https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/esc-rsc/0001.html
(in Japanese)
https://www.pmda.go.jp/english/safety/info-services/drugs/esc-rsc/0001.html (in English)

3

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated August 29, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Dabigatran etexilate methanesulfonate

Brand name (name of company)	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic category	Anticoagulants
Indications	Reduction in the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	If this drug is retained in the esophagus, oesophageal ulcer or oesophagitis may occur. Patients should be instructed as follows: •This drug should be taken with a sufficient amount (e.g., a full glass) of water to facilitate delivery to the stomach. •If symptoms of oesophageal disease (difficult swallowing or odynophagia, retrosternal pain, severe and persistent heartburn, etc.) occur, the attending physician should be consulted.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Oesophageal ulcer, oesophagitis
14. PRECAUTIONS CONCERNING USE	(deleted)
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports <Cases involving oesophageal ulcer> 14 cases, including 1 case which fell under the contraindications. (No patient mortalities) <Cases involving oesophagitis> 11 cases, including 1 case which fell under the contraindications. (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 103 000 Japanese market launch: March 2011

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Male 80s	Atrial fibrillation (cardiac failure, hypertension, interstitial lung disease, anaemia, respiratory failure, mitral valve incompetence, cognitive disorder)	220 mg for 65 days	**Oesophageal ulcer** Date unknown: The patient was admitted to the hospital due to aggravated cardiac failure. He continued to receive treatment, but cardiac failure, urinary tract infection, and pneumonia repeated. 5 days before administration: Administration of apixaban was terminated. Day 1 of administration: Administration of dabigatran etexilate methanesulfonate (110 mg, 2 times/day) was initiated. Since the patient had decreased cognitive function, it could not be deemed that he took the drug properly and had enough water and food. Date unknown: Oesophageal hiatal hernia occurred. Day 65 of administration (day of discontinuation): 14:22 Haematemesis occurred after the patient had lunch in the afternoon. 16:00 An endoscopy was performed. Esophagus: Gastrooesophageal reflux disease (GERD): The patient had oesophageal hiatal hernia. Erosions were formed at the lower end of the esophagus. Adhesion of drug-like tablet was noted. Possible drug-induced oesophageal ulcer was noted. Stomach: Cardiac varices/gastric body/antrum/pylorus section: No abnormalities Duodenum: Duodenal bulb/descending limb: No abnormalities Papilla of Vater: Not identified Biopsy: No biopsy was performed. Diagnosis: Oesophageal hiatal hernia and drug-induced oesophageal ulcer were suspected. At the time of onset of adverse reactions, the patient took dabigatran etexilate methanesulfonate in the supine position. Administration of dabigatran etexilate methanesulfonate was discontinued. Red blood cells in mannitol-adenine-phosphate medium (400 ml × 2 bottles) were transfused. Lansoprazole OD tablets (15 mg, 2 tablets/day, once a day, after dinner) and sodium alginate oral solution 5% (90 mL/day, 3 times a day, before each meal) were prescribed. 2 days after discontinuation: 09:00 An endoscopy was performed again. Esophagus: GERD: Equivalent to grade B, and it was diagnosed as drug-induced oesophageal ulcer; bleeding was

				arrested; a white coat was formed. Stomach: Cardiac varices/gastric body/antrum: No abnormalities Pylorus section: Redness was noted in the greater curvature. Duodenum: Duodenal bulb/descending limb: No abnormalities Papilla of Vater: Not identified Biopsy: No biopsy was performed. Diagnosis: Oesophageal ulcer and haemostasis were confirmed. Oesophageal hiatal hernia Drug-induced oesophageal ulcer: Recovered.
			Date unknown	The outcome of oesophageal hiatal hernia was unknown.
			Date unknown	Aggravation of chronic cardiac failure, renal failure, and atrial fibrillation occurred.
			138 days after discontinuation	The patient died. Cause of death: Aggravation of chronic cardiac failure, renal failure, atrial fibrillation

Laboratory test value

	Day 53 of administration	Day 65 of administration (day of discontinuation)	1 day after discontinuation	48 days after discontinuation	62 days after discontinuation
BUN (mg/dL)	14.9	19.4	18.9	18.8	12.3
Cre (mg/dL)	1.84	1.87	1.73	1.49	1.14
RBC(× 10 000 cells/microL)	262	258	300	294	219
Hb (g/dL)	7.1	7.1	8.6	8.8	6.4
Ht (%)	21.2	20.6	24.2	26.1	19.4
MCV (fL)	81	80	81	89	89
MCH (pg)	27.1	27.5	28.7	29.9	29.2
MCHC (%)	33.5	34.5	35.5	33.7	33
APTT (sec)	-	-	91	-	-
PT (sec)	-	25.6	23.1	-	-
INR	-	2.31	2.07	-	-

Day 65 of administration (day of discontinuation)

PT control: 11.3 PT activity: 27.0

PT control: 11.3 PT activity: 30.4

Concomitant drugs: Magnesium oxide, spironolactone, nicorandil, isosorbide dinitrate, theophylline, telmisartan, rebamipide, furosemide, risperidone, eszopiclone

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Male 80s	Paroxysmal atrial fibrillation (chronic cardiac failure, hypertension, osteoporosis)	220 mg Approximately 11 and a half years	**Oesophagitis** Day 1 of administration: The patient was transported by ambulance due to loss of consciousness, black vomit, and black stools, and was hospitalized. Approximately 11 and a half years after administration (day of discontinuation): An upper gastrointestinal tract endoscopy was performed, and inflammation was found in the area between the middle and lower esophagus region. He was followed up with fasting, starting solution, and omeprazole sodium. Administration of dabigatran etexilate methanesulfonate was discontinued. 3 days after discontinuation: Since blood sampling revealed no exacerbation of anaemia, the patient resumed eating. 8 days after discontinuation: Holter monitoring was performed. Since no atrial fibrillation was found, discontinuation of dabigatran etexilate methanesulfonate was continued. 12 days after discontinuation: Dabigatran etexilate methanesulfonate-induced oesophagitis: Recovered. The patient was discharged from the hospital.

Laboratory test value

	Approximately 11 and a half years after administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	8 days after discontinuation
Hb (g/dL)	9.6	8.2	8.8	9.3
MCV (fL)	85.8	86.1	87.3	88.1
BUN (mg/dL)	30.7	21.8	11.3	16.7
CRE (mg/dL)	1.19	1.19	1.08	1.19

Concomitant drugs: Cibenzoline succinate, carvedilol, azilsartan, famotidine, mirabegron, suvorexant, alfacalcidol, octotiamine/riboflavin/pyridoxine hydrochloride/cyanocobalamin, rebamipide, calcium L-aspartate hydrate

2 Rivastigmine

Brand name (name of company)	[1] Exelon Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg (Novartis Pharma K.K.) [2] Rivastach Patches 4.5 mg, 9 mg, 13.5 mg, 18 mg (Ono Pharmaceutical Co., Ltd.), and the others
Therapeutic category	Other agents affecting central nervous system
Indications	Suppression of progression of symptoms of dementia in mild and moderate Alzheimer's dementia

PRECAUTIONS (Revised language is underlined.)

[Under old instructions]

Important Precautions	Bradycardia, atrioventricular block, <u>prolonged QT, torsade de pointes,</u> etc. may occur following administration of this drug. In particular, patients with heart disease (e.g., myocardial infarction, cardiac valvulopathy, cardiomyopathy), patients with electrolyte abnormalities (e.g., hypokalaemia), <u>patients with prolonged QT or a history/family history of the disease,</u> etc. should be carefully monitored to prevent them from developing serious arrhythmia.
Adverse Reactions Clinically Significant Adverse Reactions	Angina pectoris, myocardial infarction, bradycardia, atrioventricular block, sick sinus syndrome<u>, prolonged QT</u>: Angina pectoris, myocardial infarction, bradycardia, atrioventricular block, sick sinus syndrome<u>, and prolonged QT</u> may occur. In such cases, administration should be discontinued immediately and appropriate measures should be taken.

[Under new instructions]

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.**	Patients with heart disease including myocardial infarction, cardiac valvulopathy, and cardiomyopathy, electrolyte abnormalities (e.g., hypokalaemia), etc.<u>, and patients with prolonged QT or a history/family history of the disease</u> Bradycardia, atrioventricular block, <u>prolonged QT, torsade de pointes,</u> etc. may occur. Patients should be carefully monitored to prevent them from developing serious arrhythmia.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Angina pectoris, myocardial infarction, bradycardia, atrioventricular block, sick sinus syndrome<u>, prolonged QT</u>
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving electrocardiogram prolonged QT reported in Japan: 5 (No patient mortalities) Cases involving electrocardiogram prolonged QT reported overseas: 3 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] approximately 16 792 [2] approximately 62 000 Japanese market launch: [1] [2] July 2011

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
administration
duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td>1</td><td>Female
80s</td><td>Alzheimer's type dementia (hypertension, dyslipidemia, Meniere's disease, cervicobrachial syndrome, memory impairment, insomnia, gastrooesophageal reflux disease, cerebral infarction, hypercholesterolaemia, dizziness)</td><td>4.5 mg
for 24 days

9 mg
for 28 days

13.5 mg
for 28 days

18 mg
for 27 days</td><td colspan="2">Electrocardiogram prolonged QT
Approximately 5 and a half months before administration: The patient fell at a department store by herself. Surgery was performed at Hospital A for right femoral neck fracture. After hospitalization for approximately 1 month, she was transferred to the rehabilitation department of Hospital B. During the hospitalization, cognitive symptoms, especially short-term memory impairment, appeared and gradually worsened. The score for the revised Hasegawa's dementia scale was around 15. After hospital discharge, she was diagnosed with Alzheimer's type dementia.
Day 1 of administration: Administration of rivastigmine was initiated at a dose of 4.5 mg.
Day 25 of administration: The dose of rivastigmine was increased to 9 mg.
Day 53 of administration: The dose of rivastigmine was increased to 13.5 mg.
Day 81 of administration: The dose of rivastigmine was increased to 18 mg, and a patch containing 18 mg of rivastigmine was applied to the patient’s body.
Day 106 of administration: The patient complained of chills, nausea, and inappetence.
Day 107 of administration (day of discontinuation): The patient visited the hospital complaining of yawning upon waking, dizziness, heaviness of head, and difficulty in walking from the morning. An ECG and biochemical tests were performed as a precautionary measure. The ECG showed QTc: 0.521 and HR: 54. Blood pressure was 152/68 mmHg (normally 120/60 mmHg). 500 mL of fluid infusion and 20 mL of sodium bicarbonate injection were administered, and application of rivastigmine was discontinued. She rested at home thereafter. A letter of referral to the department of cardiology of Hospital C was prepared.
3 days after discontinuation: At the revisit to the hospital, the patient became well and her appetite improved, and she no longer had a stumbling gait.
4 days after discontinuation: The patient was referred to the department of cardiovascular medicine at Hospital C, and similar ECG findings (prolonged QT) were confirmed.
31 days after discontinuation: The patient revisited the hospital and an ECG was performed. The results were within the normal range. The outcome of electrocardiogram prolonged QT was "recovery."</td></tr>
<tr><td colspan="6">Laboratory test value
<table>
<tr><th></th><th>Day 81 of administration</th><th>Day 107 of administration
(day of discontinuation)</th><th>31 days after
discontinuation</th></tr>
<tr><td>ECG</td><td>Within normal range</td><td>Prolonged QTc 0.521</td><td>Within normal range</td></tr>
<tr><td>HR (bpm)</td><td>−</td><td>54</td><td>−</td></tr>
</table></td></tr>
<tr><td colspan="6">Concomitant drugs: Nicardipine hydrochloride, estazolam, ifenprodil tartrate, rosuvastatin calcium, betahistine mesilate, adenosine triphosphate disodium hydrate, famotidine</td></tr>
</table>

3 Peficitinib hydrobromide

Brand name (name of company)	Smyraf Tablets 50 mg, 100 mg (Astellas Pharma Inc.)
Therapeutic category	Agents affecting metabolism, n.e.c. (not elsewhere classified)
Indications	Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage)

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with risk factors for venous thromboembolism
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Venous thromboembolism Pulmonary embolism and deep vein thrombosis may occur.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving venous thromboembolism: 1 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 3 434 Japanese market launch: July 2019

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Female 80s	Rheumatoid arthritis (latent tuberculosis infection, hypertension, osteoporosis)	100 mg for 210 days	**Deep vein thrombosis** Before initiation of administration: Administration of bucillamine (200 mg/day), salazosulfapyridine (1 000 mg/day), prednisolone (3 mg/day), loxoprofen sodium hydrate (120 mg/day) was initiated due to rheumatoid arthritis. 14 days before administration: Administration of bucillamine and salazosulfapyridine was terminated due to an inadequate response. Day 1 of administration: Administration of peficitinib hydrobromide (100 mg/day) was initiated due to rheumatoid arthritis. Classification of stage/degree of progression of rheumatoid arthritis: Stage II, classification of degree of functional impairment: Class II, joints count for pain: 4, swollen joint counts: 3, patients' global assessments of disease activity: 50/100, physicians' global assessments of disease activity:20/100 Date unknown: The level of the patient's activities of daily living (ADLs) was assessed as "independent." The patient was able to walk by herself. Day 155 of administration: Administration of prednisolone was terminated due to an inadequate response. Day 193 of administration: Oedema of lower limb was noted. The oedema in both lower limbs was exacerbated. Day 210 of administration (day of discontinuation): A stasis was found on the skin of both lower limbs. A lower limbs venous ultrasound revealed blood clots in the soleus muscle vein on both sides. Deep vein thrombosis occurred. Administration of peficitinib hydrobromide was discontinued. It was determined that inpatient treatment was unnecessary, and edoxaban tosilate hydrate (30 mg/day) was administered as treatment for deep vein thrombosis. 85 days after discontinuation: Administration of edoxaban tosilate hydrate was terminated. 86 days after discontinuation: The outcome of deep vein thrombosis was "recovery."

Laboratory test value

	Day 1	Day 22	Day 99	Day 190	Day 210 (day of discontin-uation)	15 days after discontin-uation
RBC (10^6/μL)	4.15	-	-	3.92	3.98	3.92
Haemoglobin (g/dL)	12.1	12.5	12.3	11.9	11.8	11.7
Haematocrit (%)	37.9	-	-	37.0	37.4	37.1
WBC (10^3 /μL)	6.7	6.5	4.4	3.9	6.1	5.1
Platelet count (10^4/μL)	18.9	16.2	15.1	16.5	19.3	18.3
Prothrombin time (second)	-	-	-	-	-	13
APTT (second)	-	-	-	-	-	29.6
ESR (mm/hour)	20	-	5	14	36	-
Total protein (g/dL)	6.3	-	-	-	6.6	6.4
Albumin (g/dL)	3.5	-	-	-	3.7	3.7

Total bilirubin (mg/dL)	0.8	1.0	0.8	0.7	0.8	0.6
CK (U/L)	71	126	125	163	161	82
Cr (mg/dL)	0.52	0.64	0.68	0.61	0.67	0.73
CRP (mg/dL)	0.20	0.02	0.01	0.05	0.44	0.24
D dimer (μg/ml)	-	-	-	-	8.4	3.3
Lower limbs venous ultrasound	-	-	-	-	Blood clots were noted in the veins inside the soleus muscle on both sides.	(15 days after discontin-uation, date unknown) Blood clots were noted in the veins.
Concomitant drugs: Loxoprofen sodium hydrate, amlodipine besilate, alendronate sodium hydrate, isoniazid, pyridoxal phosphate hydrate						

4
Revision of PRECAUTIONS (No.344)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated August 29, 2023.

1 Other agents affecting central nervous system
Rivastigmine

Brand name	Exelon Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg (Novartis Pharma K.K.), Rivastach Patches 4.5 mg, 9 mg, 13.5 mg, 18 mg (Ono Pharmaceutical Co., Ltd.), and the others
[Under old instructions]	
Important Precautions	Bradycardia, atrioventricular block, prolonged QT, torsade de pointes, etc. may occur following administration of this drug. In particular, patients with heart disease (e.g., myocardial infarction, cardiac valvulopathy, cardiomyopathy), patients with electrolyte abnormalities (e.g., hypokalaemia), patients with prolonged QT or a history/family history of the disease, etc. should be carefully monitored to prevent them from developing serious arrhythmia.
Adverse Reactions Clinically Significant Adverse Reactions	Angina pectoris, myocardial infarction, bradycardia, atrioventricular block, sick sinus syndrome, prolonged QT: Angina pectoris, myocardial infarction, bradycardia, atrioventricular block, sick sinus syndrome, and prolonged QT may occur. In such cases, administration should be discontinued immediately and appropriate measures should be taken.
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.**	Patients with heart disease including myocardial infarction, cardiac valvulopathy, and cardiomyopathy, electrolyte abnormalities (e.g., hypokalaemia), etc., and patients with prolonged QT or a history/family history of the disease Bradycardia, atrioventricular block, prolonged QT, torsade de pointes, etc. may occur. Patients should be carefully monitored to prevent them from developing serious arrhythmia.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Angina pectoris, myocardial infarction, bradycardia, atrioventricular block, sick sinus syndrome, prolonged QT

2 Other hormone preparations (including antihormone preparations)
Finasteride

Brand name	Propecia Tablets 0.2 mg, 1 mg (Organon K.K.), and the others
[Under old instructions]	
Careful Administration (newly added)	Patients with depression, depressed state, or a history of those diseases or patients with a history of suicidal ideation or a suicide attempt [Suicidal ideation, suicide attempt, and completed suicide have been reported, although the causal relationship with this drug is unclear.]

Important Precautions (newly added)	Suicidal ideation, suicide attempt, and completed suicide have been reported, although the causal relationship with this drug is unclear. Patients should be carefully monitored. In addition, if suicidal ideation or a suicide attempt is observed, patients should be instructed to discontinue taking this drug and contact a physician immediately.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Suicidal ideation, suicide attempt, and completed suicide have been reported, although the causal relationship with this drug is unclear. Patients should be carefully monitored. In addition, if suicidal ideation or a suicide attempt is observed, patients should be instructed to discontinue taking this drug and contact a physician immediately.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS (newly added)	9.1 Patients with Complication or History of Diseases, etc. Patients with depression, depressed state, or a history of those diseases or patients with a history of suicidal ideation or a suicide attempt Suicidal ideation, suicide attempt, and completed suicide have been reported, although the causal relationship with this drug is unclear.

3 Anticoagulants

Dabigatran etexilate methanesulfonate

Brand name	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	If this drug is retained in the esophagus, oesophageal ulcer or oesophagitis may occur. Patients should be instructed as follows: •This drug should be taken with a sufficient amount (e.g., a full glass) of water to facilitate delivery to the stomach. •If symptoms of oesophageal disease (difficult swallowing or odynophagia, retrosternal pain, severe and persistent heartburn, etc.) occur, the attending physician should be consulted.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Oesophageal ulcer, oesophagitis
14. PRECAUTIONS CONCERNING USE **Precautions Concerning Administration of the Drug**	(deleted)

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

Peficitinib hydrobromide

Brand name	Smyraf Tablets 50 mg, 100 mg (Astellas Pharma Inc.)
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	Patients with risk factors for venous thromboembolism

9.1 Patients with Complication or History of Diseases, etc. (newly added)	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Venous thromboembolism Pulmonary embolism and deep vein thrombosis may occur.

5 Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria

[1] Cefazolin sodium
[2] Cefazolin sodium hydrate

Brand name	[1] Cefazolin Sodium Injection 1 g Bag Otsuka (Otsuka Pharmaceutical Factory, Inc.), and the others [2] Cefamezin α 0.25 g for Intramuscular Injection, Cefamezin α 0.5 g for Intramuscular Injection, Cefamezin α 0.25 g for Injection, Cefamezin α 0.5 g for Injection, Cefamezin α 1 g for Injection, Cefamezin α 2 g for Injection, Cefamezin α 1 g for Infusion Kit, Cefamezin α 2 g for Infusion Kit (LTL Pharma Co., Ltd.)
[Under old instructions]	
Important Precautions	Since no methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction associated with this drug with reasonable certainty, the following measures should be taken.
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. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	Since no methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction associated with this drug with reasonable certainty, the following measures should be taken.
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Acute coronary syndrome accompanying allergic reaction

6

[1] Axicabtagene ciloleucel
[2] Idecabtagene vicleucel
[3] Ciltacabtagene autoleucel
[4] Tisagenlecleucel
[5] Lisocabtagene maraleucel

Brand name	[1] Yescarta Intravenous Drip Infusion (Gilead Sciences K.K.) [2] Abecma Intravenous Infusion (Bristol-Myers Squibb K.K.) [3] Carvykti Suspension for Intravenous Infusion (Janssen Pharmaceutical K.K.) [4] Kymriah Suspension for Intravenous Infusion (Novartis Pharma

	K.K.) [5] Breyanzi Suspension for Intravenous Infusion (Bristol-Myers Squibb K.K.)
Important Precautions (newly added)	An explanation on the possibility that this product cannot be provided due to reasons such as not conforming to specifications should be given to patients in advance.

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 August 31, 2023)
◎: Products for which EPPV was initiated after July 1, 2023

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Eculizumab (genetical recombination) Soliris for Intravenous Infusion 300 mg	Alexion Pharma Godo Kaisha	August 23, 2023
◎	Ruxolitinib phosphate[*1] Jakavi Tablets 5 mg, 10 mg	Novartis Pharma K.K.	August 23, 2023
◎	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	August 2, 2023
◎	Purified pineapple stem juice NexoBrid gel 5 g	Kaken Pharmaceutical Co., Ltd.	August 1, 2023
◎	Foslevodopa/foscarbidopa hydrate Vyalev combination subcutaneous infusion	AbbVie GK	July 26, 2023
◎	Anti-human thymocyte immunoglobulin, equine Atgam Intravenous Infusion 250 mg	Pfizer Japan Inc.	July 24, 2023
	Pneumococcal 15-valent conjugate vaccine, adsorbed (conjugate with a non toxic variant of diphtheria toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F)[*2] Vaxneuvance Aqueous Suspension Syringes	MSD K.K.	June 26, 2023
	Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg	Teijin Pharma Limited.	June 26, 2023
	Somapacitan (genetical recombination)[*3] Sogroya Subcutaneous Injection 5 mg, 10 mg, 15 mg	Novo Nordisk Pharma Ltd.	June 26, 2023

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Mirikizumab (genetical recombination) Omvoh Intravenous Infusion 300 mg, Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes	Eli Lilly Japan K.K.	June 21, 2023
Cholic acid Orphacol Capsules 50 mg	ReqMed Company, Ltd.	June 19, 2023
Vedolizumab (genetical recombination) Entyvio Pens for S.C. Injection 108 mg, Entyvio Syringes for S.C. Injection 108 mg	Takeda Pharmaceutical Company Limited.	June 19, 2023
Crisantaspase Erwinase for intramuscular injection 10000	Ohara Pharmaceutical Co., Ltd.	June 14, 2023
Tirzepatide Mounjaro Subcutaneous Injection Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos	Eli Lilly Japan K.K.	June 12, 2023
Ropeginterferon alfa-2b (genetical recombination) Besremi Subcutaneous Injection Syringes 250 μg, 500 μg	PharmaEssentia Japan KK	June 1, 2023
Oxybutynin hydrochloride[*4] Apohide Lotion 20%	Hisamitsu Pharmaceutical Co., Inc.	June 1, 2023
Avatrombopag maleate Doptelet tablets 20 mg	Swedish Orphan Biovitrum Japan Co., Ltd.	June 1, 2023
Pegvaliase (genetical recombination) Palynziq Subcutaneous Injection 2.5 mg, 10 mg, 20 mg	BioMarin Pharmaceutical Japan K.K.	May 24, 2023
Mifepristone/misoprostol Mefeego Pack	Linepharma KK	May 16, 2023
Treprostinil Treprost Inhalation Solution 1.74 mg	Mochida Pharmaceutical Co., Ltd.	May 16, 2023
Tirzepatide Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos	Eli Lilly Japan K.K.	April 18, 2023
Edaravone Radicut Ors 2.1%	Mitsubishi Tanabe Pharma Corporation	April 17, 2023
Donepezil Allydone Patches 27.5 mg, 55 mg	Teikoku Seiyaku Co., Ltd.	April 14, 2023
Pneumococcal 15-valent conjugate vaccine, adsorbed (conjugate with a non toxic variant of diphtheria toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F)	MSD K.K.	April 10, 2023

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Vaxneuvance Aqueous Suspension Syringes		
	Isavuconazonium sulfate Cresemba Capsules 100 mg, Cresemba for i.v. infusion 200 mg	Asahi Kasei Pharma Corporation	April 6, 2023
	Fostamatinib sodium hydrate Tavalisse Tablets 100 mg, 150 mg	Kissei Pharmaceutical Co., Ltd.	April 6, 2023
	Cemiplimab (genetical recombination) Libtayo I.V. Infusion 350 mg	Sanofi K.K.	March 30, 2023
	Tremelimumab (genetical recombination) Imjudo Injection 25 mg, 300 mg	AstraZeneca K.K.	March 15, 2023
	Ferric derisomaltose MonoVer for I.V. Injection 500 mg, 1000 mg	Nippon Shinyaku Co., Ltd.	March 15, 2023
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) *5 Comirnaty intramuscular injection for 5 to 11 years old	Pfizer Japan Inc.	March 3, 2023

*1 Graft versus host disease after haematopoietic stem cell transplant (when steroids are not sufficiently effective)

*2 Prevention of invasive disease caused by *Streptococcus pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in children

*3 Growth hormone-deficient short stature without epiphyseal closure

*4 Primary palmar hyperhidrosis

*5 Prevention of infectious disease caused by SARS-CoV-2