Pharmaceuticals and Medical Devices Safety Information

No. 334 June 2016

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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.

Medi-navi is an email service that provides essential safety information released by the MHLW and PMDA. By registering, you can receive this information on the day of release.

Register here

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Pharmaceuticals and Medical Devices Safety Information

No. 334 June 2016

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

[Outline of Information]

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
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
D-Bil	Direct bilirubin
DM	Direct mail
DNA	Deoxyribonucleic acid
DSU	Drug Safety Update
DVT	Deep vein thrombosis
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
γ-GTP	Gamma-glutamyl transpeptidase
HBc	Hepatitis B core
HBe	Hepatitis B e
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBs	Hepatitis B surface
HBV	Hepatitis B virus
HCV	Hepatitis C virus
INR	International normalized ratio
LDH	Lactate dehydrogenase
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MR	Medical representative
MS	Marketing specialist
PE	Pulmonary embolism
PSEHB/ELD	Pharmaceutical Safety and Environmental Health Bureau / Evaluation and Licensing Division
PFSB/SD	Pharmaceutical and Food Safety Bureau / Safety Division
PLT	Platelets
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PT	Prothrombin/prothrombin time
RMP	Risk Management Plan
RNA	Ribonucleic acid
S/CO	Signal to cutoff ratio
T-Bil	Total bilirubin
TP	Total protein

1

Risk Management Plan Outline Sheets

1. Introduction

The RMP system was implemented in April 2013. On March 31, 2016, to deepen understanding of the Risk Management Plan (RMP) system in clinical practice and help to promote its use, we published “Creation and Publication of RMP Outline Sheets.”

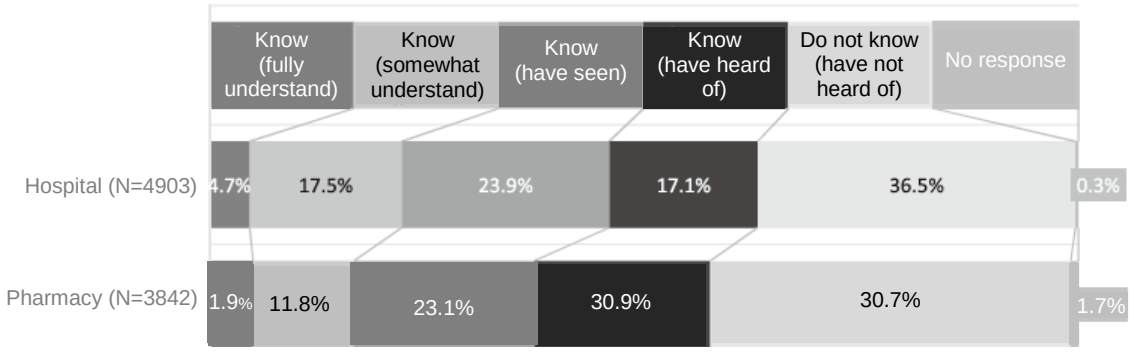
This section discusses the current state of awareness and utilization of the RMP system, and describes the work of creating an RMP Outline Sheet.

2. Awareness and utilization of RMPs

As of June 1, 2016, more than 200 RMPs are published on the Pharmaceuticals and Medical Devices Agency (PMDA) website, and it is expected that RMPs will be used in clinical practice.

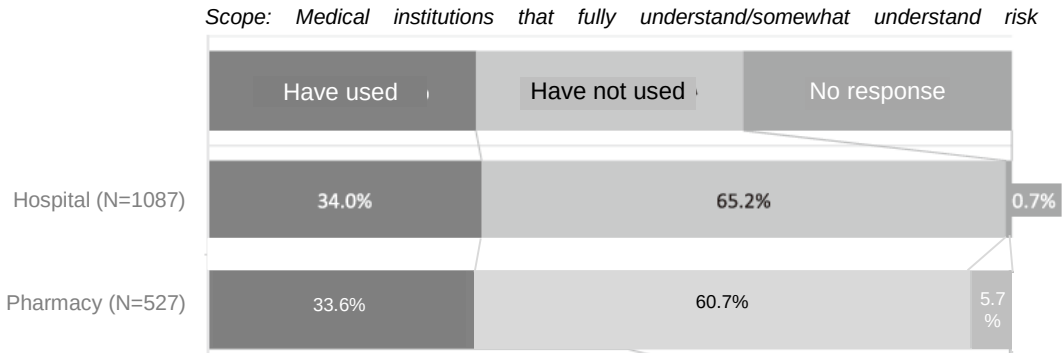
On the other hand, there is certainly not a high level of awareness and understanding of RMPs in clinical practice. In the “Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Medical Institutions” [Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 325], conducted in fiscal years (FY) 2014 and 2015, the percentage of hospitals and pharmacies stating they “fully understand” or “somewhat understand” the contents of RMPs was 4.7% and 17.5% respectively for the hospitals, and 1.9% and 11.8% respectively for the pharmacies, which was not a relatively high level (Figure 1).

Figure 1: Awareness of RMP



Even when the RMP system was known, the percentage of institutions utilizing it was not very high, approximately 30%. (Figure 2).

Figure 2: Utilization of RMP



Considering the situation described, we have published a notification on RMP Outline Sheets to assist in the creation and use of RMP Outline Sheets, with the goal of increasing the utilization of RMPs and making them more useful.

3. RMP Outline Sheets

(1) Summary of notification

The notification sets down 3 rules: (1) the format of RMP Outline Sheets (Format 1, attached), (2) the method for submitting RMP Outline sheets, and (3) the effective date (May 9, 2016)

(2) Format of RMP Outline Sheets

The aim of the notification of RMP Outline Sheets is to promote the utilization of RMPs, which may consist of tens of pages. To assist this, we have collected the items and activities covered by RMPs on 1 page.

A published RMP is composed of the following 5 main items

1. Safety specifications and efficacy considerations
2. Outline of the pharmacovigilance plan
3. Outline of the efficacy surveillance and study plan
4. Outline of the risk minimization plan
5. List of the pharmacovigilance plan, efficacy surveillance and study plan, and risk minimization plan

The RMP Outline Sheets show the items listed from 1 to 4 above, as well as names of activities, together with the corresponding pages, on one page. The design is such that when viewing an RMP using an electronic terminal, there are links to each of the items and activities so that you can jump to the main text by clicking the relevant location.

(3) Publication on the PMDA website

RMPs are published on the PMDA website. The latest materials can be obtained from the following URL. Outline Sheets are currently attached to part of RMPs published and will be attached all the published RMPs within one year of the enforcement date of the notification.
http://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html

(*) To access from the PMDA top page

Click for Healthcare professionals, RMP, and List of RMP-submitted products

4. Closing comments

RMPs contribute to enhancing drug safety measures. To further increase the utilization of RMPs in clinical practice, the creation of RMP Outline Sheets have been decided upon, through a process of finding out about the actual state of clinical practice and considering better ways of providing RMPs, and with the cooperation of healthcare professionals. We plan to continue to consider how to make RMPs better in the future, including the active use of materials for proper use of drugs prepared by pharmaceutical companies based on RMP.

We ask for all healthcare professionals to utilize RMP Outline Sheets, and for your understanding and further cooperation with planned surveillance and clinical studies relating to RMPs.

5. References

1. RMP, PMDSI (No. 324, issued in July 2015)
2. Publication of the RMP [Joint Pharmaceutical and Food Safety Bureau (PFSB)/ Evaluation and Licensing Division (ELD) Notification No. 0304-1 and PFSB/ Safety Division (SD) Notification No. 0304-1, by the Director of SD and the Director of ELD, PFSB, Ministry of Health, Labour and Welfare (MHLW), dated March 4, 2013) (Only available in Japanese language)
3. Creation and Publication of RMP Outline Sheets [Joint Pharmaceutical Safety and Environmental Health Bureau (PSEHB)/SD Notification No. 0331-13 and PSEHB/ELD Notification No. 0331-13, by the Director of SD and the Director of ELD, PSEHB, MHLW, dated March 31, 2016]
4. List of RMP-submitted Products (PMDA website) (Only available in Japanese language) http://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html
5. Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Hospitals in FY 2014 https://www.pmda.go.jp/files/000205744.pdf (Only available in Japanese language)
6. Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Pharmacies in FY 2015 https://www.pmda.go.jp/files/000211645.pdf (Only available in Japanese language)

Format 1: Format of RMP Outline Sheet

RMP Outline Sheet
Relating to xxxxxx (Brand Name)

Brand name	Xxxxxx	**Active ingredient**	Xxxxxx
MAH	xxxxxx K.K.	**Drug class**	Xxxxxx
Date submitted		MM DD YY	

1.1. Safety Specification					
Important identified risks	**Page**	**Important potential risks**	**Page**	**Important missing information**	**Page**
(name of important identified risk)	**X**	(name of important potential risk)	**x**	(name of important missing information)	**X**
1.2. Efficacy considerations					
(name of efficacy considerations)	**Page x**				**Page x**

↓Pharmacovigilance activities based on the above

2. Outline of Pharmacovigilance Plan	**Page**
Normal pharmacovigilance activities	X
Additional pharmacovigilance activities	
(name of pharmacovigilance activity)	X
3. Outline of Plan for Efficacy Studies and Surveillance	**Plan**
(name of efficacy study/surveillance)	x

↓Risk minimization activities based on the above

4. Outline of Risk Minimization Plan	**Page**
Normal risk minimization activities	x
Additional risk minimization activities	
(name of risk minimization activity)	x

2

Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Clinics and Pharmacies

1. Introduction

In order to ensure proper use of drugs and medical devices, the MHLW and PMDA have been jointly conducting safety measures such as revisions of the Precautions section of package inserts based on evidence including case reports of adverse reactions. Safety information on these measures is being provided by the MHLW, PMDA, and pharmaceutical companies to medical institutions via various routes. It is essential that the latest information available be disseminated to and utilized by healthcare professionals at clinical settings in an appropriate manner.

Based on the Second and Third Mid-term Plans, PMDA has been conducting surveillance to understand the status of the access to, dissemination, and utilization of safety information at medical institutions and to determine appropriate methods for utilization of such information by these institutions so that follow-up of regulatory safety measures can be consolidated and enhanced. From these surveillance results, PMDA aims to summarize information on desirable directions for healthcare professionals to receive, distribute, and utilize safety information, thereby promoting safe use of drugs in the clinical setting.

This section presents the results of the surveillance conducted by PMDA in FY 2015 and methods for using safety information summarized from these results.

2. Surveillance in FY 2015 (Clinic Surveillance and Pharmacy Surveillance)

(1) Methods

The surveillance was conducted from October 6, 2015 to December 14, 2015 and targeted 10% of general clinics nationwide providing insurance-based healthcare (a total of 8 737 facilities) and 10% of all health insurance pharmacies (a total of 5 664 facilities). Surveillance of hospitals was conducted in FY 2014, and the results have been presented in PMDSI No. 325 (issued in August 2015).

In the surveillance of clinics (clinic surveillance), the questionnaire was mailed out to the directors of the target clinics and it was requested that the clinic director or the person collecting drug information answer the questions, and in the surveillance of pharmacies (pharmacy surveillance), the questionnaire was mailed out to the supervising pharmacists, and it was requested that the supervising pharmacist or the pharmacists responsible for drug information management answer the questions. Responses were generally submitted through an online questionnaire, but respondents could choose to mail back their answers on the paper-based questionnaire.

The main topics of the surveillance are listed in Table 1 and include questions regarding handling of pharmaceutical safety information.

Furthermore, the surveillance was conducted and the results evaluated based on the recommendations of the “Review Committee on the Status of Access to, Dissemination, and Utilization of Safety Information on Drugs in Medical Institutions” (hereinafter referred to as “the Committee”) consisting of experts on physician’s and pharmaceutical practices and drug information established in PMDA.

Table 1. Main Surveillance Topics

Clinic surveillance

- Basic information about the facility
- Sources of information used when accessing drug safety information, status of dissemination of such safety information within the clinic
- Status of internet and PMDA website usage, registration status for PMDA Medi-navi, etc.
- Cooperation with other institutions, how and what kind of patient information is shared, etc.
- Awareness of the Drugs and Medical Devices Safety Information Reporting System and the Relief System for Sufferers from Adverse Drug Reactions (ADRs), etc.

Pharmacy surveillance

- Basic information about the facility
- Sources of information used when accessing drug safety information, status of dissemination of such safety information within the pharmacy (including actual case studies)
- Awareness and utilization status of the RMP, patient-targeted pharmaceutical guides, and Manuals for Management of Individual Serious ADRs
- Status of internet and PMDA website usage, registration status for PMDA Medi-navi, etc.
- Cooperation with other institutions, how patient information is shared, etc. (including actual case studies)
- Status of giving information to patients about the PMDA website and awareness of the Drugs and Medical Devices Safety Information Reporting System and the Relief System for Sufferers from ADRs, etc.

(2) Surveillance results

Answers for the clinic surveillance were obtained from 4 611 clinics (53.1%) and answers for the pharmacy surveillance were obtained from 3 842 pharmacies (68.2%).

An overview of these facilities is shown in Figures 1 and 2.

Figure 1: Total Outpatient Prescriptions (Clinics)

* Status as of September 2015; totals for in-clinic and out-of-clinic prescriptions

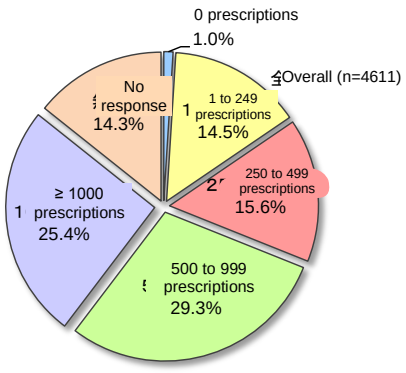
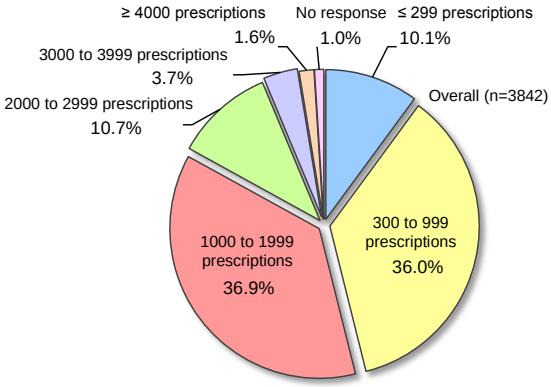


Figure 2: Total On-demand Prescriptions (Pharmacies)

* Status as of September 2015 or the past month at the time of the response



The surveillance results have been summarized by the items listed in Table 2, based on opinions from the Committee.

Table 2. Summary of the surveillance results

Clinic surveillance • Usage of the PMDA website and PMDA Medi-navi • Prompt and comprehensive access to important information • Accessing information by taking the characteristics of the information source into consideration • Communicating information as appropriate for the actual situation at the facility • Sharing patient information between clinics and pharmacies
Pharmacy surveillance • Organizational response for access to information • Collecting information using the internet • Usage of the PMDA website and PMDA Medi-navi • Prompt and comprehensive access to and management of important information • Accessing appropriate information at appropriate times, taking the characteristics of the information source into consideration • Communicating information as appropriate for the actual situation at the facility • Sharing patient information between medical institutions and pharmacies • Promoting utilization of risk communication tools such as RMPs, patient-targeted pharmaceutical guides, and Manuals for Management of Individual Serious ADRs

Of these, details for the following will be provided in this text: "Usage of the PMDA website and PMDA Medi-navi," "Prompt and comprehensive access to and management of important information," "Accessing appropriate information at appropriate times, taking the characteristics of the information source into consideration," "Promoting utilization of risk communication tools," and "Cooperation with other facilities such as sharing of patient information."

1) Usage of the PMDA website and PMDA Medi-navi

Surveillance results

PMDA sends out the latest safety information using its website and PMDA Medi-navi. The frequency with which the PMDA website is used during daily work at clinics was "frequently" at 2.4% of facilities, "sometimes" at 14.1% of facilities, and "not used" at 54.6% of facilities. At pharmacies, the frequency was "frequently" at 11.5% of facilities, "sometimes" at 32.9% of facilities, and "not used" at 21.0% of facilities (Figure 3).

The percentages of facilities with someone at the facility registered with PMDA Medi-navi were 12.8% for clinics and 44.1% for pharmacies (Figure 4). Considering the sources of information used for obtaining safety information, broken down by whether or not PMDA Medi-navi was available, showed that of the facilities registered with PMDA Medi-navi, the percentages of clinics and pharmacies listing PMDA Medi-navi as a useful source of information were only 32.9% and 36.9% respectively, and thus it was found that PMDA Medi-navi, which is the fastest information tool, is not being fully utilized (Report on Clinic Surveillance Results, p. 11, Report on Pharmacy Surveillance Results, p. 14).

Figure 3. Status of Usage of PMDA Website

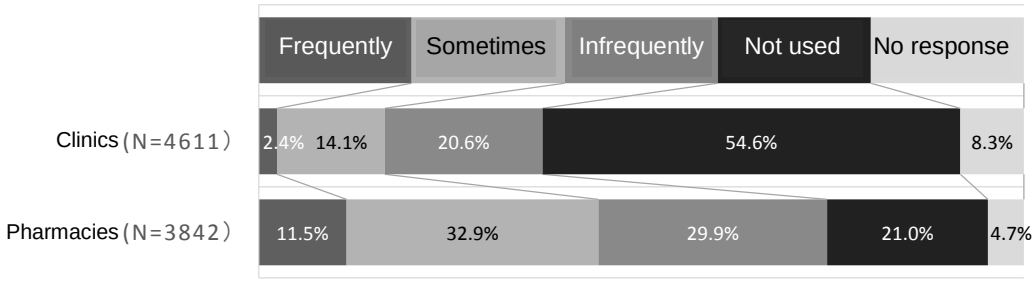
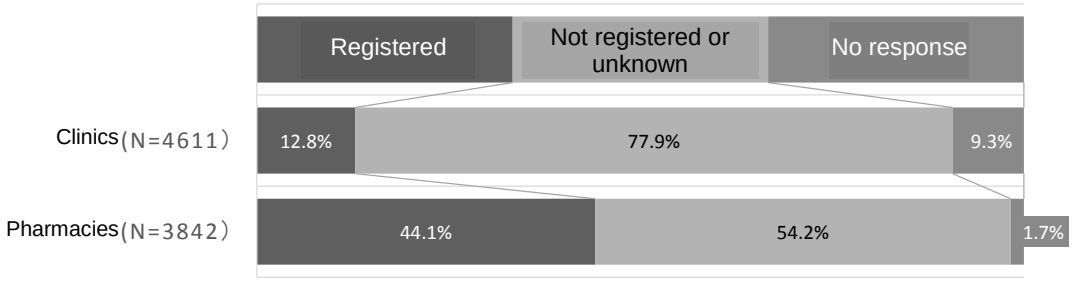


Figure 4. Status of Registration with PMDA Medi-navi



Summary

Drug safety information is updated daily, with at least 100 revisions to the Precautions sections of package inserts by MHLW every year, and also announcements on proper use by PMDA, pharmaceutical companies, relevant societies, and the like, and thus in drug safety management work it is important to have constant access to the latest information.

The PMDA website contains a comprehensive range of important safety information such as the above-stated updates and announcements, and the listing of drug package inserts on this site is a legal obligation. PMDA Medi-navi is a useful tool that provides prompt notification when updates are made to important safety information, from among the vast amount of information listed on the PMDA website, and is also a necessary tool, with registration for PMDA Medi-navi being one of the criteria for additional dispensing fees for standard operation in the FY 2016 revision of the reimbursement of medical fees. It is desirable that the PMDA website and PMDA Medi-navi are utilized effectively in drug safety management work.

An opinion expressed by the Committee was that the PMDA website and PMDA Medi-navi are not fully utilized is due to usability issues, and therefore PMDA will cooperate with various professional organizations to promote the utilization of these tools by increasing awareness of them and spreading knowledge about the methods for utilizing them, and will make them easier to use based on the needs in clinical practice.

2) Prompt and comprehensive access to and management of important information

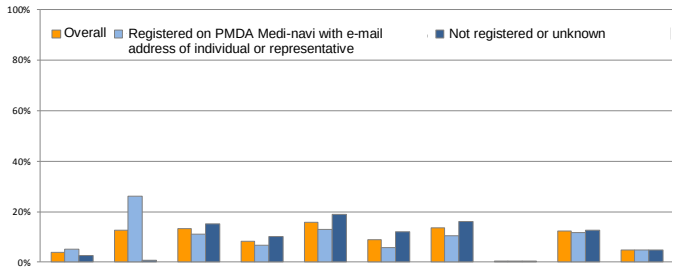
Surveillance results

A pharmacy may be required to have information on all drugs, even those not handled at that pharmacy, for example when consulted by a patient being dispensed drugs by multiple pharmacies. Given this, it is necessary for a pharmacy to access and continuously manage information, including information on drugs not handled at that pharmacy. Investigation of awareness of the contents of the precautions in the Blue Letter for Lamictal Tablets (issued on February 4, 2015) found that only 80.7% of all pharmacies were aware of the precautions, and 17.8% of pharmacies were not aware of this information (Report on Pharmacy Surveillance Results, p. 15).

In addition, even in cases where there was awareness of the information, the Drug Safety Update (DSU), issued about 1 month after the issue of the Blue Letter, and the PMDSI, issued about 2 months after the Blue Letter were listed as the fastest source of information by 8.4% and 13.2% of pharmacies, respectively, and thus it was found that information is not being collected promptly (Figure 5).

Figure 5. Fastest Sources of Information when the Blue Letter for Lamictal Tablets was

Issued [Pharmacies]
* Only some of the options provided are shown



	Number surveyed	PMDA website	PMDA Medi-navi	PMDSI (issued by MHLW)	DSU (issued by the Federation of Pharmaceutical Manufacturers' Associations of Japan)	MRs of pharmaceutical companies	MSs of pharmaceutical companies	DM from pharmaceutical companies	Pharmaceutical company websites	Information from professional organizations (such as the Japan Pharmaceutical Association, or local pharmaceutical associations)	Communications (such as e-mail) from management departments outside the pharmacy (such as the head office, when in chain main format)
Overall	3102	3.8	12.8	13.2	8.4	15.9	9.0	13.5	0.2	12.3	4.8
Registered on PMDA Medi-navi with e-mail address of individual or representative	1486	5.0	26.0	11.2	6.6	13.0	5.7	10.6	0.2	11.6	4.9
Not registered or unknown	1581	2.6	0.6	15.1	10.1	18.8	12.1	16.2	0.2	12.8	4.7

Summary

To provide safe healthcare to patients, it is important to have prompt and definite access to safety information in medical practice, and utilize this information appropriately. In order to fulfill the functions required of family pharmacists and pharmacies, such as following up on ADRs, it is desirable for healthcare professionals to access at least the important safety information about all drugs, not only drugs handled by their own facilities, such as Yellow Letters, Blue Letters, and notifications on proper use, and continuously manage this information.

Clinics may also be visited by patients making visits to another department or medical institution who have signs of ADRs due to a drug not normally handled by the clinic. Therefore, to enable early detection of ADRs, it is desirable for clinics to have prompt and comprehensive access to important information.

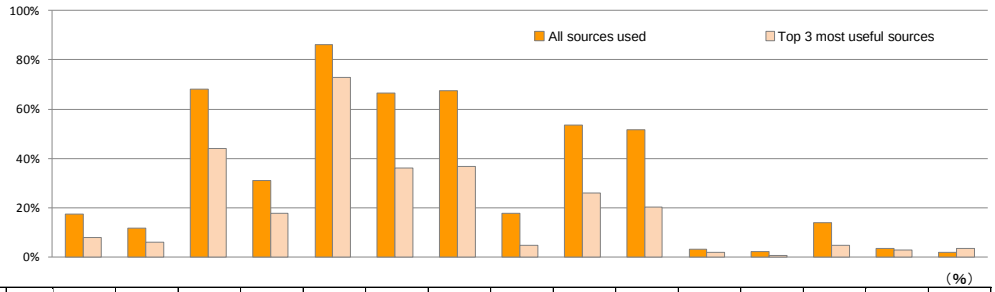
3) Accessing appropriate information at appropriate times, taking the characteristics of the information source into consideration

Surveillance results

Investigation of what sources of drug safety information were used found that at clinics, the most frequent sources of information used to obtain safety information were MRs (i.e. pharmaceutical company employees in charge of drug information) (86.3%), PMDSI (this bulletin) (68.0%), direct mail (DM) from pharmaceutical companies (67.4%), and MSs (i.e. drug wholesalers) (66.5%), and the percentages of facilities listing the PMDA website and PMDA Medi-navi were 17.2% and 11.6% respectively. The sources of information most frequently listed as useful were MRs (73.0%), PMDSI (43.9%), DM (36.7%), and MSs (36.1%), and the percentages of facilities listing the PMDA website and PMDA Medi-navi were 7.7% and 5.9% respectively (Figure 6).

At pharmacies, the most frequent sources of information used to obtain safety information were MRs (87.9%), MSs (82.1%), DM (77.0%), PMDSI (76.0%), and DSU (73.5%), and the percentages of facilities listing the PMDA website and PMDA Medi-navi were 49.0% and 41.3% respectively. The sources of information most frequently listed as useful were MRs (54.2%), MSs (39.8%), DSU (38.6%), DM (34.2%), and PMDSI (30.7%), and the percentages of facilities listing the PMDA website and PMDA Medi-navi were 22.1% and 18.5% respectively (Figure 7).

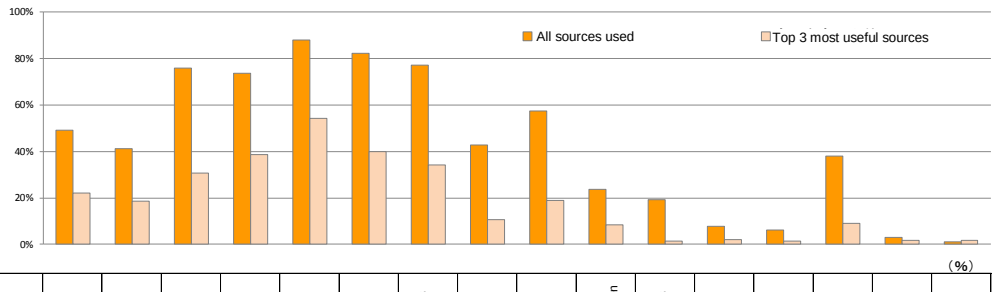
Figure 6. Sources of Information Used to Access Safety Information (Updated Information such as Precautions) [Clinics]



(%)

	Number surveyed	PMDA website	PMDA Medi-navi	PMDSI (issued by MHLW)	DSU (issued by the Federation of Pharmaceutical Manufacturers' Associations of Japan)	MRs of pharmaceutical companies	MSs of pharmaceutical companies	DM from pharmaceutical companies	Pharmaceutical company websites	Information from professional organizations (such as the Japan Medical Association or local medical associations)	Information from academic societies	Websites besides PMDA and pharmaceutical company websites	Mail services besides PMDA Medi-navi	Use of added-value functions of electronic medical record software	Others	No response
All sources used	4611	17.2	11.6	68.0	31.0	86.3	66.5	67.4	17.7	53.5	51.5	3.2	2.0	13.9	3.3	1.7
Top 3 most useful sources	4611	7.7	5.9	43.9	17.8	73.0	36.1	36.7	4.5	25.8	20.1	1.7	0.6	4.8	2.6	3.4

Figure 7. Sources of Information Used to Access Safety Information (Updated Information such as Precautions) [Pharmacies]



(%)

	Number surveyed	PMDA website	PMDA Medi-navi	PMDSI (issued by MHLW)	DSU (issued by the Federation of Pharmaceutical Manufacturers' Associations of Japan)	MRs of pharmaceutical companies	MSs of pharmaceutical companies	DM from pharmaceutical companies	Pharmaceutical company websites	Information from professional organizations (such as the Japan Pharmaceutical Association, or local pharmaceutical associations)	Communications (such as e-mail) from management departments outside the pharmacy (such as the head office, when in chain main format)	Information from academic societies	Websites besides PMDA and pharmaceutical company websites	Mail services besides PMDA Medi-navi	Use of added-value functions of electronic medical record software	Others	No response
All sources used	3842	49.0	41.3	76.0	73.5	87.9	82.1	77.0	42.9	57.4	23.6	19.2	7.9	6.2	37.9	3.1	1.0
Top 3 most useful sources	3842	22.1	18.5	30.7	38.6	54.2	39.8	34.2	10.6	18.9	8.4	1.4	2.0	1.5	9.1	1.8	1.6

Summary

Each type of source has unique characteristics associated to speed, volume, content and whether or not it is interactive.

To access important information promptly and without omissions, it is important to register with PMDA Medi-navi and utilize the PMDA website, and in addition, it is desirable to take the characteristics of each information source into consideration, to access appropriate information at appropriate times, for example:

- PMDSI, which provides detailed information including case summaries a certain period after the information is issued
- DSU, which are lacking in speed, but provide comprehensive information including voluntary revisions of precautions by pharmaceutical companies

- MRs and MSs, who may make visits at varying frequencies and provide information with varying speeds, depending on the facility, but provide necessary information for the facility through interactive communication.

4) Promoting utilization of risk communication tools

Surveillance results

PMDA provides risk communication tools including RMPs, patient-targeted pharmaceutical guides, and Manuals for Management of Individual Serious ADRs on its website. The percentages of pharmacies stating that they "fully understand" or "somewhat understand" the content of RMPs, patient-targeted pharmaceutical guides, and Manuals for Management of Individual Serious ADRs were 1.9% and 11.8% respectively for RMPs, 3.5% and 14.0% respectively for patient-targeted pharmaceutical guides, and 6.1% and 18.8% respectively for Manuals for Management of Individual Serious ADRs, and thus awareness tended to be lower than that for the results of hospital surveillance conducted in FY 2014 (Figure 8).

Furthermore, of the facilities that stated that they "fully understand" or "somewhat understand" the contents of these risk communication tools, the percentages of institutions that stated they "have used such tools in daily operations" are as follows: 33.6% for RMPs, 56.7% for patient-targeted pharmaceutical guides, and 49.8% for Manuals for Management of Individual Serious ADRs (Figure 9).

Figure 8. Awareness of Risk Communication Tools [Pharmacies]

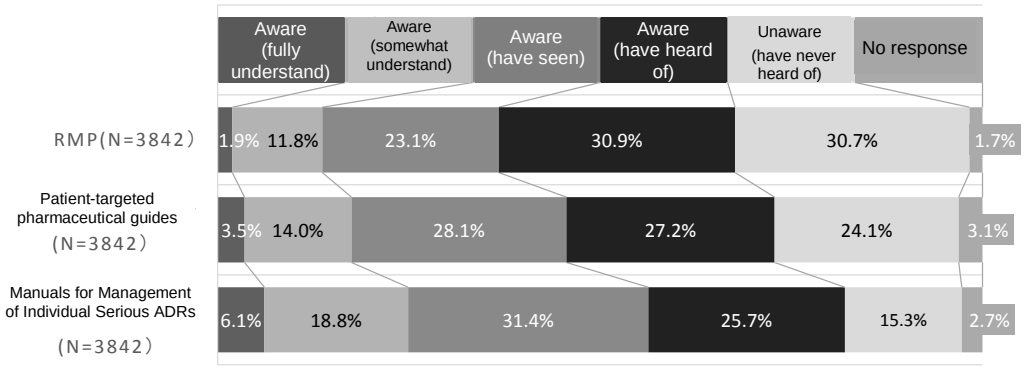
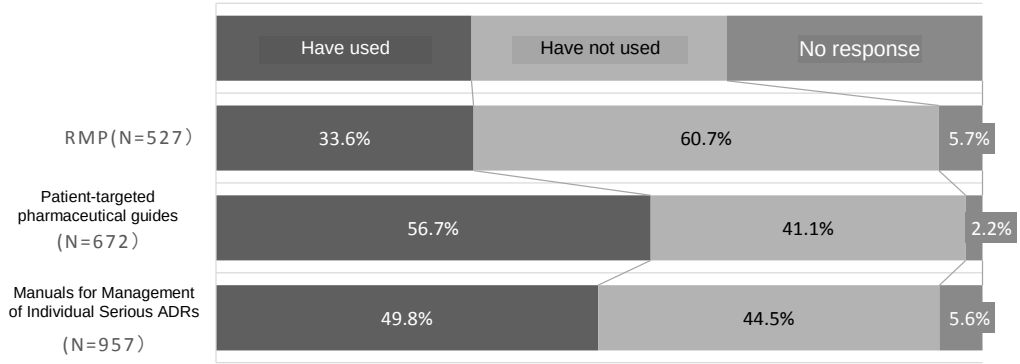


Figure 9. Utilization of Risk Communication Tools

Scope: Pharmacies that fully understand/somewhat understand risk communication tools



Summary

RMPs, patient-targeted pharmaceutical guides, and Manuals for Management of Individual Serious ADRs are beneficial risk communication tools, and it is desirable that the usage of these tools becomes more widespread.

Moreover, with the cooperation of relevant parties, PMDA aims to improve these risk communication tools so that they are easier to use in clinical practice and to make their content and the methods for using them more well-known.

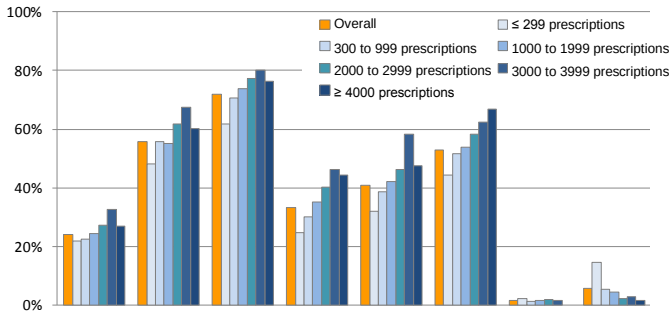
5) Cooperation with other facilities such as sharing of patient information

Surveillance results

In response to the question about the sharing of information between medical institutions and pharmacies, many pharmacies stated that the information they feel cannot be fully obtained during checking of prescriptions was “disease names etc.” (71.8%) and “test results such as laboratory test values” (55.8%), and there was the trend that the higher the number of on-demand prescriptions, the greater the percentage of pharmacies that feel they cannot obtain sufficient information (Figure 10).

Some clinics provided pharmacies with patient information such as disease names or test results such as laboratory test values regardless of whether there were inquiries, including “printing / notes on prescriptions” (5.9% and 1.2% respectively), “use of information liaison on proper use of drugs” (4.3%, 2.1%), “printing / notes on medication record books” (3.1%, 2.4%), “systems employed by local networks or the like” (0.8%, 0.5%), and “meetings and other consultations” (7.6%, 3.3%) (Figure 11).

Figure 10. Information Felt not to be Obtained Sufficiently During Checking of Prescriptions [Pharmacies]

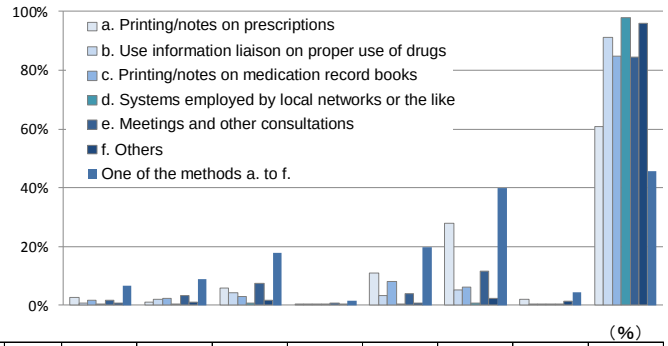


（%）

(By number of on-demand prescriptions)	Number surveyed	Height, weight, body surface area, etc.	Test results such as laboratory test values	Disease names, etc.	Anticancer treatment plans (regimens) etc.	Inpatient drug therapy and history of ADRs	Physician's findings and considerations	Others	No response
Overall	3842	23.9	55.8	71.8	33.2	40.9	52.8	1.5	5.6
≤ 299 prescriptions	387	21.7	48.1	61.8	24.5	31.8	44.4	2.1	14.5
300 to 999 prescriptions	1385	22.5	55.8	70.7	30.0	38.6	51.5	1.2	5.3
1000 to 1999 prescriptions	1418	24.3	55.1	73.8	35.0	42.2	53.9	1.4	4.2
2000 to 2999 prescriptions	411	27.3	61.8	77.4	40.1	46.2	58.2	1.7	2.2
3000 to 3999 prescriptions	141	32.6	67.4	80.1	46.1	58.2	62.4	1.4	2.8
≥ 4000 prescriptions	63	27.0	60.3	76.2	44.4	47.6	66.7	0.0	1.6

Figure 11. Contents of Patient Information Provided by Clinics to Pharmacists and Methods for Providing Information [Clinics]

Scope: Clinics issuing prescriptions to external pharmacies



(%)

	Number surveyed	Height, weight, body surface area, etc.	Test results such as laboratory test values	Disease names, etc.	Anticancer treatment plans (regimens) etc.	Records of administration guidance	Other comments (such as physician's findings and considerations)	Others	No response
a. Printing/notes on prescriptions	3821	2.6	1.2	5.9	0.2	11.0	27.9	2.1	60.8
b. Use information liaison on proper use of drugs	3821	0.8	2.1	4.3	0.3	3.2	5.2	0.4	91.0
c. Printing/notes on medication record books	3821	1.7	2.4	3.1	0.1	8.0	6.2	0.4	84.7
d. Systems employed by local networks or the like	3821	0.3	0.5	0.8	0.1	0.4	0.9	0.3	97.9
e. Meetings and other consultations	3821	1.7	3.3	7.6	0.8	4.0	11.6	0.6	84.6
f. Others	3821	0.8	1.0	1.6	0.3	0.9	2.3	1.3	96.0
One of the methods a. to f.	3821	6.8	8.9	17.9	1.7	19.7	39.8	4.3	45.5

Summary

Sharing patient information that is useful for tasks such as checking the contents of prescriptions, with the consent of patients, is expected to be one way to advance cooperation between medical institutions and pharmacies so that proper pharmacological management and guidance can be given by the family pharmacist, as pointed out in "Vision of Pharmacies for Patients*."

*: "Vision of Community Pharmacies for Patients" (MHLW, November 23, 2015)

3. Conclusion

Appropriate access, dissemination, and utilization of the latest drug safety information in clinical practice are important to ensure proper use of drugs. In addition to using PMDA Medi-navi, taking advantage of the characteristics of each information source when collecting information allows for more definite and prompt access to safety information. Please register with PMDA Medi-navi on its exclusive page to utilize it.

[PMDA Medi-navi]
http://www.pmda.go.jp/safety/info-services/medi-navi/0007.html (Only available in the Japanese language)

Additionally, the risk communication tools mentioned during this surveillance are available on the following pages of the PMDA website. These tools are provided to aid your institution in safety management for pharmaceuticals when adopting drugs into the hospital formulary, providing administration guidance to patients, early detection of adverse reactions and prevent these reactions from becoming severe, etc.

[RMPs]
http://www.pmda.go.jp/english/safety/info-services/drugs/0001.html
[Patient-targeted Pharmaceutical Guides]
http://www.pmda.go.jp/safety/info-services/drugs/items-information/guide-for-

patients/0001.html (Only available in the Japanese language)
[Manuals for Management of Individual Serious ADRs (for healthcare professionals)]
http://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html (Only available in the Japanese language)

The section above provides only a portion of the results of the surveillance conducted in FY 2015. The outline and detailed report of the surveillance results are posted on the following pages of PMDA website. (Only available in the Japanese language)

[Outline of the Surveillance on Dissemination and Utilization of Safety Information in Medical Institutions]
http://www.pmda.go.jp/safety/surveillance-analysis/0010.html

Clinic Surveillance:	Main Points of Surveillance Results: http://www.pmda.go.jp/files/000211636.pdf Report on Surveillance Results: http://www.pmda.go.jp/files/000211637.pdf All Results: http://www.pmda.go.jp/files/000211638.pdf
Pharmacy Surveillance:	Main Points of Surveillance Results: http://www.pmda.go.jp/files/000211644.pdf Report on Surveillance Results: http://www.pmda.go.jp/files/000211645.pdf All Results: http://www.pmda.go.jp/files/000211641.pdf

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated May 18 and 31, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 (1) Telaprevir, (2) Simeprevir Sodium, (3) Daclatasvir Hydrochloride, (4) Asunaprevir, (5) Vaniprevir, (6) Sofosbuvir, (7) Ledipasvir Acetonate / Sofosbuvir, (8) Ombitasvir Hydrate / Paritaprevir Hydrate / Ritonavir

Brand name (name of company)	(1) Telavic Tablets 250 mg (Mitsubishi Tanabe Pharma Corporation) (2) Sovriad Capsules 100 mg (Janssen Pharmaceutical K.K.) (3) Daklinza Tablets 60 mg (Bristol-Myers K.K.) (4) Sunvepra Capsules 100 mg (Bristol-Myers K.K.) (5) Vanihep Capsules 150 mg (MSD K.K.) (6) Sovaldi Tablets 400 mg (Gilead Sciences K.K.) (7) Harvoni Combination Tablets (Gilead Sciences K.K.) (8) Viekirax Combination Tablets (AbbVie G.K.)
Therapeutic category	Antivirals
Indications	(1) 1. Improvement of viremia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection) (1) Treatment-naïve patients with high blood HCV RNA load (2) Patients who have failed to respond to, or have relapsed after, therapy including interferon 2. Improvement of viremia in patients with serogroup 2 (genotype III [2a] or IV [2b]) chronic hepatitis C virus infection who have failed to respond to, or have relapsed after, interferon monotherapy or interferon and ribavirin combination therapy (2) and (5) Improvement of viremia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection (1) Treatment-naïve patients with high blood HCV RNA load (2) Patients who have failed to respond to, or have relapsed after, therapy including interferon (3), (4), (7), and (8) Improvement of viremia in patients with serogroup 1 (genotype 1) chronic hepatitis C virus infection or compensated cirrhosis type C (6) Improvement of viremia in patients with serogroup 2 (genotype 2) chronic hepatitis C virus infection or compensated cirrhosis type C

PRECAUTIONS (underlined parts are revised)

Careful administration	**<u>Patients currently infected with hepatitis B virus or patients with a history of hepatitis B virus infection</u>**

Important precautions

Reactivation of hepatitis B virus has been reported in association with decrease in hepatitis C viral load after initiating treatment with hepatitis C direct acting antivirals among patients who are infected with the hepatitis B virus or patients who have a history of being infected [i.e. Hepatitis B surface (HBs) antigen negative and Hepatitis B core (HBc) antibody or HBs antibody positive]. The presence or absence of hepatitis B virus infection should be confirmed prior to administrating this drug. If this drug is administered to patients who are infected with the hepatitis B virus or to patients who have a history of infection, attention should be paid to the occurrence of signs or symptoms related to reactivation of hepatitis B virus by monitoring results of hepatitis B virus markers such as HBV DNA load.

Reference information

Reports of ADRs over a period of approximately 3 years up to the present (April 2013 to April 2016), for which a causal relationship cannot be ruled out.
Cases related to reactivation of hepatitis B virus
(1) 0 cases
(2) 1 case (no fatal outcome)
(3) (4) 8 cases (1 fatal case)
(5) 0 cases
(6) 1 case (no fatal outcome)
(7) 2 cases (no fatal outcome)
(8) 0 cases
Estimated patient exposure estimated by the companies:
(1) Approximately 20 patients (April 2015 to March 2016)
(2) Approximately 22 000 patients (December 2013 to March 2016)
(3) (4) Approximately 51 000 patients (September 2014 to March 2016)
(5) Approximately 1800 patients (January 2015 to December 2015)
(6) Approximately 36 000 patients (May 2015 to March 2016)
(7) Approximately 75 000 patients (September 2015 to March 2016)
(8) Approximately 2100 patients (November 2015 to March 2016)
Launch dates:
(1) November 2011
(2) December 2013
(3) (4) September 2014
(5) November 2014
(6) May 2015
(7) September 2015
(8) November 2015

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
1	Female 50s	Chronic hepatitis C (Chronic hepatitis B, hypertension, spinal osteoarthritis, cataract subcapsular)	Daklinza Tablets 60 mg Sunvepra Capsules 200 mg 66 days ↓ Discontinued	**ADRs: Hepatitis B reactivation, hepatic function abnormal, hepatic failure**
				History of prior treatment: none
				Historical conditions: none
				Before the start of administration (date unknown) The patient was a double carrier of hepatitis B virus and hepatitis C virus. After seroconversion, with HBs antigen: positive, Hepatitis B e (HBe) antigen: negative, and HBe antibody: positive, progression of F2-F3 moderate or severe hepatic fibrosis was suspected from abdominal ultrasound. Start date of administration As progression of hepatitis C was considered to be relatively more severe, coadministration of the 2 drugs Daklinza Tablets (60 mg once daily) and Sunvepra Capsules (100 mg twice daily) was started for chronic hepatitis C

				Day 43 of administration Mild hepatic function disorder appeared. AST: 46 IU/L, ALT: 65 IU/L, T-Bil: 1.3 mg/dL Day 57 of administration Hepatic function had aggravated. Administration of oral ursodeoxycholic acid (600 mg/day) and intravenous monoammonium glycyrrhizinate/glycine/amino acids/L-cysteine hydrochloride hydrate (80 mL/day) was started. AST: 296 IU/L, ALT: 389 IU/L, γ-GTP: 48 IU/L Day 61 of administration Some improvement in AST and ALT levels was observed, but prolongation of PT appeared. AST: 236 IU/L, ALT: 331 IU/L, T-Bil: 2.4 mg/dL, LDH: 258 IU/L, γ-GTP: 79 IU/L, PT: 67% Approximately day 66 of administration (date of discontinuations) Daklinza Tablets and Sunvepra Capsules were discontinued. Day 1 after discontinuation Aggravation of liver disorder and marked prolongation of PT were present. The patient was transported to an advanced emergency medical service center. Steroid pulse therapy with methylprednisolone sodium succinate (1000 mg/day), piperacillin sodium by intravenous drip (2 g/day), fresh frozen plasma transfusion (4 units/day), oral entecavir, and freeze-dried human antithrombin III concentrate (1500 units) were started. From then on, fresh frozen plasma at 4 to 6 units was transfused as necessary. HBc antibody: positive, HBe antibody: positive, HBe antigen: negative, HBs antibody: negative, HBs antigen: positive Day 3 after discontinuation Administration of freeze-dried human antithrombin III concentrate was ended. Day 4 after discontinuation The dose of methylprednisolone sodium succinate was decreased to 500 mg/day. Day 6 after discontinuation The dose of methylprednisolone sodium succinate was decreased to 250 mg/day. Day 7 after discontinuation Decreases in hepatic enzyme and bilirubin levels were observed, and the patient's course was good. AST: 175 IU/L, ALT: 519 IU/L, T-Bil: 9.43 mg/dL, D-Bil: 5.83 mg/dL Day 9 after discontinuation The dose of methylprednisolone sodium succinate was decreased to 125 mg/day. Day 12 after discontinuation Steroid therapy was switched from injected drugs to oral drugs. Administration of oral prednisolone (40 mg/day) was started. As bilirubin was again tending to increase, intravenous monoammonium glycyrrhizinate/glycine/amino acids/L-cysteine hydrochloride hydrate was administered (100 mL). Day 15 after discontinuation Administration of oral ursodeoxycholic acid (300 mg/day) was started. Intravenous monoammonium glycyrrhizinate/glycine/amino acids/L-cysteine hydrochloride hydrate was administered (80 mL). Day 16 after discontinuation Intravenous monoammonium glycyrrhizinate/glycine/amino acids/L-cysteine hydrochloride hydrate was administered (60 mL). Day 18 after discontinuation An MRI scan was performed. Ascites was present. No obvious abnormalities suggesting hepatic necrosis were present. Pleural effusion was present. No other notable abnormal findings in the abdominal region were present. Administration of intravenous monoammonium glycyrrhizinate/glycine/amino acids/L-cysteine hydrochloride hydrate was started (40 mL/day). Day 19 after discontinuation The dose of prednisolone was decreased to 20 mg/day. Administration of piperacillin sodium was ended. Day 22 after discontinuation The dose of prednisolone was decreased to 10 mg/day. Day 25 after discontinuation Abdominal pain was observed, and lancing of ascites was performed. The risk of intestinal perforation was considered, but radiography found no obvious free air.

				Day 26 after discontinuation The dose of prednisolone was decreased to 5 mg/day. As the patient's general condition was relatively stable, the patient was moved to a general ward (in the department of gastrointestinal medicine). Day 27 after discontinuation From the morning, pyrexia with a body temperature of 37 to 38°C, tachycardia (120 bpm), and blood pressure decreased (60/32 mmHg) appeared, and the patient entered a state of shock. Blood tests found increased inflammatory response, aggravation of hepatic failure, and a tendency towards disseminated intravascular coagulation. It was considered likely that an infection had triggered septic shock as a complication, and the patient was moved to the critical care center. Administration of piperacillin hydrate (9.0 mg/day), noradrenaline, and dopamine was started. The patient complained strongly of abdominal pain, and administration of midazolam (2 mg/hour) for sedation was started. Administration of intravenous monoammonium glycyrrhizinate/glycine/amino acids/L-cysteine hydrochloride hydrate was ended. Day 34 after discontinuation Pain was relieved, but the patient's level of consciousness gradually decreased. Anuria was also present, and administration of midazolam was discontinued. After midazolam was discontinued, the patient's consciousness level did not recover, and blood tests also found that coagulation and fibrinolytic system levels had aggravated. Day 36 after discontinuation From around 21:00 hours, gradually blood pressure decreased, and a tendency towards bradycardia appeared. At 22:46 hours, cardio-respiratory arrest appeared, and the patient died. Cause of death: reactivation of HBV, hepatic failure. The proximal cause of death was multi-organ failure due to septic shock Autopsy results were as follows: Liver: Sub massive necrosis, Ascending colon: Erosion
	Concomitant medications: olmesartan medoxomil / azelnidipine, bromfenac sodium hydrate, kakkonto, etodolac			

Laboratory examination

Test item	7 days before administration	Day 15 of administration	Day 43 of administration	Day 57 of administration	Day 61 of administration	1 day after discontinuation
AST (IU/L)	37	16	46	296	236	2311
ALT (IU/L)	37	10	65	389	331	1950
LDH (IU/L)	228	196	214	-	258	696
ALP (IU/L)	236	236	251	-	337	391
γ-GTP (IU/L)	39	28	22	48	79	75
T-Bil (mg/dL)	-	1.1	1.3	-	2.4	11.81
D-Bil (mg/dL)	-	-	-	-	-	9.09
TP (g/dL)	-	-	-	-	-	5.91
ALB (g/dL)	-	-	-	-	-	3.21
PLT (× 10^4 cells/mm^3)	17.6	24.5	24.0	19.7	-	14.7
INR	-	-	-	-	-	3.23
PT activity (%)	-	-	-	-	67	16
HBV DNA (log copies /mL)	3.9	-	-	-	-	7.4
HCV RNA (log IU/mL)	4.9	-	Not detected	-	-	Not detected

Test item	11 days after discontinuation	18 days after discontinuation	25 days after discontinuation	27 days after discontinuation	30 days after discontinuation
AST (IU/L)	123	54	46	75	457
ALT (IU/L)	352	152	72	58	487
LDH (IU/L)	293	270	297	278	640
ALP (IU/L)	330	406	491	362	400
γ-GTP (IU/L)	81	81	74	49	63
T-Bil (mg/dL)	15.52	20.77	22.03	18.46	24.54
D-Bil (mg/dL)	11.19	15.73	16.30	14.30	18.25
TP (g/dL)	5.18	-	5.05	4.08	4.02

ALB (g/dL)	2.77	-	2.69	2.46	2.35
PLT (× 10^4 cells/mm^3)	-	-	6.2	5.6	3.8
INR	1.76	1.87	1.75	2.50	3.38
PT activity (%)	36	33	36	23	15
HBV DNA (log copies /mL)	-	3.7	3.4	-	-
HCV RNA (log IU/mL)	-	Not detected	Not detected	-	-

Case 2

No. 2016-0204133	Patient: Sex/ Age	Patient: Primary disease (complications)	Daily dose/ Treatment duration	Adverse reactions: Clinical course and therapeutic measures
2	Female 40s	Chronic hepatitis C (chronic hepatitis B, hepatitis B, seasonal allergy)	Unknown 63 days	**Hepatic function abnormal** **Hepatitis B DNA increased** 17 years before administration Interferon therapy was discontinued due to consciousness disturbed / hallucination / hallucination, visual. Nucleoside analog was not used to treat hepatitis B virus. 92 days before administration Abdominal ultrasound found only findings of haemangioma of liver. Start date of administration To treat hepatitis C, this drug was started at a dose of 1 tablet. Day 47 of administration The patient visited a local physician due to a migraine. Loxoprofen sodium hydrate 60 mg and tizanidine hydrochloride 1 mg were prescribed and taken (until day 47 of administration). Day 55 of administration The patient started administration of epinastine hydrochloride 20 mg due to pollinosis. Day 56 of administration At a regular visit, increased AST and ALT levels were found (hepatic function disorder). The patient had the concomitant symptom malaise. The following concomitant symptoms were absent: pyrexia, jaundice, inappetence, nausea / vomiting, abdominal pain, rash, itching, encephalopathy, and ascites. Oral administration of other drugs, including epinastine hydrochloride, was discontinued. This drug was continued. Day 63 of administration HBV DNA increased (9.0 Log copy/mL) Day 64 of administration (date of discontinuation) Administration of this drug was discontinued. 2 days after discontinuation The patient was admitted, and the patient's course was observed. 3 days after discontinuation Abdominal ultrasound found chronic hepatitis. Malaise continued until the same date. 12 days after discontinuation Abdominal ultrasound found chronic hepatitis. 20 days after discontinuation The patient was discharged. 24 days after discontinuation HBV DNA decreased (4.5 Log copy/mL) Date unknown Hepatic function disorder was recovering.
	Concomitant medications: loxoprofen sodium hydrate, tizanidine hydrochloride, epinastine hydrochloride			

Laboratory examination

	78 days before ad-ministration	1 day before ad-ministration	Day 14 of ad-ministration	Day 28 of ad-ministration	Day 42 of ad-ministration	Day 56 of ad-ministration	Day 63 of ad-ministration	2 days after dis-continuation	3 days after dis-continuation
ALT		40 (IU/L)	12 (IU/L)	13 (IU/L)	18 (IU/L)	84 (IU/L)	552 (IU/L)	1417 (IU/L)	1372 (IU/L)
AST		38 (IU/L)	16 (IU/L)	16 (IU/L)	17 (IU/L)	52 (IU/L)	432 (IU/L)	1134 (IU/L)	1025 (IU/L)
HBV-DNA	3.6 (Log						9.0 Log		

	copy/mL)						copy/mL		
HCV-RNA	6.1 (Log IU/mL)			Not detected		Not detected			
HBeAb INHIBITION	91								99
HBeAg S/CO	< 0.50								1.06

	4 days after dis-continuation	6 days after dis-continuation	9 days after dis-continuation	11 days after dis-continuation	13 days after dis-continuation	16 days after dis-continuation	19 days after dis-continuation	24 days after dis-continuation	31 days after dis-continuation
ALT	1286 (IU/L)	1033 (IU/L)	878 (IU/L)	618 (IU/L)	373 (IU/L)	225 (IU/L)	143 (IU/L)	94 (IU/L)	48 (IU/L)
AST	847 (IU/L)	551 (IU/L)	469 (IU/L)	233 (IU/L)	108 (IU/L)	79 (IU/L)	59 (IU/L)	53 (IU/L)	30 (IU/L)
HBV-DNA								4.5 Log copy/mL	
HCV-RNA								Not detected	
HBeAb INHIBITION								99	
HBeAg S/CO								< 0.50	

2 Levetiracetam

Brand name (name of company)	(1) E Keppra Tablets 250 mg, 500 mg, E Keppra Dry Syrup 50% (UCB Japan Co. Ltd.) (2) E Keppra for I.V. Infusion (UCB Japan Co. Ltd.)
Therapeutic category	Antiepileptics
Indications	(1) * Partial onset seizures in epilepsy patients (including secondary generalized seizures) * Concomitant therapy with other antiepileptic drugs for tonic-clonic seizures in epilepsy patients who fail to show a satisfactory response to other antiepileptic drugs (2) As an alternative to levetiracetam oral tablets for the following treatment in patients who are not able to use the oral treatment temporarily: * Partial onset seizures in epilepsy patients (including secondary generalized seizures) * Concomitant therapy with other antiepileptic drugs for tonic-clonic seizures in epilepsy patients who fail to show a satisfactory response to other antiepileptic drugs

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Acute renal failure:** Acute renal failure may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.
Reference information	Reports of ADRs over a period of approximately 2 years and 11 months years up to the present (April 2013 to March 2016), for which a causal relationship cannot be ruled out.. Case related to acute renal failure 2 cases (no fatal outcomes) Estimated patient exposure estimated by the company: Approximately 165 000 patients (January 2015 to December 2015) Launch dates: (1) 250 mg tablets, 500 mg tablets: September 2010 Dry syrup 50%: August 2013 (2) December 2015

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 20s	Epilepsy (mental disability)	250 mg 33 days ↓ 375 mg 35 days ↓ 500 mg 10 days	**Acute renal failure** This drug was added at 250 mg/day in addition to phenytoin and zonisamide. Day 34 of administration: The dose was increased to 375 mg/day. Day 69 of administration: The dose was increased to 500 mg/day. The patient had some sleepiness, but his general condition was good. Day 78 of administration: The patient made a visit due to vomiting and lack of vitality since 2 days earlier. From tests, renal failure was diagnosed, and the patient was admitted. This drug was discontinued. Day after discontinuation: The patient's course was observed, with rest and fluid management (fluid restriction) only. 14 days after discontinuation: With only the above treatment, the patient recovered and was discharged.
	Concomitant drugs: phenytoin, zonisamide			

Laboratory examination

	43 days before administration	Day 78 (discontinuation date)	Day after discontinuation	5 days after discontinuation	13 days after discontinuation
BUN (mg/dL)	10	37	41	12	10
Serum creatinine(mg/dL)	0.79	5.82	6.75	1.31	0.86
Blood sodium (mEq/L)		130	128	140	141
Blood potassium (mEq/L)		3.5	3.8	4	3.9
Urinary protein	-	3+	2+		-
Urinary occult blood	-	1+	2+		
Urinary beta-2 microglobulin (mg/dL)		16.776	11.353	0.442	
Cystatin C		3.44	3.07		

4

Revision of Precautions (No. 275)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated May 31, 2016.

1

Miscellaneous metabolism agents-Miscellaneous

(1) Alendronate sodium hydrate
(2) Ibandronate sodium hydrate
(3) Etidronate disodium
(4) Zoledronic acid hydrate
(5) Pamidronate disodium
(6) Minodronic acid hydrate
(7) Risedronate sodium hydrate

Brand name	(1) Teiroc Injection 5 mg, 10 mg, Bonalon Tablets 5 mg, 35 mg, Bonalon Oral Jelly 35 mg, Bonalon Bag for I.V. Infusion 900 μg (Teijin Pharma Limited), Fosamac Tablets 5 mg, 35 mg (MSD K.K.), and the others (2) Bonviva Injection 1 mg Syringe, Bonviva Tablets 100 mg (Chugai Pharmaceutical Co., Ltd.) (3) Didronel Tablets 200 mg (Sumitomo Dainippon Pharma Co., Ltd.) (4) Zometa for I.V. Infusion 4 mg/5 mL, 4 mg/100 mL (Novartis Pharma K.K.), and the others (5) Aredia for I.V. Infusion 15 mg, 30 mg (Novartis Pharma K.K.), and the others (6) Bonoteo Tablets 1 mg, 50 mg (Astellas Pharmacy Inc.), Recalbon Tablets 1 mg, 50 mg (Ono Pharmaceutical Co., Ltd.) (7) Actonel Tablets 2.5 mg, 17.5 mg, 75 mg, Benet Tablets 2.5 mg, 17.5 mg, 75 mg (EA Pharma Co., Ltd., Takeda Pharmaceutical Company Limited), and the others
Important precautions	Cases of osteonecrosis of external auditory canal have been reported in patients treated with bisphosphonates. In several cases, osteonecrosis of external canal occurred in association with ear infection and trauma. Healthcare professionals should advise patients to consult an otolaryngologist if symptoms such as otitis externa, otorrhoea, and ear pain persist.
Adverse reactions (clinically significant adverse reactions)	Osteonecrosis of external auditory canal: Osteonecrosis of external auditory canal may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

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 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 Marketing Authorization Holder (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, 2016)

◎: Products for which EPPV was initiated after May 1, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Perampanel Hydrate Fycompa Tablets 2 mg, 4 mg	Eisai Co., Ltd.	May 26, 2016
◎	Asenapine Maleate Sycrest Sublingual Tablets 5 mg, 10 mg	Meiji Seika Pharma Co., Ltd.	May 26, 2016
◎	Sebelipase Alfa (Genetical Recombination) Kanuma Injection for Intravenous 20 mg	Alexion Pharma G.K.	May 25, 2016
◎	Osimertinib Mesilate Tagrisso Tablets 40 mg, 80 mg	AstraZeneca K.K.	May 25, 2016
◎	Ceritinib Zykadia Capsules 150 mg	Novartis Pharma K.K.	May 25, 2016
◎	Ibrutinib Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	May 25, 2016
◎	Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg*1	Teijin Pharma Limited	May 23, 2016
◎	Botulinum Toxin Type A Botox Vista Injection 50 Units*2	Allergan Japan K.K.	May 23, 2016
◎	Iloprost Ventavis Inhalation Solution 10 μg	Bayer Yakuhin, Ltd.	May 16, 2016
◎	Methacholine Chloride (1) Provocholine Powder for Inhalation Solution 100 mg (2) Kenbran Powder for Inhalation Solution 100 mg	(1) Sanwa Kagaku Kenkyusho Co., Ltd. (2) Santen Pharmaceutical Co., Ltd.	May 10, 2016
◎	Nonacog Gamma (Genetical Recombination) Rixubis Intravenous 250, 500, 1000, 2000, 3000	Baxter Limited	May 9, 2016
	Luliconazole Luconac Solution 5% *3	Sato Pharmaceutical Co., Ltd.	April 25, 2016
	Progesterone Luteum Vaginal Suppository 400 mg	Aska Pharmaceutical Co., Ltd.	April 21, 2016

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
Evolocumab (Genetical Recombination) Repatha SC Injection 140 mg syringe, 140 mg pen	Amgen Astellas BioPharma K.K.	April 21, 2016
Ibandronate Sodium Hydrate Bonviva Tablets 100 mg	Chugai Pharmaceutical Co., Ltd.	April 21, 2016
Duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg *4	Shionogi & Co., Ltd.	March 18, 2016
Eribulin Mesilate Halaven Intravenous Injection 1 mg*5	Eisai Co., Ltd.	February 29, 2016
Risperidone Risperdal Tablets, 1 mg, 2 mg, Fine Granules 1 %, Risperdal OD Tablets 0.5 mg 1 mg, 2 mg, Risperdal Oral Solution 1 mg/mL *6	Janssen Pharmaceutical K.K.	February 29, 2016
Rituximab (Genetical Recombination) Rituxan Injection 10 mg/mL*7	Zenyaku Kogyo Co., Ltd.	February 29, 2016
Progesterone Utrogestan vaginal capsules 200mg	Fuji Pharma Co., Ltd.	February 18, 2016
Indium pentetreotide (^{111}In) OctreoScan Kit for Intravenous Use	FUJIFILM RI Pharma Co., Ltd.	January 27, 2016
Esflurbiprofen/Mentha oil Loqoa Tape	Taisho Pharmaceuticals Co., Ltd.	January 21, 2016
Bosentan hydrate Tracleer 32 mg dispersible tablets for pediatrics	Actelion Pharmaceuticals Japan Ltd.	January 12, 2016
Ozenoxacin Zebiax Lotion 2%	Maruho Co., Ltd.	January 7, 2016
Vandetanib Caprelsa Tablets 100 mg	AstraZeneca K.K.	December 24, 2015
infliximab (genetical recombination) Remicade Intravenous Infusions 100 mg*8	Mitsubishi Tanabe Pharma Corporation	December 21, 2015
Apixaban Eliquis Tablets 2.5 mg, 5 mg*9	Bristol-Myers K.K.	December 21, 2015
nivolumab (genetical recombination) Opdivo Intravenous Infusions 20 mg, 100 mg*10	Ono Pharmaceutical Co., Ltd.	December 17, 2015
leuprorelin acetate Leuplin PRO Injections Kit 22.5 mg	Takeda Pharmaceutical Co., Ltd.	December 15, 2015
absorbed diphtheria-purified pertussis-tetanus- inactivated polio (salk vaccine) combined vaccine Square Kids Subcutaneous Injections Syringe	Kitasato Daiichi Sankyo Vaccine Co., Ltd.	December 9, 2015
venlafaxine hydrochloride Effexor SR Capsules 37.5 mg, 75 mg	Pfizer Japan Inc.	December 8, 2015
Trabectedin Yondelis Intravenous Infusions 0.25 mg, 1 mg	Taiho Pharmaceutical Co., Ltd.	December 7, 2015
Rivaroxaban Xarelto Fine Granules 10 mg, 15 mg*11	Bayer Yakuhin, Ltd.	December 7, 2015
None Miticure House Dust Mite Sublingual Tablets	Torii Pharmaceutical Co., Ltd.	December 3, 2015

Nonproprietary name Brand name on		Name of the MAH	Date of EPPV initiate
	3,300 JAU, 10,000 JAU		
	tiotropium bromide hydrate Spiolto Respimat 28 puffs	Nippon Boehringer Ingelheim Co., Ltd.	December 3, 2015
	Lusutrombopag Mulpleta Tablets 3 mg	Shionogi & Co., Ltd.	December 1, 2015
	Levetiracetam E Keppra Intravenous Infusions 500 mg	UCB Japan Co., Ltd.	December 1, 2015
	insulin degludec (genetical recombination) / insulin aspart (genetical recombination) Ryzodeg FlexTouch	Novo Nordisk Pharma Ltd.	December 1, 2015

*1 Hyperuricemia associated with cancer chemotherapy
*2 Lateral canthal lines in adult patients under the age of 65
*3 Nail tinea
*4 Pain associated with chronic lumbago
*5 Malignant soft tissue sarcoma
*6 Irritability associated with autism spectrum disorder in childhood
*7 Prophylaxis of antibody-related type rejection in the ABO blood group incompatibility transplant of kidney and liver transplants
*8 Acute stage of Kawasaki's disease
*9 Treatment of venous thromboembolism [deep vein thrombosis (DVT) and pulmonary embolism (PE)], and prophylaxis of recurrent DVT and PE
*10 Unresectable advanced/recurrent non-small cell lung cancer
*11 Treatment of DVT and PE, and prophylaxis of recurrent DVT and PE