Pharmaceuticals and Medical Devices Safety Information

No. 324 July 2015

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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).

Available information is listed here

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

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Pharmaceuticals and Medical Devices Safety Information

No. 324 July 2015

Ministry of Health, Labour and Welfare & Pharmaceutical and Food 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 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
ALK	Anaplastic lymphoma kinase
BNP	Brain natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
Cl	Chloride
Cre	Creatinine
CRP	C-reactive protein
CT	Computed tomography
DBP	Diastolic blood pressure
ECOG PS	Eastern Cooperative Oncology Group performance status
Eos	Eosinophil
ELD	Evaluation and Licensing Division
EPPV	Early Post-marketing Phase Vigilance
GPSP	Good Post-marketing Study Practice
GVP	Good Vigilance Practice
K	Potassium
Lym	Lymphocyte
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Mono	Monocyte
Na	Sodium
Neu	Neutrophil
PFSB	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
QTc	Corrected QT
RMP	Risk Management Plan
SBP	Systolic blood pressure
SD	Safety Division
SpO_2	Oxygen saturation
WBC	White blood cell count

1

Risk Management Plan

1. Introduction

Two years have elapsed since the preparation of a document referred to as the "Risk Management Plan" (RMP) is required for new drugs and biosimilars/follow-on biologics for which a marketing application was submitted on or after April 1, 2013, in compliance with the "RMP Guidance" and the "Preparation of the RMP" that were issued as notifications in April 2012.

The following implementation of the RMP has been widely announced during these 2 years by the "Publication of the RMP" issued on March 4, 2013; the "Application of the RMP Guidance for Generic Drugs" issued on August 26, 2014; the revised Good Vigilance Practice (GVP) Ordinance* and the revised Good Post-marketing Study Practice (GPSP) Ordinance** that came into effect on October 1, 2014, etc.

The implementation of the RMP had been explained in Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 300 just before the preparation of RMP was started in April 2012. The explanation included a discussion of the operating method for generic drugs; the revision and enforcement of both the GVP Ordinance and the GPSP Ordinance were mentioned as "future actions."

In the current issue, an outline of the overall RMP will be provided. Then, application of the RMP to generic drugs, items related to the RMP in the revised GVP Ordinance and GPSP Ordinance, and publication on the Pharmaceuticals and Medical Devices Agency (PMDA) website will be presented.

* Ministerial Ordinance on GVP for Drugs, Quasi-drugs, Cosmetics, Medical Devices, and Regenerative Products (Ministry of Health, Labour and Welfare [MHLW] Ministerial Ordinance No.135 of 2004)

**Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ministerial Ordinance No. 171 of 2004)

2. Summary

The objective of the RMP is intended to achieve ensuring of post-marketing safety to perform the necessary safety measures by evaluating the benefits and risks of drugs through the stage of development, approval review, and post-marketing. The RMP basically consists of 3 elements, namely "Safety Specifications," the "Pharmacovigilance Plan," and the "Risk Minimization Plan." They respectively summarize the following issues. 1) Safety specification: important adverse drug reactions (ADRs), which are clarified or suspected to be associated with the drug, and important missing information. 2) Pharmacovigilance activities: activities for collecting information performed during post-marketing. 3) Risk minimization activities: activities related to safety measures taken to minimize risks, such as providing information to healthcare professionals and establishing conditions of the drug use, etc. (**Figure**).

With regard to pharmacovigilance and risk minimization activities, there are 2 types of activities, i.e., "routine activities" and "additional activities." "Routine activities" are activities to be commonly conducted for all drugs by Marketing Authorization Holders (MAHs). Specifically, "routine activities" of pharmacovigilance include collecting information on ADRs. "Routine activities" of risk minimization include information to be provided on the package inserts of drugs.

"Additional activities" are activities to be individually conducted based on drug properties. "Additional activities" of pharmacovigilance include Early Post-marketing Phase

Vigilance (EPPV), use-results surveys, and post-marketing clinical studies. “Additional activities” of risk minimization include information provision based on EPPV and information provided by the materials for the proper use of drugs.

When “additional activities” are deemed necessary during the process of review for approval or when new concerns regarding safety are identified in the post-marketing phase and the preparation of the RMP is required, the PMDA will publish the RMP on its website after MAHs submit the RMP including the “additional activities” performed or new concerns regarding safety to the PMDA.

To ensure the preparation and implementation of the RMP, it is to be included in the conditions for approval, and its preparation and implementation are to be included in the post-marketing safety management regulations that MAHs must comply with.

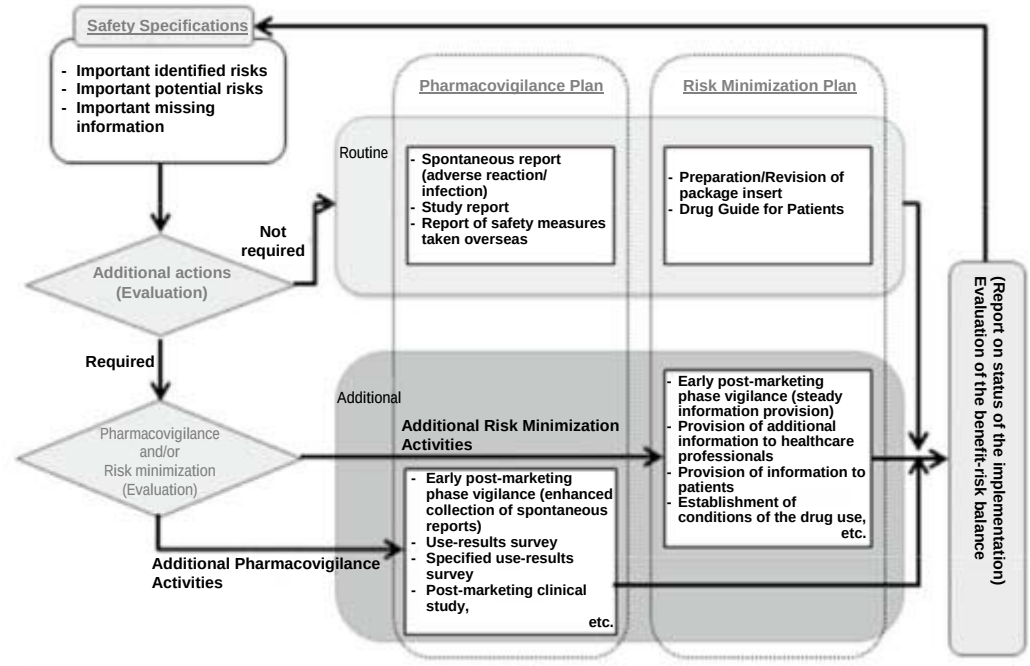

Figure: Conceptual diagram

3. Recent Actions

(1) Application to generic drugs

When the “RMP Guidance” mentioned above was issued, the timing of application to generic drugs was to be informed separately. The “Application, etc. of the RMP Guidance for Generic Drugs” was issued on August 26, 2014, and timing to discuss the preparation of the RMP and other issues were provided (it was applicable from the date of issue). In this guidance, the time to discuss the preparation of the RMP for generic drugs was stipulated as follows, regardless of “1.2 Scope” in the above guidance.

a. At the time of submission of approval application for generic drugs whose “Indications,” etc. are the same as those of the original drugs for which the RMP has already been published based on the “Publication of the RMP” (dated March 4, 2013)
b. At the time when new concerns regarding safety have been identified in the post-marketing phase

(2) Revision and enforcement of the Good Vigilance Practice Ordinance and the Good Post-marketing Study Practice Ordinance

To ensure the preparation and implementation of the RMP by MAHs of drugs, the GVP Ordinance and the GPSP Ordinance were revised on March 11, 2013 and enforced on October 1, 2014.

Major revised points in the Good Vigilance Practice Ordinance

"Risk Management" is newly defined. EPPV, which had been conventionally implemented, is now included as a part of risk management.

The elements of the RMP introduced above are positioned in conformity with the definition of risk management in the GVP Ordinance.

RMP	GVP Ordinance
Safety Specifications	Topics to be specially discussed on safety
Pharmacovigilance activities	Information collection, surveys, and studies related to safety
Risk minimization activities	Activities to minimize the risk associated with using drugs

In addition, the functions of the marketing supervisor-general and safety management supervisor related to the RMP are defined. Furthermore, the preparation of procedures related to the RMP and obligation of preparation and revision of the RMP were added.

Major revised points in the Good Post-marketing Study Practice Ordinance

The functions of the post-marketing surveillance supervisor related to the RMP are defined. Furthermore, the ordinance stipulates that when MAHs implement use-results surveys and post-marketing clinical studies or commit these implementations, they shall be subject to the RMP.

(3) Publication on the PMDA website

The publication of RMPs is aimed to provide healthcare professionals further understanding on the safety measures for drugs and to promote proper use as well as to contribute to the smooth implementation of post-marketing surveillance and studies.

The "Publication of the RMP" was issued on March 4, 2013 and clarified the handling of the publication. Publication of the subjects was as follows.

(i) RMP submitted to the PMDA on new drugs and biosimilars/follow-on biologics for application of marketing approval on and after April 1, 2013

(ii) RMP submitted to the PMDA after new concerns regarding safety had been identified in the post-marketing phase on and after April 1, 2013

(iii) RMP submitted after changing of the RMP that had been already submitted to the PMDA based on (i) or (ii) above

Other than the RMPs listed above, in the "Application of the RMP Guidance for Generic Drugs" introduced in above (1), RMPs for generic drugs are to be published according to the "Publication of the RMP"

The number of products requiring the RMP to be published has been increasing. RMPs of 105 products have been published on the PMDA website as of June 11, 2015. The latest RMPs are available from the following URL (only available in Japanese language).
http://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html

4. Requests to healthcare professionals and future actions

To enhance the safety measures for drugs, the announcement and steady implementation of the RMP are expected. The RMP is a summary of identified Safety Specifications and safety measures. The RMP will be properly reviewed based on the assessment of the benefit-risk balance of drugs, when new safety concerns are identified in the post-marketing phase or at milestones that are set for each activity. It is extremely important in promoting the proper use of drugs and to ensure their safety by the understanding by healthcare professionals of currently what important safety concerns (Safety Specifications)

or efficacy specifications there are for the drug, what kind of basis they were set on, and what kind of activity and purpose is planned and conducted for the RMP.

To further promote the utilization of the RMP in clinical practice, provision of an RMP closer to the actual clinical practice is planned in the future. Healthcare professionals are encouraged to support surveys or clinical studies planned to be implemented in the RMP based on an understanding of their objectives.

References

1. Implementation of the “RMP” in PMDSI No. 300 issued in March 2013
2. RMP Guidance (Joint Pharmaceutical and Food Safety Bureau [PFSB]/ Safety Division [SD] Notification No. 0411-1 and PFSB/ Evaluation and Licensing Division (ELD) Notification No. 0411-2, by the Director of SD and the Director of ELD PFSB, MHLW, dated April 11, 2012)
3. Preparation of the RMP (Joint PFSB/ELD Notification No. 0426-2 and PFSB/SD Notification No. 0426-1, by the Director of ELD and the Director of SD, PFSB, MHLW, dated April 26, 2012)
4. Questions and Answers (Q&A) on the RMP (Administrative Notice, by ELD and SD, PMSB, MHLW, dated September 7, 2012) (only available in Japanese language)
5. Application of the RMP Guidance for Generic Drugs (Joint PFSB/ELD Notification No. 0826-3 and PFSB/SD Notification No. 0826-1, by the Director of ELD and the Director of SD, PFSB, MHLW, dated August 26, 2014) (only available in Japanese language)
6. Enforcement of Ministerial Ordinance to Partially Revise the Ministerial Ordinance on GVP for Drugs, Quasi-drugs, Cosmetics, and Medical Devices and the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (PFSB Notification No. 0311-7, by the Secretary-General of PFSB, MHLW, dated March 11, 2013) (only available in Japanese language)
7. Publication of the RMP (Joint PFSB/ELD Notification No. 0304-1 and PFSB/SD Notification No. 0304-1, by the Director of SD and the Director of ELD, PFSB, MHLW, dated March 4, 2013) (only available in Japanese language)
8. List of RMP-submitted products (PMDA website) (only available in Japanese language)

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Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated June 2, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Crizotinib

Brand name (name of company)	Xalkori Capsules 200 mg and 250 mg (Pfizer Japan Inc.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	*Anaplastic lymphoma kinase (ALK)*-positive, unresectable, advanced, or relapsed non-small-cell lung cancer

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Cardiac failure:** Cardiac failure may occur. Patients should be carefully monitored. If the fluid retention (pulmonary oedema, pleural effusion, pericardial effusion, etc.), rapid increased weight, cardiac failure symptoms (shortness of breath, dyspnoea, oedema, etc.) are observed, appropriate measures such as drug suspension, dose reduction, or discontinuation of administration should be adopted.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years and 11 months (from initial marketing to March 2015) Case of adverse events associated with cardiac failure: 6 cases (no fatal case) The number of patients using these drugs estimated by MAH: 1 000* (from February 2014 to February 2015) *The number of patients who newly used these drugs during the above period Launched in Japan: May 2012

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Non-small cell lung cancer (metastases to bone, metastases to lymph nodes)	500 mg for 12 days ↓ Discontinuation ↓ 400 mg for 29 days ↓ 250 mg, ongoing	**Cardiac failure** The patient had a history of prior treatment of non-small cell lung cancer with vinorelbine ditartrate and cisplatin as first-line therapy and with pemetrexed sodium hydrate as second-line therapy. The patient had a history of bone radiotherapy as surgical/radiologic therapy for non-small cell lung cancer. The sites of metastases were bone and lymph nodes. Eastern Cooperative Oncology Group performance status (ECOG PS) was 1 at the start of administration of crizotinib. Day 1 of administration: The administration of 500 mg/day of crizotinib was

				started as third-line therapy for non-small cell lung cancer. Day 7 of administration: Sinus bradycardia (grade 1) developed. (On day 204 of re-administration, the patient recovered.) Day 12 of administration (day of discontinuation): Blood pressure decreased to 79/42 mmHg. Bilateral pleural effusion, pulmonary congestion, and symptoms of lower limb oedema developed. Corrected QT (QTc) mildly prolonged to 0.454, and the level of brain natriuretic peptide (BNP) increased to 0.3084 ng/mL. The patient was diagnosed with cardiac failure. The administration of crizotinib was discontinued. Date unknown: Cardiac failure subsequently improved, and the above findings improved. 11 days after discontinuation (Day 1 of re-administration): The patient was judged to recover from cardiac failure. The administration of crizotinib was restarted at 400 mg/day. The level of BNP increased again after the re-administration of crizotinib. Day 12 of re-administration: The patient was discharged from the hospital. Day 30 of re-administration: The dose of crizotinib was decreased to 250 mg/day. The level of BNP subsequently decreased.
	Concomitant medications: denosumab (genetical recombination), precipitated calcium carbonate, fentanyl citrate, celecoxib, lansoprazole, teprenone, zolpidem tartrate, alprazolam, metoclopramide, sennoside, magnesium oxide, sodium picosulfate hydrate, cefditoren pivoxil, lanoconazole, and bisacodyl			

Laboratory examination

	Day 1 of administration	Day 12 of administration (day of discontinuation)	2 days after discontinuation	4 days after discontinuation	9 days after discontinuation	2 days after re-administration
WBC (cells/mm^3)	2 300	5 000	2 300	2 800	2 000	2 100
Na (mEq/L)	142	136	139	138	140	142
K (mEq/L)	4.6	4.5	4.5	4.3	4.5	5.0
Cl (mEq/L)	105	100	104	101	104	105
CRP (mg/dL)	0.42	1.43	1.65	1.15	0.24	0.09
BNP (ng/dL)	-	0.3084	0.0836	0.0322	0.0218	-
BUN (mg/dL)	18.4	14.2	9.6	8.2	11.1	10.5
Cre (mg/dL)	0.55	0.76	0.69	0.59	0.58	0.66
QTc	-	0.454	-	-	-	-
BP (mmHg)	-	79/42	-	-	-	-

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 40s	Non-small cell lung cancer (lymphangiosis carcinomatosa, metastases to bone, metastases to lung, metastases to central nervous system, uterine leiomyoma, headache, peripheral neuropathy, anxiety disorder, insomnia)	500 mg for 28 days	**Pulmonary oedema** The patient had a history of prior treatment of non-small cell lung cancer with cisplatin and pemetrexed sodium hydrate. The patient had a history of brain radiotherapy as surgical/radiologic therapy for non-small cell lung cancer. The sites of metastases were bone, lung, and central nervous system. ECOG PS was 0 at the start of administration of crizotinib. Day 1 of administration The administration of 500 mg/day of crizotinib was started as second-line therapy for *ALK*-positive, unresectable, advanced, or relapsed non-small cell lung cancer. Day 6 of administration: Sinus bradycardia (grade 1) developed. Day 9 of administration: The patient recovered from sinus bradycardia. Day 23 of administration: The patient had symptoms of lower limb oedema and increased weight. Day 24 of administration: Decreased size of primary lesions was found on chest computed tomography (CT). Oral steroid administration was discontinued. Day 28 of administration (day of discontinuation): The patient had shortness of breath on exercise and worsened lower limb oedema, and visited the outpatient department. Hypoxia was found and cardiomegaly and worsened ground-glass opacities mainly in the hilar area of the lung were found on radiography. Ground-glass opacities mainly in the lower lobe and interlobular septal thickening were found on CT. The patient was admitted to the hospital on the same day (body weight was 53 kg at the time of hospitalization). Although ground-glass opacities were found on CT, the patient had no cough and had a normal Krebs von den Lunge-6 level. Because generalised oedema, mild pericardial effusion, and increased BNP level were found, the patient was diagnosed with pulmonary oedema caused by pulmonary congestion. The administration of crizotinib was discontinued on the same day. The patient received diuresis-based treatment with furosemide, low-dose dopamine, etc. 3 days after discontinuation: Ground-glass opacities improved, and primary lesions and metastases to lymph nodes reduced on CT. 4 days after discontinuation: Body weight decreased to 47 kg. Generalised oedema and hypoxia improved.

				13 days after discontinuation: Hypoxia and generalized oedema almost disappeared. Because ground-glass opacities on CT remained, carperitide was administered for further diuresis, which was immediately discontinued because of decreased blood pressure. Oral diuretics were continued to be administered. Dopamine hydrochloride injection was administered (until 15 days after discontinuation). 20 days after discontinuation: No clearly worsened ground-glass opacities were found on CT. 24 days after discontinuation: The patient was discharged from the hospital. 36 days after discontinuation: Ground-glass opacities considered to be caused by pulmonary oedema further improved. 50 days after discontinuation: Pulmonary oedema was remitted. 64 days after discontinuation: Ground-glass opacities almost disappeared. A mild increasing trend of primary lesions was found.
	Concomitant medications: sertraline hydrochloride, rabeprazole sodium, precipitated calcium carbonate/cholecalciferol/magnesium carbonate, dexamethasone, mecobalamin, hydroxyzine hydrochloride, zopiclone, pregabalin, oxycodone hydrochloride hydrate, magnesium oxide, loxoprofen sodium hydrate, etizolam, and prochlorperazine maleate			

Laboratory examination

	2 days before administration	Day 7 of administration	Day 9 of administration	Day 28 of administration (day of discontinuation)	50 days after discontinuation
WBC (cells/mm^3)	7 170	8 350	7 470	6 720	3 720
Eos (%)	3.2	3.0	3.2	1.0	5.4
Neu (%)	57.0	63.1	61.3	73.5	55.6
Lym (%)	33.8	29.1	29.9	21.0	32.8
Mono (%)	5.4	4.8	5.5	4.5	5.4
BUN (mg/dL)	15.2	18.9	18.9	16.8	17.0
Cre (mg/dL)	0.65	0.79	0.72	0.71	0.76

2 Technetium (^{99m}Tc) hydroxymethylenediphosphonate injection, Kit for the preparation of technetium (^{99m}Tc) hydroxymethylenediphosphonate injection

Brand name (name of company)	a. Clearbone Injectable (Nihon Medi-Physics Co., Ltd.) b. Clearbone Kit (Nihon Medi-Physics Co., Ltd.)
Therapeutic category	Radioactive drugs
Indications	Diagnosis of bone diseases by scintigraphic imaging of the bone

PRECAUTIONS (underlined parts are revised)

Contraindications

Patients with a history of hypersensitivity to any ingredients of this product

Adverse reactions (clinically significant adverse reactions)

Shock and anaphylaxis: Shock and anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities such as dyspnoea, decreased blood pressure, or rash are observed, appropriate measures should be adopted.

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 (from April 2012 to March 2015)

Case of adverse events associated with shock or anaphylaxis
a. 1 case (no fatal case)
b. No case

The number of patients using these drugs estimated by MAH:
a. Approximately 157 000 (April 2014 to March 2015)
b. Approximately 38 000 (April 2014 to March 2015)

Launched in Japan:
a. February 1983
b. December 1986

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Metastases to bone (malignant lung neoplasm, benign prostatic hyperplasia, emphysema)	555 MBq for 1 day	**Anaphylactic reaction** The patient had a history of surgeries for gastric ulcer and intervertebral disc herniation. Before administration (measurement time unknown), the systolic blood pressure (SBP) was 157 mmHg, diastolic blood pressure (DBP) was 99 mmHg, and pulse rate was 86 beats per minute. Day 1 of administration (day of completion): The administration of this drug was started. 5 to 10 minutes after the end of administration: When the patient returned to the room, nausea and vomiting developed. Increased serous sputum and wheezing subsequently developed, and oxygen saturation (SpO_2) decreased. The administration of oxygen was started. In addition, because redness developed on the extensor surface of the extremities and on the trunk, the patient was diagnosed with anaphylaxis. Drip infusion of hydrocortisone sodium succinate was started. Redness decreased several tens of minutes after the start of the drip infusion. Wheezing also decreased and improved. Approximately 12 hours after the end of administration: SpO_2 became >90%. The administration of oxygen was

				discontinued. The patient recovered from anaphylactic reaction. After administration (measurement time unknown), the SBP was 203 mmHg, DBP was 116 mmHg, and pulse rate was 115 beats per minute.
	Concomitant medications: imidapril hydrochloride, tamsulosin hydrochloride, chlormadinone acetate, bethanechol chloride, ambroxol hydrochloride, and replacement fluid			

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Bone scintigrams (Rectal cancer, multiple metastases to liver, metastases to lung)	740 Mbq for 1 day	**Anaphylactoid reaction** The patient had a history of ovarian surgery. The patient had an ADR history of vomiting caused by fluorouracil and irinotecan hydrochloride. 36 days before administration: The administration of fluorouracil was started. 22 days before administration The administration of irinotecan hydrochloride was started. 2 days before administration: From the indwelling reservoir on the celiac artery, 1 g of fluorouracil was intra-arterially administered. Chemotherapy with intravenous drip infusion of 40 mg of irinotecan hydrochloride was performed. Nausea continued. Day 1 of administration (day of completion): This drug labeled with sodium pertechnetate (^{99m}Tc) injection (740 MBq, 1 mL) was intravenously administered. 3 minutes after the end of administration: The patient had vomiting. When the patient woke up to go to the toilet, she fell down on the bed and her eyeballs were raised upward. Redness appeared on the forearm. 5 minutes after the end of administration: Respiratory arrest was found. The patient lost consciousness. The pulse of the patient was non-palpable. 8 minutes after the end of administration: Artificial ventilation using an Ambu bag was performed. Adrenaline injection was administered. 13 minutes after the end of administration: The patient recovered consciousness. Methylprednisolone sodium succinate injection was intravenously administered. 23 minutes after the end of administration: Blood pressure was 50/unknown mmHg. A vasopressor was used. 73 minutes after the end of administration: Blood pressure was 115/56 mmHg. The event was remitted. The patient was hospitalized in the intensive care unit. 1 day after the end of administration: The patient was discharged from the hospital. (The patient recovered from anaphylactoid reaction.)
	Concomitant medications: sodium pertechnetate (^{99m}Tc) injection, fluorouracil, and irinotecan hydrochloride			

3

List of Products Subject to 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 ADR 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 ADR. EPPV is specified as a condition of approval.

(As of May 31, 2015)
◎: Products for which EPPV was initiated after May 1, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	trelagliptin succinate Zafatek Tablets 50 mg, 100 mg	Takeda Pharmaceutical Company Limited	May 28, 2015
◎	peginterferon alfa-2b (genetical recombination) Pegintron Powder for Injections 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL[*1]	MSD K.K.	May 26, 2015
◎	ramosetron hydrochloride a. Irribow Tablets 2.5 μg, 5 μg[*2] b. Irribow OD Tablets 2.5 μg, 5 μg[*2]	Astellas Pharma Inc.	May 26, 2015
◎	duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg[*3]	Shionogi & Co., Ltd.	May 26, 2015
◎	nalfurafine hydrochloride Nopicor Capsules 2.5 μg[*4]	Toray Medical Co., Ltd.	May 26, 2015
◎	aripiprazole hydrate Abilify Prolonged Release Aqueous Suspension for IM Injections 300 mg, 400 mg, Abilify Prolonged Release Aqueous Suspension for IM Injections 300 mg Syringe, 400 mg Syringe	Otsuka Pharmaceutical Co., Ltd.	May 25, 2015
◎	colistin sodium methanesulfonate Aldreb for Infusions 150 mg	GlaxoSmithKline K.K.	May 25, 2015
◎	a. sofosbuvir b. ribavirin a. Sovaldi Tablets 400 mg b. Copegus Tablets 200 mg[*5]	a. Gilead Sciences K.K. b. Chugai Pharmaceutical Co., Ltd.	May 25, 2015
◎	pomalidomide Pomalyst Capsules 1 mg, 2 mg, 3 mg, 4 mg	Celgene K.K.	May 21, 2015
◎	nalfurafine hydrochloride Remitch Capsules 2.5 μg	Toray Industries, Inc.	May 20, 2015
◎	lenvatinib mesilate Lenvima Capsules 4 mg, 10 mg	Eisai Co., Ltd	May 20, 2015
◎	aclidinium bromide	Kyorin	May 20, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
	Eklira 400 μg Genuair Inhalations 30 doses, 60 doses	Pharmaceutical Co., Ltd.	
◎	tetravalent meningococcal vaccine (diphtheria toxoid conjugate) Menactra Intramuscular Injections	Sanofi K.K.	May 18, 2015
◎	metronidazole Rozex Gel 0.75%	Galderma Pharma S.A.	May 11, 2015
	elosulfase alfa (genetical recombination) Vimizim Intravenous Infusions 5 mg	BioMarin Pharmaceutical Japan K.K.	April 23, 2015
	N/A Mite Allergen Extract Subcutaneous Injections for Treatment "Torii" 10,000 JAU/mL, 100 000 JAU/mL	Torii Pharmaceutical Co., Ltd.	April 21, 2015
	nitisinone Orfadin Capsules 2 mg, 5 mg, 10 mg	Astellas Pharma Inc.	April 14, 2015
	dolutegravir sodium/lamivudine/abacavir sulfate Triumeq Combination Tablets	ViiV Healthcare K.K.	April 10, 2015
	benzoyl peroxide Bepio Gel 2.5%	Maruho Co., Ltd.	April 1, 2015
	efraloctocog alfa (genetical recombination) Eloctate Intravenous 250, 500, 750, 1000, 1500, 2000, 3000	Biogen Idec Japan Ltd.	March 9, 2015
	secukinumab (genetical recombination) Cosentyx for S.C. Injection 150 mg Syringe, Cosentyx for S.C. Injection 150 mg	Novartis Pharma K.K.	February 27, 2015
	vonoprazan fumarate Takecab Tablets 10 mg, 20 mg	Takeda Pharmaceutical Company Limited	February 26, 2015
	vemurafenib Zelboraf Tablets 240 mg	Chugai Pharmaceutical Co., Ltd.	February 26, 2015
	rabeprazole sodium Pariet Tablets 5 mg, 10 mg*6	Eisai Co., Ltd.	February 26, 2015
	empagliflozin Jardiance Tablets 10 mg, 25 mg	Nippon Boehringer Ingelheim Co., Ltd.	February 24, 2015
	streptozocin Zanosar IV Infusion 1 g	Nobelpharma Co., Ltd.	February 23, 2015
	fexofenadine hydrochloride Allegra 5% Dry Syrup	Sanofi K.K.	January 19, 2015
	alemtuzumab (genetical recombination) MabCampath 30 mg I.V. Infusion	Sanofi K.K.	January 15, 2015
	sirolimus Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	December 22, 2014
	caspofungin acetate Cancidas for Intravenous Drip Infusion 50 mg, 70 mg*7	MSD K.K.	December 18, 2014

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
darbepoetin alfa (genetical recombination) Nesp Injection 5 μg Plastic Syringe, 10 μg Plastic Syringe, 15 μg Plastic Syringe, 20 μg Plastic Syringe, 30 μg Plastic Syringe, 40 μg Plastic Syringe, 60 μg Plastic Syringe, 120 μg Plastic Syringe, 180 μg Plastic Syringe*8	Kyowa Hakko Kirin Co., Ltd.	December 18, 2014
midazolam Midafresa Injection 0.1%	Alfresa Pharma Corporation	December 17, 2014
rilpivirine hydrochloride/tenofovir disoproxil fumarate/emtricitabine Complera Combination Tablets	Janssen Pharmaceutical K.K.	December 12, 2014
bosutinib hydrate Bosulif Tablets 100 mg	Pfizer Japan Inc.	December 5, 2014
progesterone Lutinus Vaginal Tablets 100 mg	Ferring Pharmaceuticals Co., Ltd.	December 5, 2014
ripasudil hydrochloride hydrate Glanatec Ophthalmic Solution 0.4%	Kowa Company, Ltd.	December 2, 2014
anhydrous caffeine Respia Injection or oral solution 60 mg	Nobelpharma Co., Ltd.	December 1, 2014
edoxaban tosilate hydrate Lixiana Tablets 15 mg, 30 mg, 60 mg*9	Daiichi Sankyo Company, Limited	September 26, 2014

*1 Postoperative adjuvant therapy for malignant melanoma

*2 Diarrhea-predominant irritable bowel syndrome in females

*3 Pain associated with fibromyalgia

*4 Improvement of pruritus in patients with chronic liver disease

*5 Improvement of viremia in patients with serogroup 2 chronic hepatitis C or compensated cirrhosis type C in combination therapy with sofosbuvir

*6 An additional indication for “the treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low doses of aspirin”

*7 An additional administration for “pediatrics”

*8 An additional indication for “the treatment of patients with anaemia associated with myelodysplastic syndrome”

*9 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),” EPPV was initiated in December 8, 2014 for Lixiana 60 mg tablets.