Pharmaceuticals and Medical Devices Safety Information

No. 317 October 2014

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

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Pharmaceuticals and Medical Devices Safety Information

No. 317 October 2014

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

[Outline of Information]

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of Precautions *C*: Case Reports

PMDA medi-navi
(Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
CT	Computed tomography
DAVE	Diffuse antral vascular ectasia
DLST	Drug lymphocyte stimulation test
EMC	Electro-magnetic compatibility
EMCC	Electromagnetic Compatibility Conference Japan
EPPV	Early Post-marketing Phase Vigilance
GIF	Gastrointestinal tract fiberscope
GAVE	Gastric antral vascular ectasia
Hb	Hemoglobin
ICU	Intensive care unit
IU	International unit
LAN	Local area network
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Ph	Philadelphia
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Prothrombin time
RBC	Red blood cell count
RFID	Radio frequency identification
T-Bil	Total bilirubin
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Guidelines for Use of Mobile Phones and Other Devices in Hospitals

Electromagnetic Compatibility Conference Japan (EMCC; consists of academic experts, relevant Ministries, and specialized organizations to discuss measures to prevent/remove electrical and other device damage caused by radio waves) has established a working group to conduct investigations and reviews to develop "Guidelines for Use of Mobile Phones and Other Devices in Hospitals." With the participation of the Ministry of Internal Affairs and Communications as well as the Ministry of Health, Labour and Welfare (MHLW) in the working group, the guideline has been completed after 5 meetings. The summary of the guideline is presented below. The MHLW requests all medical institutions to establish reasonable rules for the use of mobile phones based on the guidelines to ensure medical safety.

References

- EMCC website: Announcement of "Guidelines for Use of Mobile Phones and Other Devices in Hospitals" (http://www.emcc-info.net/info/pubcom2/2608_5.pdf)
- Joint HPB/GAD Notification No.0819-1 and PFSB/SD Notification No.0819-1, by the Director of General Affairs Division, Health Policy Bureau and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 19, 2014, "Guidelines for Use of Mobile Phones and Other Devices in Hospitals"

1. Objective and background to guidelines

Hospitals have been setting their own rules for using mobile phones and other devices at their facilities, taking into account the regulations concerning the electromagnetic immunity of medical electrical equipment in accordance with the Pharmaceutical Affairs Act (Act No. 145 of 1960), the guidelines published in 1997 by the EMCC, and public manners in a comprehensive way.

In the meantime, we have seen drastic changes in pertinent circumstances, such as the penetration of mobile phones into daily life, and the improvement of medical electrical equipment for electromagnetic immunity. These Guidelines have been created through a review by experts, medical associations, wireless service providers, and relevant ministries and agencies in order to use mobile phones and other wireless communication devices more securely and safely in hospitals.

New regulations are not implemented according to these Guidelines. Individual hospitals are expected to establish their own rules for the proper usage of mobile phones referencing these Guidelines, taking into account their own situations in a comprehensive manner.

2. Establishing rules for using mobile handsets targeted at users of hospitals

As mobile handsets (which hereinafter mean to include smartphones and tablets with a built-in cell-phone function) have become increasingly essential to daily life in recent years. It is desirable to allow the use of mobile handsets by patients and hospital visitors in hospitals (hereinafter called "Hospital Users") to the extent possible for improvement of convenience and quality of life for patients. On the other hand, while medical electrical equipment (medical equipment driven by electricity that has an electrical circuit and/or a sensor) is required to have a certain level of immunity for electromagnetic fields, their operation may be affected by mobile handsets when they are used in close proximity. Another concern is public manners, such as sounds made during phone calls, of ringtones, of incoming mail tones, of operation, and of watching TV (hereinafter called "Calls").

Therefore, it is necessary to place certain restrictions on the use of mobile handsets in hospitals and establish proper rules for using them. General precautions and concepts on how to establish rules for using mobile handsets are described below.

(1) Setting a separation

By reference to the recommended separation distance used in the international standards for the electromagnetic compatibility (EMC) of medical electrical equipment, a general suggestion of the proper separation distance would be to separate mobile handsets about one meter from the medical electrical equipment that may be affected. If hospitals have confirmed safety based on their own test results, information from the instruction manual for specific medical electrical equipment, and other sources, they may set a separation lower than one meter.

(2) Public manners, protecting personal and medical information, and improving a structure for electromagnetic compatibility

It is appropriate for hospitals to place use restrictions from a perspective of public manners. While many mobile handsets have recording and camera functions, it is appropriate to avoid the use of such functions in hospitals in light of protecting personal information and preventing the leakage of medical information as a rule. In hospitals, it is preferable to put someone in charge of realizing a favorable EMC environment (a status that two or more instruments operate normally without receiving electromagnetic interference mutually when either or both emit electromagnetic fields).

(3) Setting area-specific rules for use

Since the kinds of medical electrical equipment, the need for using mobile handsets, and the need for consideration of others appear to differ greatly among specific areas in hospitals, hospitals need to set area-specific rules. For the areas where the use of mobile handsets is allowed, they also need to set up the conditions for use (e.g., separations, precautions for use).

(Reference cases: Establishment of rules by area)

Area	Calls	E-mail, web, and other applications	Approach to the establishment of rules, precautions
(1) Cafeterias, waiting rooms, corridors, elevator halls, etc.	Allowed	Allowed	• Since there is no medical electrical equipment in this area normally, mobile handsets may be used. • Mobile handsets in use should be separated by at least the specified separation from medical electrical equipment. • Use should be restricted as necessary if mobile handsets in use are in the vicinity of the restricted areas. • Texting while walking is dangerous and should be avoided.
(2) Patient rooms, etc.	Partly allowed	Allowed	• As medical electric equipment used in this area is usually limited and the level of interference effect on the equipment appears to be relatively low, mobile handsets may be used. • Mobile handsets in use should be separated by at least the specified separation from medical electrical equipment. • In a patient room for multiple patients, certain consideration is necessary from a perspective of public manners, such as placing restrictions on Calls.
(3) Consultation rooms	Not allowed	Partly allowed	• As much of the medical electrical equipment used in this area are diagnostic devices and examination rooms are under the control of hospital staff, there is no need to turn off mobile handsets (provided that mobile-phone users keep distance from medical electrical equipment for at least the specified separation). • Consideration is necessary. For example, use should be avoided to prevent the disturbance to medical examination or other patients.

(4) Operation rooms, intensive care units (ICUs), laboratories, treatment rooms, etc.	Not allowed	Not allowed	• Since much of the medical electrical equipment used in this area, such as life-support devices, carry a significant risk if radio waves interfere with such equipment, mobile handsets should not be used and should be turned off (or they should be switched to the mode that does not emit radio waves).
(5) Space for mobile phones, etc.	Allowed	Allowed	• It is desirable to set up space for the use of mobile handsets in the appropriate location for the convenience and quality of life for Hospital Users.

3. Establishing rules for using mobile handsets targeted at hospital staff

Considering that the use of mobile handsets for medical practice contributes to the swift and optimum operation of medical services, the use thereof, including Calls, may be allowed in principle, on the condition that hospital staff is fully educated about the prevention of interference with medical electrical equipment.

It is necessary to take a measure to avoid confusion among Hospital Users, such as attaching a dedicated strap to these mobile handsets.

4. Keeping people informed about the rules for using mobile handsets in hospitals

It is necessary to fully inform Hospital Users, hospital staff, and relevant business operators of the content of the rules for using mobile handsets to ensure compliance with the rules. Hospitals should carefully explain the rules to patients orally and through leaflets when admitted, and post signs on the content of the rules for use in an easy-to-understand manner in a highly visible location in each area inside their facilities. Signs should contain rules for using mobile handsets for Calls as distinguished from e-mail, Web, and other applications in a straightforward manner (see reference example below). Hospital staff and relevant business operators are expected to take the lead in complying with the rules. Therefore, hospitals should ensure that these individuals are particularly well informed about the rules by, for example, distributing memos and posting alert messages.

(Reference: Examples of signs used in hospitals)

Use of mobile phones: Allowed

- Separate mobile handsets away from medical electrical equipment for at least one meter.
- Users may make call, e-mail, or browse.

Use of mobile phones: Partly allowed

- Separate mobile handsets away from medical electrical equipment for at least one meter.
- Users may e-mail or browse. No phone calls, please.

Turn off mobile phones

5. Using wireless communications systems other than mobile handsets

The approach to the usage of wireless communication systems other than mobile phones, which are expected to increase in the future, is presented below. Each hospitals should, however, confirm that the use of wireless communications systems does not affect any medical electrical equipment in such areas as operation rooms and ICUs based on the test result if they have conducted a test on their own, information from the instruction manual for specific medical electrical equipment, and other sources. Putting wireless communication devices or wireless local area network (LAN) devices on medical electrical equipment should be prohibited.

(1) Personal handy-phone system

Personal handy-phone system handsets for hospital use have been already implemented at many hospitals. These handsets may be used in hospitals in principle.

(2) Wireless LAN

Since wireless LAN devices generally used in Japan have lower output power than mobile handsets, it is considered appropriate to use them in hospitals. Use of wireless LAN devices brought by hospital visitors needs to be restricted because it may cause interference and other problems.

(3) Others

In implementing radio frequency identification (RFID), ZigBee, Bluetooth, or other technologies used to identify and manage medical electrical equipment. Hospitals should check the interference effects of such technologies on medical electrical equipment based on the test result if they have conducted a test on their own, information from the instruction manual for specific medical electrical equipment, and other sources (since some types of RFID readers may emit strong electromagnetic waves, interference effects need to be checked carefully).

6. Improving a management structure in hospitals

It is preferable to assign an EMC manager with the following responsibilities to work on EMC in hospitals.

(Efforts expected of EMC managers)

- Evaluating EMC for wireless communication devices and medical electrical equipment used in hospitals
- Evaluating and improving the electromagnetic environment
- Formulating rules for Hospital Users and hospital staff on the use of mobile handsets
- Building a structure for procuring, implementing, operating, and managing medical electrical equipment and wireless communication devices to build a favorable EMC environment
- Keeping Hospital Users informed and educating hospital staff
- Collecting latest technical information on an ongoing basis

2

Change in the Submission Place of Reports in the Safety Information Reporting System

Collection, evaluation and provision to hospitals and clinics of post-marketing information on adverse drug reactions (ADRs), infections, and malfunctions (hereinafter referred to as "ADR information") are important to ensure the safety of drugs and medical devices. The Pharmaceutical Affairs Act (Act No. 145, 1960) requires physicians, dentists, pharmacists and other medical and pharmaceutical providers to report ADR information possibly associated with drugs and medical devices to MHLW. Medical and pharmaceutical providers have been requested to understand and cooperate with the Drugs and Medical Devices Safety Information Reporting System.

With the enforcement of the Act to Partially Revise the Pharmaceutical Affairs Act (Act No. 84, 2013), **the submission place for the system has been changed to the Safety Information Division of Office of Safety I in Pharmaceuticals and Medical Devices Agency (PMDA) since November 25, 2014.** Information reported to PMDA will be input into a database, given a serial number and reported to MHLW. The information will also be provided by PMDA to the marketing authorization holders (MAHs) of the drug, medical device or cellular and tissue-based product.

Medical and pharmaceutical providers are encouraged to report serious ADRs, infections, and malfunctions they have found in their daily practice by mail, fax, or e-mail.

(References)

- "Revision of operating procedure for reporting of ADRs, infections, and malfunctions associated with drugs and medical devices from medical institutions" (provisionally translated title) (PFSB Notification No. 0729-2, dated July 29, 2010)
- Dear healthcare professionals (request for ADR/infection/malfunction reporting) *The report form can be downloaded from the website.
  http://www.info.pmda.go.jp/info/houkoku.html (only available in Japanese language)

	Current submission place	**After November 25, 2014**
Address to	Safety Division, Pharmaceutical and Food Safety Bureau, MHLW	**Safety Information Division, Office of Safety I, PMDA**
Mail	1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8916	**Shin-Kasumigaseki Bldg. 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013**
FAX	03-3508-4364	**0120-395-390**
E-mail	anzensei-hokoku@estrigw.mhlw.go.jp	**anzensei-hokoku@pmda.go.jp**
e-Gov	"e-Gov electronic application system" http://shinsei.e-gov.go.jp/menu/ An electronic certificate will be required to use the system.	

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated September 16, 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Imatinib Mesilate

Brand Name (name of company)	Glivec Tablets 100 mg (Novartis Pharma K.K.) and the others
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	• Chronic myeloid leukaemia • KIT (CD117)-positive gastrointestinal stromal tumor • Philadelphia (Ph) chromosome-positive acute lymphocytic leukaemia • The following Fip-1-like 1-platelet-derived growth factor receptor alpha - positive diseases: Hypereosinophilic syndrome and chronic eosinophilic leukaemia

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Haemorrhage (cerebral haemorrhage and subdural haemorrhage):
Cerebral haemorrhage and/or subdural haemorrhage may occur. Patients should be carefully monitored through periodical blood tests, etc. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken.

Gastrointestinal haemorrhage <u>and gastric antral vascular ectasia (GAVE)</u>:
Gastrointestinal haemorrhage may occur. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken.

<u>In addition, caution should be exercised because sometimes anaemia progresses without apparent symptoms such as melaena and/or haematemesis in gastrointestinal haemorrhage caused by GAVE.</u>

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 4 months (April 2011 to July 2014)
GAVE-associated cases: 3 cases (no fatal cases)
The number of patients using this drug per year estimated by MAHs:
Approximately 8 500 (June 2013 to May 2014)
Launched in Japan: July 2005

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Ph chromosome-positive acute biphenotypic leukaemia (depression)	600 mg for 49 days	**GAVE** Date unknown: The patient, who had been making outpatient visits due to depression, experienced Ph chromosome-positive acute biphenotypic leukaemia. 7 days before administration: Remission-induction therapy was started. Day 1 of administration: Concomitant use of imatinib mesilate was started at 600 mg/day. Day 49 of administration (day of discontinuation): With epigastric pain and aggravation of anaemia, upper gastrointestinal tract endoscopy showed a finding of GAVE, and diffuse haemorrhage per diapedesis was observed at the same site. Haemostasis was performed with argon plasma coagulation. Administration of oral medications including imatinib mesilate was discontinued and the patient was fasted. 2 days after discontinuation: Oral administration was started with liquid diet. 8 days after discontinuation: An endoscopy showed that the finding of diffuse telangiectasia remained, but haemorrhage was not found. 17 days after discontinuation: Consolidation therapy with high-dose methotrexate + cytarabine was performed. There was no aggravation of GAVE. 38 days after discontinuation: Imatinib mesilate was changed to dasatinib 140 mg/day. Dasatinib was administered for 28 days. On an endoscopy, the finding of GAVE had disappeared. 65 days after discontinuation: Haemorrhage and GAVE did not recur after the change to dasatinib.
	Concomitant medications: allopurinol, sertraline hydrochloride, prednisolone, itraconazole, sulfamethoxazole/trimethoprim, vincristine sulfate, sodium rabeprazole			

Laboratory Examination

Parameters	12 days before administration	Day 46 of administration	Day 49 of administration (day of discontinuation)
RBC ($\times 10^4/mm^3$)	151	206	137
Hb (g/dL)	5.0	6.9	4.9
Hematocrit level (%)	15.6	21.4	14.0
WBC ($/mm^3$)	61 400	2 200	1 800
Platelet ($x10^4/mm^3$)	11.9	9.8	5.6

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Chronic myeloid leukaemia (hypertension)	400 mg for 1 626 days ↓ 600 mg for 154 days ↓ (No administration for 6 days) ↓ 300 mg for 22 days ↓ 400 mg for 1 792 days	**Diffuse antral vascular ectasia (DAVE)** Day 1 of administration: The patient started receiving imatinib mesilate at 400 mg/day. Day 1 317 of administration: Computed tomography (CT) finding showed no particular abnormality. Day 1 401 of administration: Abdominal echo showed normal spleen. Day 1 415 of administration: As a decrease in haemoglobin (Hb) level and positive occult blood were observed, an upper gastrointestinal tract fiberscope (GIF) was performed. Gastritis was the only finding. Administration of iron preparation 200 mg/day was started. Day 1 479 of administration: The dose of iron preparation was reduced to 100 mg/day. Day 1 626 of administration: As polymerase chain reaction analysis showed that leukemic cells remained, the dose of imatinib mesilate was increased to 600 mg/day. Day 1 773 of administration: The Hb level decreased and DAVE was suspected on GIF. Administration of dried aluminum hydroxide gel/magnesium hydroxide solution 60 mL/day, sodium alginate 60 mL/day, and rebamipide tablets 300 mg/day was started. Day 1 779 of administration (day of discontinuation): The Hb level further decreased (Hb: 5.3 g/dL). Administration of imatinib mesilate was discontinued. Day after discontinuation: GIF was performed. There was a small amount of blood coagulation in the stomach. This was determined to be haemorrhage from DAVE, and cauterization for haemostasis was performed. The dose of dried aluminum hydroxide gel/magnesium hydroxide solution was increased to 80 mL/day, and the dose of sodium alginate was increased to 80 mL/day. Administration of omeprazole 20 mg/day was started. 7 days after discontinuation (day 1 of readministration): Administration of imatinib mesilate was restarted at 300 mg/day. Day 23 of readministration: The dose of imatinib mesilate was increased to 400 mg/day. Day 36 of readministration: The dose of iron preparation was increased to 200 mg/day. Day 64 of readministration: Omeprazole was changed to ranitidine 300 mg/day. Day 113 of readministration: GIF was performed. As gastritis was the only finding, administration of sodium alginate was discontinued. Day 134 of readministration: Administration of dried aluminum hydroxide gel/magnesium hydroxide solution was discontinued. Day 876 of readministration: Ranitidine was changed to lansoprazole 30 mg/day. Day 1 495 of readministration: After that, administration of lansoprazole was discontinued after administration suspension and dose reduction.

				Day 1 814 of readministration (day of discontinuation of readministration): As Hb level tended to decrease again, administration of imatinib mesilate was discontinued. Day after discontinuation of readministration: Imatinib mesilate was changed to nilotinib 800 mg/day. 57 days after discontinuation of readministration: The decrease in Hb level improved.
	Concomitant medications: antibiotic-resistant lactobacillus preparation, amlodipine besilate			

Laboratory Examination

Parameters	Day 1 of administration	Day 1 415 of administration	Day 1 773 of administration	Day 1 779 of administration (day of discontinuation)	Day 113 of readministration	Day 1 815 of readministration (day after discontinuation of readministration)	57 days after discontinuation of readministration
WBC ($\times 10^4/mm^3$)	366	281	230	178	426	282	430
Hb (g/dL)	12.4	8.1	6.9	5.3	12.5	8.7	12.2
Hematocrit level (%)	36.0	25.8	22.1	16.8	38.1	27.4	37.6

2 Pregabalin

Brand Name (name of company)	Lyrica Capsules 25 mg, 75 mg, 150 mg (Pfizer Japan Inc.)
Therapeutic Category	Central nervous system agents-Miscellaneous
Indications	Neuropathic pain and pain associated with fibromyalgia

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Hepatitis fulminant and hepatic dysfunction: Fulminant hepatitis and/or hepatic dysfunction with elevations of aspartate aminotransferase (AST or glutamate oxaloacetate transaminase), alanine aminotransferase (ALT or glutamate pyruvate transaminase), etc. 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.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 4 months (April 2011 to July 2014)
Fulminant hepatitis: 1 case (1 fatal case)
Hepatic dysfunction-associated cases*: 7 cases (no fatal cases)

*: Cases with either AST ≥ 500 U/L, ALT ≥ 500 U/L, or total bilirubin (T-Bil) ≥ 10 mg/dL.

The number of patients using this drug per year estimated by MAHs:
Approximately 1.97 million (March 2013 to February 2014)
Launched in Japan: June 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Post herpetic neuralgia (hepatic cyst)	150 mg for 14 days ↓ 75 mg for 7 days	**Hepatitis fulminant** 19 days before administration: The patient started receiving loxoprofen sodium hydrate, famciclovir, and mecobalamin for herpes zoster. 15 days before administration: Administration of famciclovir was discontinued. 5 days before administration: As the patient complained of dizziness, cefcapene pivoxil hydrochloride hydrate was administered, but she felt physically sick after taking and suspended it at her discretion. Day 1 of administration: Administration of pregabalin 150 mg/day was started for post herpetic neuralgia (post herpes zoster pain). Day 15 of administration: As pain decreased, the dose of pregabalin was reduced to 75 mg/day. Day 19 of administration: The patient complained of general malaise. Day 22 of administration (day of discontinuation): The patient visited hospital with chief complaints of impaired appetite and oedema, and was admitted to the hospital on the same day. A blood test showed marked increases in AST, ALT, alkaline phosphatase, gamma-glutamyl transpeptidase (γ-GTP), and T-Bil and a decrease in prothrombin activity. CT showed an image of periportal inflammation. Acute severe hepatitis was diagnosed, and administration of all oral medications was discontinued. Administration of

				menatetrenone and monoammonium glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate combination injectable solution was started. 1 day after discontinuation: Liver biopsy was performed, and drug-induced liver injury was observed. 6 days after discontinuation: Grade 2 encephalopathy occurred, and subacute fulminant hepatitis was diagnosed. Central venous nutrition was started the next day. 8 days after discontinuation: CT showed hepatic atrophy and accumulation of ascites. The results of drug lymphocyte stimulation test (DLST) were positive for pregabalin and loxoprofen sodium hydrate. 11 days after discontinuation: Administration of amino acid injection to improve hepatic encephalopathy, spironolactone, and steroid was started. 14 days after discontinuation: The results of DLST were negative for famciclovir and cefcapene pivoxil hydrochloride hydrate. 26 days after discontinuation: Furosemide was added. As pneumonia was suspected, tazobactam sodium/piperacillin sodium was administered. 30 days after discontinuation: The patient fell into a coma, and died from fulminant hepatitis.
	The other suspected medications: loxoprofen sodium hydrate, famciclovir Concomitant medications: mecobalamin, famotidine, ecabet sodium hydrate, cefcapene pivoxil hydrochloride hydrate			

Laboratory Examination

	Approximately 4 months before administration	Day 22 of administration (day of discontinuation)	3 days after discontinuation	6 days after discontinuation	14 days after discontinuation	28 days after discontinuation
AST (IU/L)	22	2 340	680	341	97	42
ALT (IU/L)	20	1 655	791	461	110	31
ALP (IU/L)	269	1 014	873	851	620	322
LDH (IU/L)	156	692	278	285	230	336
γ-GTP (IU/L)	30	313	263	230	77	40
T-Bil (mg/dL)	0.6	7.0	12.5	18.6	19.1	24.8
Ammonia (μg/dL)	—	—	—	100	—	—
Total protein (g/dL)	7.4	6.5	5.7	6.1	5.0	4.3
PT (sec)	—	18.2	20.7	20.6	28.4	33.8
PT (%)	—	44	—	37	—	—

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early post-marketing phase vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting the ADRs from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADRs. EPPV is specified as a condition of approval.

(As of October 1, 2014)

◎: Products for which EPPV was initiated after September 2, 2014

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	bimatoprost GlashVista Cutaneous Solution 0.03% 5 mL	Allergan Japan K.K.	September 29, 2014
◎	edoxaban tosilate hydrate Lixiana Tablets 15 mg, 30 mg*1	Daiichi Sankyo Company, Limited	September 26, 2014
◎	voriconazole Vfend Tablets 50 mg, 200 mg, Vfend Intravenous 200 mg*2	Pfizer Japan Inc.	September 26, 2014
◎	metronidazole Anaemetro Intravenous Infusions 500 mg	Pfizer Japan Inc.	September 26, 2014
◎	delamanid Deltyba Tablets 50 mg	Otsuka Pharmaceutical Co., Ltd.	September 26, 2014
◎	treprostinil Treprost Injections 20 mg, 50 mg, 100 mg, 200 mg	Mochida Pharmaceutical Co., Ltd.	September 26, 2014
◎	anti-human thymocyte immunoglobulin, rabbit Thymoglobuline Intravenous Infusions 25 mg*3	Sanofi K.K.	September 19, 2014
◎	donepezil hydrochloride Aricept Tablets 3 mg, 5 mg, 10 mg, Aricept D Tablets 3 mg, 5 mg, 10 mg, Aricept Fine Granules 0.5%, Aricept Oral Jelly 3mg, 5mg, 10 mg, Aricept Dry Syrup 1%*4	Eisai Co., Ltd.	September 19, 2014
◎	aflibercept (genetical recombination) Eylea Solution Intravitreal Injections 40mg/mL, Eylea Solution Intravitreal Injections Kit 40 mg/mL*5	Bayer Yakuhin, Ltd.	September 19, 2014
◎	calcipotriol hydrate/betamethasone dipropionate Dovobet Ointment	Leo Pharma K.K.	September 12, 2014
◎	eftrenonacog alfa (genetical recombination) Alprolix Intravenous 500, 1000, 2000, 3000	Biogen Idec Japan Ltd.	September 8, 2014
◎	alectinib hydrochloride Alecensa Capsules 20 mg, 40 mg	Chugai Pharmaceutical Co., Ltd.	September 5, 2014

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	cabazitaxel acetonate Jevtana Intravenous Infusions 60 mg	Sanofi K.K.	September 4, 2014
◎	umeclidinium bromide/vilanterol trifenatate Anoro Ellipta 7 doses	GlaxoSmithKline K.K.	September 4, 2014
◎	(1) daclatasvir hydrochloride (2) asunaprevir (1) Daklinza Tablets 60 mg (2) Sunvepra Capsules 100 mg	Bristol-Myers K.K.	September 3, 2014
◎	cysteamine bitartrate Nicystagon Capsules 50 mg, 150 mg	Mylan Seiyaku Ltd.	September 3, 2014
◎	canagliflozin hydrate Canaglu Tablets 100 mg	Mitsubishi Tanabe Pharma Corporation	September 3, 2014
◎	nivolumab (genetical recombination) Opdivo Intravenous Infusions 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	September 2, 2014
◎	ruxolitinib phosphate Jakavi Tablets 5 mg	Novartis Pharma K.K.	September 2, 2014
◎	velaglucerase alfa (genetical recombination) Vpriv Intravenous Injections 400 U	Shire Japan KK	September 2, 2014
◎	abiraterone acetate Zytiga Tablets 250 mg	Janssen Pharmaceutical K.K.	September 2, 2014
◎	efinaconazole Clenafin Topical Solution 10% for nail	Kaken Pharmaceutical Co., Ltd.	September 2, 2014
	rituximab (genetical recombination) Rituxan Injections 10 mg/mL*[6]	Zenyaku Kogyo Co., Ltd.	August 29, 2014
	phenothrin Sumithrin Lotion 5%	Kracie Pharma, Ltd.	August 22, 2014
	tapentadol hydrochloride Tapenta Tablets 25 mg, 50 mg, 100 mg	Janssen Pharmaceutical K.K.	August 18, 2014
	fentanyl citrate Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg*[7]	Hisamitsu Pharmaceutical Co., Inc.	June 20, 2014
	sorafenib tosilate Nexavar Tablets 200 mg*[8]	Bayer Yakuhin, Ltd.	June 20, 2014
	pneumococcal 13-valent conjugate vaccine (diphtheria CRM_{197} protein) Prevenar 13 Suspension Liquid for Injections*[9]	Pfizer Japan Inc.	June 20, 2014
	azilsartan/amlodipine besilate Zacras Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 18, 2014
	natalizumab (genetical recombination) Tysabri. for I.V. Infusions 300 mg	Biogen Idec Japan Ltd.	June 4, 2014
	prasugrel hydrochloride Efient Tablets 3.75 mg, 5 mg	Daiichi Sankyo Company, Limited	May 27, 2014
	betaine Cystadane	ReqMed Company, Ltd.	May 27, 2014
	trifluridine/tipiracil hydrochloride Lonsurf Combination Tablets T15, T20	Taiho Pharmaceutical Co., Ltd.	May 26, 2014
	denosumab (genetical recombination) Ranmark Subcutaneous Injections 120 mg*[10]	Daiichi Sankyo Company, Limited	May 23, 2014

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
enzalutamide Xtandi Capsules 40 mg	Astellas Pharma Inc.	May 23, 2014
valsartan/cilnidipine Atedio Combination Tablets	Ajinomoto Pharmaceuticals Co., Ltd	May 23, 2014
tofogliflozin hydrate (1) Deberza Tablets 20 mg (2) Apleway Tablets 20 mg	(1) Kowa Company, Ltd. (2) Sanofi K.K.	May 23, 2014
luseogliflozin hydrate Lusefi Tablets 2.5 mg, 5 mg	Taisho Pharmaceutical Co., Ltd.	May 23, 2014
dapagliflozin propylene glycolate hydrate Forxiga Tablets 5 mg, 10 mg	Bristol-Myers K.K.	May 23, 2014
tenofovir disoproxil fumarate Tenozet Tablets 300 mg	GlaxoSmithKline K.K.	May 16, 2014
turoctocog alfa (genetical recombination) Novoeight for Intravenous Infusions 250, 500, 1000, 1500, 2000, 3000	Novo Nordisk Pharma Ltd.	May 12, 2014
ferric citrate hydrate Riona Tablets 250 mg	Japan Tobacco Inc.	May 12, 2014
afatinib maleate Giotrif Tablets 20 mg, 30 mg, 40 mg, 50 mg	Nippon Boehringer Ingelheim Co., Ltd.	May 7, 2014
trastuzumab emtansine (genetical recombination) Kadcyla Intravenous Infusions 100 mg, 160 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2014
riociguat Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg	Bayer Yakuhin, Ltd.	April 18, 2014
levocetirizine hydrochloride Xyzal Syrup 0.05%	GlaxoSmithKline K.K.	April 17, 2014
dolutegravir sodium Tivicay Tablets 50 mg	ViiV Healthcare K.K.	April 17, 2014
brentuximab vedotin (genetical recombination) Adcetris for Intravenous Infusions 50 mg	Takeda Pharmaceutical Company Limited	April 17, 2014
ipragliflozin l-proline Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	April 17, 2014
tadalafil Zalutia Tablets 2.5 mg, 5 mg	Eli Lilly Japan K.K.	April 17, 2014

*1 An additional indication for “the reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and the treatment and suppression of relapse for venous thromboembolisms (deep vein thrombosis and pulmonary thromboembolism)”

*2 An additional administration for “pediatrics”

*3 An additional indication for “the treatment of acute rejection after heart transplant, lung transplant, liver transplant, pancreas transplant, and small intestine transplant”

*4 An additional indication for “the suppression of progression of dimentia symptoms in patients with dementia with lewy bodies”

*5 An additional indication for “the treatment of choroidal neovascularization in pathologic myopia”

*6 An additional indication for “the treatment of patients with refractory nephrotic syndrome (frequently relapsing or steroid-resistant)”

*7 An additional indication for “the treatment of moderate to severe chronic pain”

*8 An additional indication for “the treatment of patients with radically unresectable differentiated thyroid carcinoma”

*9 An additional indication for “the prevention of infection caused by Streptococcus pneumonia serotypes 1, 3, 4, 5, 6A,

6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in elderly patients”

*10 An additional indication for “the treatment of patients with bone giant cell tumour”