Pharmaceuticals and Medical Devices Safety Information

No. 325 August 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.

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. 325 August 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
ALB	Albumin
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
APTT	Activated partial thromboplastin time
AQP	Anti-aquaporin
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
AT-III	Antithrombin III
BUN	Blood urea nitrogen
CHDF	Continuous hemodiafiltration
Ch-E	Cholinesterase
s-Cr	Serum creatinine
CRP	C-reactive protein
CT	Computed tomography
D-Bil	Direct bilirubin
DM	Direct mail
DSU	Drug Safety Update
EPPV	Early Post-marketing Phase Vigilance
FDP	Fibrin/fibrinogen degradation product
FY	Fiscal year
γ-GTP	gamma-glutamyl transpeptidase
HCV	Hepatitis C virus
INR	International normalized ratio
IV	Intravenous
JCS	Japan Coma Scale
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MBP	Myelin basic protein
MHLW	Ministry of Health, Labour and Welfare
MR	Medical representative
MRI	Magnetic resonance imaging
MS	Drug wholesalers
ND	Not detected
Neu	Neutrophil
NH_3	Ammonia
PE	Plasma exchange
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PT	Prothrombin time
PaO_2	Arterial oxygen partial pressure
Plt	Platelet count
RBC	Red blood cell count
RMP	Risk Management Plan
HCV-RNA	Hepatitis C virus-Ribonucleic acid
T-Bil	Total bilirubin

TEN	Toxic epidermal necrolysis
TP	Total protein
TTT	Tilt table test
WBC	White blood cell count
ZTT	Zinc sulfate turbidity test

1

Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Medical Institutions

1. Introduction

In order to ensure proper use of drugs and medical devices, the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (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 propose 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 fiscal year (FY) 2014 and PMDA's desirable directions considered from these results.

2. Surveillance in FY 2014

(1) Methods

The surveillance was conducted from December 15, 2014 to March 13, 2015 and targeted hospitals nationwide (a total of 8 481 institutions).

The questionnaire was mailed out to the hospital director of the target institutions and requested that the drug safety management supervisor or the pharmacists responsible for drug information management at the respective hospitals answered the questions. Responses were generally submitted through an online questionnaire, but respondents could choose to submit their answers electronically (i.e. using a Microsoft Excel questionnaire) or 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 pharmaceutical practices and drug information established in PMDA.

Table 1. Main Survey Topics

- Basic information about the medical institution
- Source of information used when accessing drug safety information, status of dissemination of such safety information within the hospital (including actual case studies).
- Usage of the internet, registration status for PMDA Medi-navi, etc.
- Rules associated to adoption of drugs in the hospital formulary, information utilized when adopting a drug, etc.
- Awareness and utilization status of risk communication tools such as the Risk Management Plan (RMP), review reports, patient-targeted pharmaceutical guides, and Manuals for Management of Individual Serious Adverse Drug Reaction (ADR)
- Cooperation between the hospital and pharmacy, how and what kind of patient information is shared, etc.

Table 2. Desirable directions from the Surveillance Results

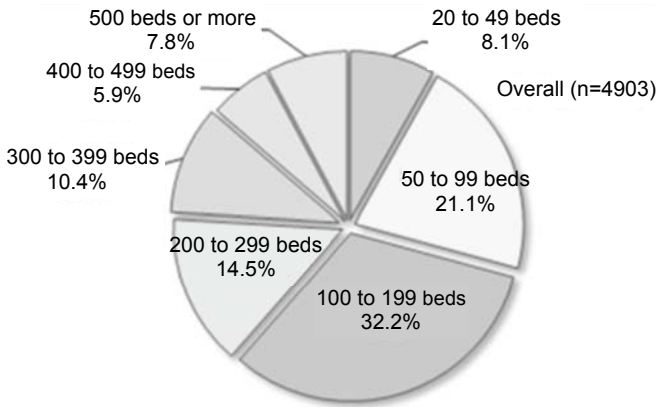
- Access appropriate information by taking the characteristic of the information source (such as speed, volume, content, and interactivity) into consideration
- Utilization of relevant information such as review reports or RMP when adopting drugs into the hospital formulary
- Accurate assessment of safety information, and definite and effective dissemination of such information by contriving ways and timing
- Promotion of utilization of risk communication tools such as RMP, review reports, patient-targeted pharmaceutical guides, and Manuals for Management of Individual Serious ADR
- Promotion of cooperation between the hospitals and pharmacies including sharing patient information such as laboratory test results that would be helpful for pharmacies when checking prescriptions

(2) Surveillance Results

Answers were obtained from 4 903 facilities (57.8%).

The breakdown in terms of number of beds for these facilities is as shown in **Figure 1**. In addition, 75.3% of respondents were drug safety management supervisors, and 22.0% were drug information experts.

Figure 1. Number of Beds



Based on the surveillance results and opinions from the Committee, desirable directions on utilization of such safety information in clinical practice is as shown in **Table 2**.

Of these desirable directions, the details for the following will be provided in this text: “Access appropriate information by taking the characteristic of the information source into consideration”, “Promotion of utilization of risk communication tools”, and “Promotion of cooperation between the hospitals and pharmacies including sharing patient information such as those that would be helpful for pharmacies when checking prescriptions”.

a. Accessing appropriate information by taking the characteristic of the information source into consideration

Surveillance Results

The main sources for safety information include medical representatives (MRs) (i.e. pharmaceutical company employees in charge of drug information) (87.2%), Pharmaceuticals and Medical Devices Safety Information (PMDSI) (79.4%), and Drug Safety

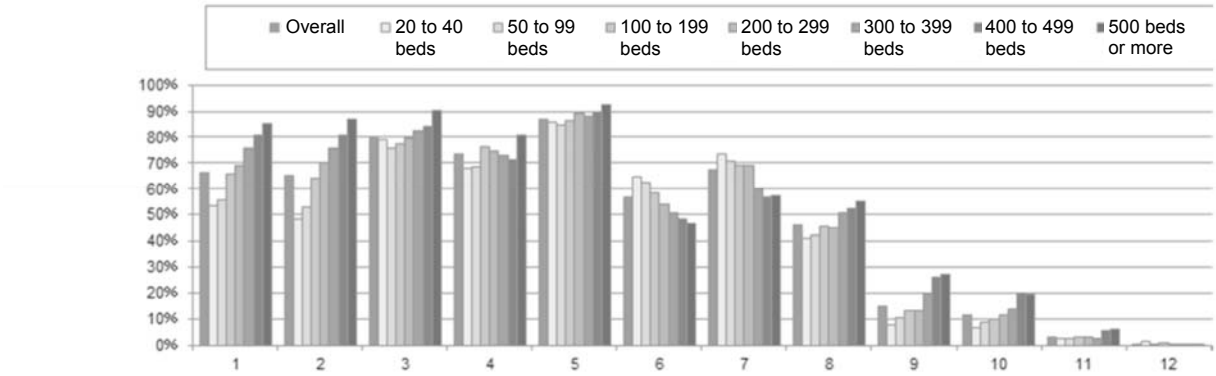
Update (DSU) (73.5%). Various sources of information are used, and utilization seems to differ depending on the size of the medical institution. (**Fig. 2**)

The useful sources of information when gathering safety information depends on the facility size. The top 3 sources of information are MRs, PMDSI, and DSU for hospitals with less than 100 beds, whereas these are PMDA Medi-navi, MRs, and PMDA website for hospitals with 400 beds or more. As for each information source, there was no significant difference by the facility size in terms of the percentage of facilities that considered MRs and PMDSI to be useful. On the contrary, direct mail (DM) by pharmaceutical companies and drug wholesalers (MS) are considered useful by a higher percentage of respondents from smaller facilities, and PMDA Medi-navi and PMDA website are considered useful by a higher percentage of respondents from larger facilities. (**Fig. 3**)

77.3% of facilities have drug safety management supervisors or someone in the pharmacy department registered with PMDA Medi-navi, which suggests that usage is more widespread compared to when surveillance was conducted in FY 2012 (67.5%). However, there are 22.3% of facilities where no one in the pharmacy department has registered, and this percentage tends to be higher among facilities that are smaller. (**Fig. 4**)

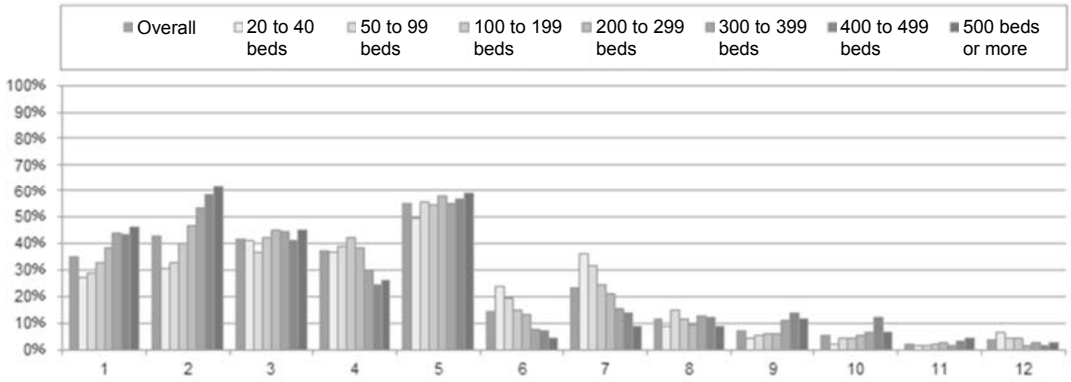
If useful sources of information for accessing safety information is analyzed based on whether or not facilities have registered with PMDA Medi-navi, PMDA Medi-navi is mentioned most often (54.4%) as one of the top 3 most useful sources among respondents from facilities registered with PMDA Medi-navi. (**Fig. 5**)

Figure 2. Sources of Safety Information (Updates on Revision of Precautions): All Sources of Information Utilized



	PMDA website	PMDA Medi-navi	PMDSI	DSU	MR	MS	DM	Pharma company website	Website besides PMDA and pharma compa-nies	Mail service besides PMDA Medi-navi	Other	No response
Overall (n=4903)	66.5	65.3	79.4	73.5	87.2	56.8	67.3	46.1	14.8	11.4	3.4	0.7
20 to 49 beds (n=398)	53.5	48.2	78.9	68.1	85.7	64.8	73.6	41.0	7.5	6.5	2.8	1.5
50 to 99 beds (n=1035)	55.6	52.9	75.7	68.8	84.8	62.2	70.8	42.4	10.3	8.7	2.6	0.5
100 to 199 beds (n=1579)	65.5	64.2	77.5	76.3	86.4	58.6	69.3	45.5	13.4	10.1	3.3	0.9
200 to 299 beds (n=711)	69.2	70.3	79.5	74.5	89.0	53.9	69.3	44.9	13.4	11.8	3.4	0.3
300 to 399 beds (n=511)	75.9	75.5	82.6	72.8	87.9	50.5	60.1	50.5	20.2	13.7	2.7	0.4
400 to 499 beds (n=288)	80.9	80.6	84.4	71.5	89.6	48.6	56.9	52.1	26.0	19.8	5.6	0.3
500 beds or more (n=381)	85.0	86.9	90.6	80.6	92.4	46.7	57.2	55.1	27.3	19.4	6.0	0.3

Figure 3. Sources of Safety Information (Updates on Revision of Precautions): Top 3 Most Useful Sources



	PMDA website	PMDA Medi-navi	PMDSI	DSU	MR	MS	DM	Pharma company website	Website besides PMDA and pharma compa-nies	Mail service besides PMDA Medi-navi	Other	No response
Overall (n=4903)	35.1	42.9	41.7	37.0	55.4	14.3	23.5	11.8	7.2	5.3	2.1	3.7
20 to 49 beds (n=398)	27.4	30.4	41.2	36.9	49.7	23.6	36.2	8.8	4.5	2.3	1.8	6.8
50 to 99 beds (n=1035)	29.0	32.9	36.6	39.0	55.6	19.6	31.6	15.2	5.4	4.4	1.7	4.2
100 to 199 beds (n=1579)	32.6	40.1	42.2	42.2	54.4	14.8	24.3	11.7	6.0	4.4	1.8	4.5
200 to 299 beds (n=711)	38.1	46.8	44.9	38.5	57.7	13.1	21.0	9.4	5.9	5.5	2.4	1.7
300 to 399 beds (n=511)	44.0	53.4	44.4	30.1	55.4	7.8	15.5	12.9	11.2	6.7	1.4	2.7
400 to 499 beds (n=288)	43.4	58.7	41.3	24.7	56.9	6.9	13.5	12.2	13.5	12.2	3.1	1.4
500 beds or more (n=381)	46.5	61.7	45.1	26.2	59.1	4.2	8.7	8.7	11.8	6.6	4.2	2.6

Figure 4. Status of Registration with PMDA Medi-Navi among Drug Safety Management Supervisors or Someone from the Pharmacy Department

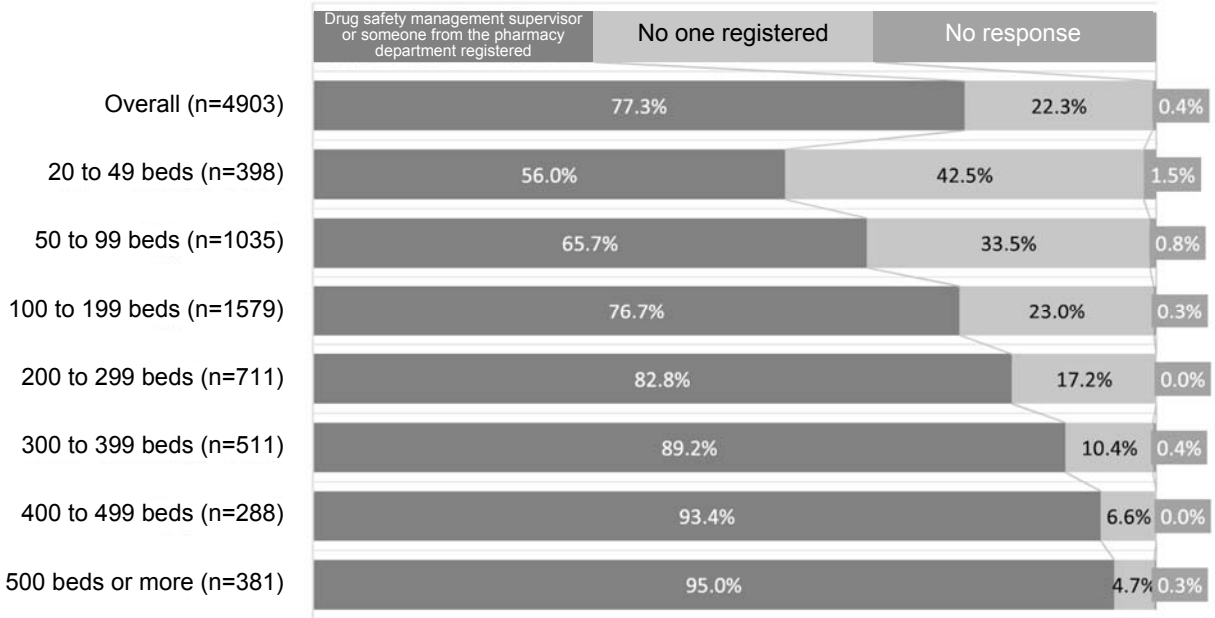
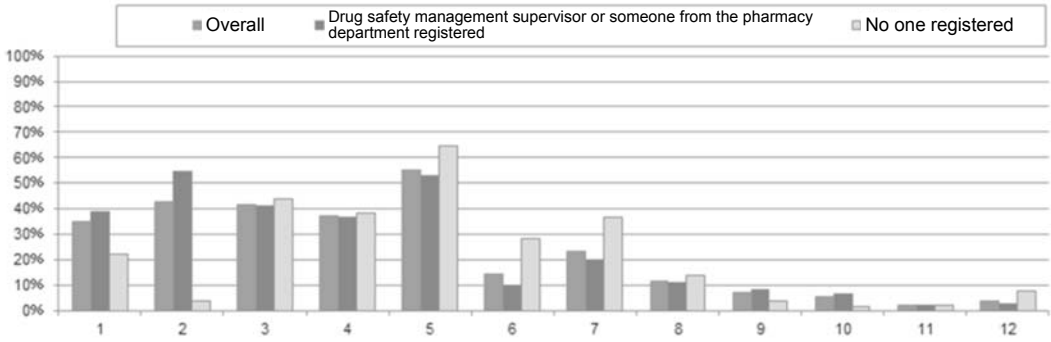


Figure 5. Sources of Safety Information (Updates on Revision of Precautions): Top 3 Most Useful Sources



	PMDA website	PMDA Medi-navi	PMDSI	DSU	MR	MS	DM	Pharma company website	Website besides PMDA and pharma compa-nies	Mail service besides PMDA Medi-navi	Other	No respons e
Overall (n=4903)	35.1	42.9	41.7	37.0	55.4	14.3	23.5	11.8	7.2	5.3	2.1	3.7
Drug safety management supervisor or pharmacy registered (n=3790)	38.9	54.4	41.0	36.7	52.6	10.1	19.8	11.1	8.3	6.3	2.2	2.5
No one registered	21.9	3.8	44.1	38.5	64.7	28.6	36.6	13.9	3.6	1.6	1.9	7.8

Desirable directions

Each type of source has unique characteristics associated to speed, volume, content and whether or not it is interactive. The following outlines some unique characteristics of each source:

- PMDA Medi-navi and PMDA websites provide information promptly as soon as safety measures are taken
- PMDSI lacks rapidness relative to the above sources but includes detailed information such as case reports
- DSU also lacks rapidness but provides comprehensive summary of all revisions to precautions
- Through direct communication, MRs are able to provide detailed information specifically needed by each institution

It is desirable that these unique characteristics are taken into consideration and utilized effectively and appropriately according to the situation.

PMDA Medi-navi is a useful and necessary tool for managing safety information as it allows users to access safety information promptly and consistently without requiring additional human resources. In addition, by incorporation into the standard operating procedures for management of safety information, etc., it is desirable that PMDA Medi-navi is incorporated and effectively utilized as part of safety information management through daily checks of information distributed.

PMDA will consider improving usability of PMDA Medi-navi based on the needs of the medical society and will continue to further promote registration/utilization of the application through cooperation with various professional organizations.

b. Promoting utilization of risk communication tools

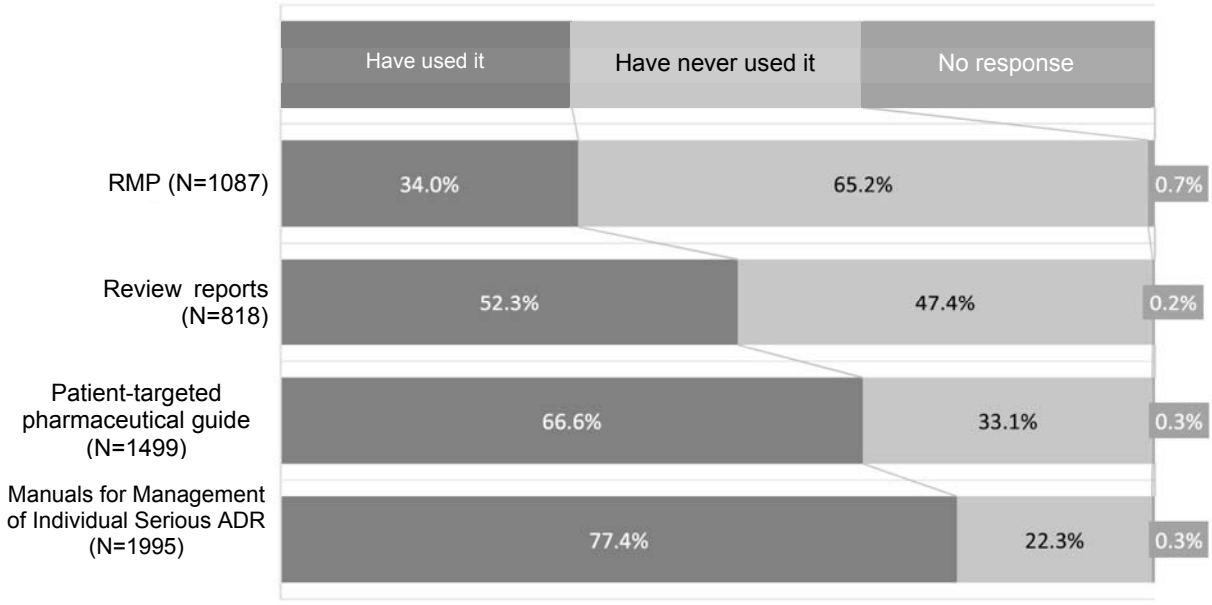
Surveillance Results

The percentage of institutions stated they "fully understand the contents" or "somewhat understand the contents" of each risk communication tool is as follows: 4.7% and 17.5% for RMP, 5.1% and 11.6% for review reports, 9.6% and 21.0% for patient-targeted pharmaceutical guides, and 15.2% and 25.5% for Manuals for Management of Individual Serious ADR. (**Fig. 6**)

Furthermore, of the institutions stated that they "fully understand" or "somewhat understand" the contents of these risk communication tools, the percentage of institutions that stated they "have used such tools in daily operations" are as follows: 34.0% for RMP, 52.3% for review reports, 66.6% for patient-targeted pharmaceutical guides, and 77.4% for Manuals for Management of Individual Serious ADR. (**Fig. 7**)

Figure 6. Awareness of Risk Communication Tools

Figure 7. Utilization of Risk Communication Tools



Desirable directions

RMP, review reports, patient-targeted pharmaceutical guide, and Manuals for Management of Individual Serious ADR are beneficial risk communication tools provided on PMDA website; 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 them more well-known.

c. Promoting cooperation between hospitals and pharmaceuticals including sharing patient information such as those that would be helpful for pharmacies when checking prescriptions

Surveillance Results

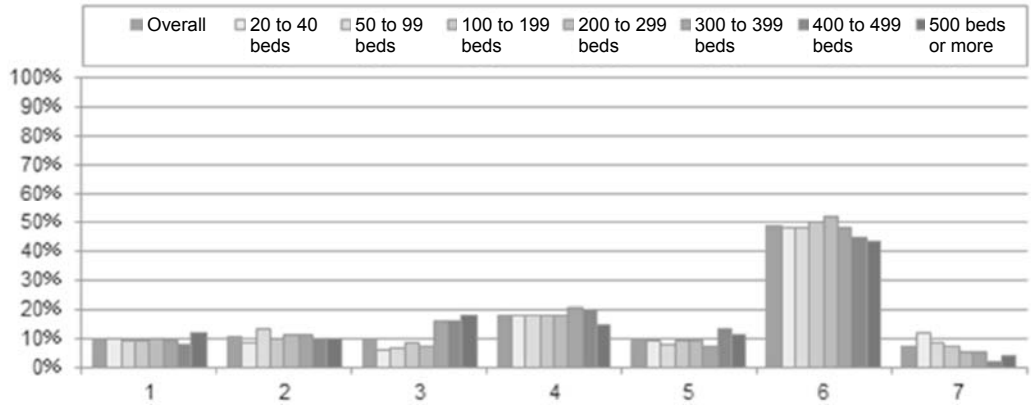
18.2% of institutions provide patient information to dispensing pharmacies upon request from patients; 11.0% of institutions provide such information for patients using specific drugs; 9.9% of institutions provide such information for patients suffering from specific diseases; and 9.6% of institutions provide such information for almost all patients. 48.8% of institutions do not provide any patient information voluntarily to dispensing pharmacies. (Refer to **Fig. 8**)

Of the institutions that stated they provide patient information to dispensing pharmacies (i.e. 44.0% of the overall respondents or 2156 facilities in total, excluding respondents and facilities that stated they “do not provide patient information voluntarily to dispensing pharmacies” or did not respond), the percentage that disclose information regarding test results such as laboratory test results and diagnoses is: provide information on electronic medical charts (13.5%, 13.1%), use information liaison on proper use of drugs (10.6%, 11.3%), print/note on medication record book (9.2%, 6.4%), and print/note on prescription form (5.1%, 3.3%), respectively. (Refer to **Fig. 9**)

Desirable directions

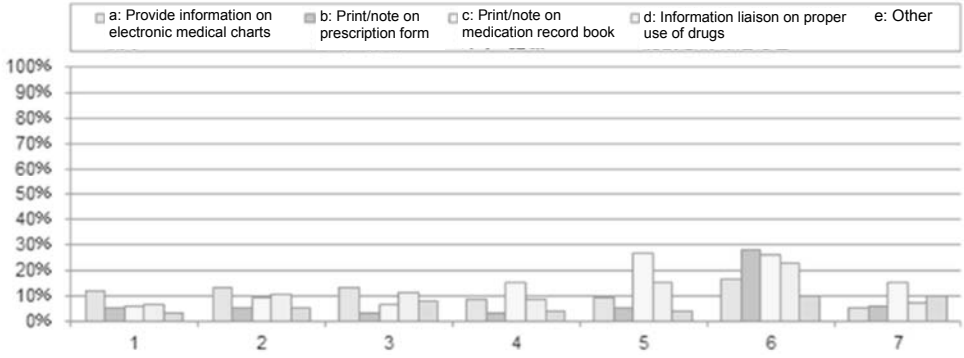
In order for dispensing pharmacies to provide more precise prescription checking with the aim to guarantee safety for patients, sharing patient information related to laboratory test results and diagnoses is crucial. Certain institutions are already sharing such information through provision of medical chart information, use of information liaison between institutions regarding proper use of drugs, and notes on prescriptions or medicine notebooks. It is desirable that such cooperation between hospitals and pharmacies will be further implemented.

Figure 8. Extent to which Patient Information is Provided to Dispensing Pharmacies



	For almost all patients (excluding those who disagree)	Patients who use specific drugs (e.g. drugs for which lab results need to be taken into consideration)	Patients with specific diseases (e.g. cancer)	Patients requesting information to be shared	Other	Do not provide patient information voluntarily to dispensing pharmacies	No response
Overall (n=4903)	9.6	11.0	9.9	18.2	9.3	48.8	7.2
20 to 49 beds (n=398)	10.1	8.8	6.0	18.1	9.3	48.0	12.1
50 to 99 beds (n=1035)	9.7	13.6	6.9	18.0	8.1	48.3	9.0
100 to 199 beds (n=1579)	9.1	10.1	8.9	18.2	9.7	50.2	7.7
200 to 299 beds (n=711)	10.1	11.1	7.6	17.9	9.1	52.3	5.6
300 to 399 beds (n=511)	9.2	11.7	15.9	20.7	7.2	47.9	5.7
400 to 499 beds (n=288)	8.0	10.1	16.3	19.8	13.5	44.4	2.4
500 beds or more (n=381)	12.3	10.0	18.1	14.4	11.3	43.3	3.9

Figure 9. Type and Method of Patient Information Provided to Dispensing Pharmacies



	Height, weight, body surface area, etc.	Test results such as laboratory test results	Diagnosed disease, etc.	Dosing regimen for anticancer drugs, etc.	Record on administration guidance	Other comments (e.g. physician's findings, precautions)	Other
a Provide information on electronic medical charts (n=2156)	12.0	13.5	13.1	9.0	9.6	16.6	5.4
b Print/note on prescription form (n=2156)	5.3	5.1	3.3	3.1	5.6	28.0	6.4
c Print/note on medication record book (n=2156)	5.9	9.2	6.4	15.4	26.6	26.2	15.7
d Information liaison on proper use of drugs (n=2156)	7.0	10.6	11.3	9.0	15.4	22.7	7.4
e Other (n=2156)	3.7	5.7	7.8	4.4	4.0	9.9	10.0

3. Conclusion

Appropriate access, dissemination, and utilization of the latest drug safety information in clinical practice are important to ensure proper use of drugs. PMDA Medi-navi is useful to ensure access to drug safety information in a prompter manner. Please subscribe to 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 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.

[RMP]
http://www.pmda.go.jp/english/safety/info-services/drugs/0001.html
[Review Reports]
https://www.pmda.go.jp/english/review-services/reviews/approved-information/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 ADR (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 2014. 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
[Main Surveillance Results and Recommendations from FY 2014 Surveillance]
http://www.pmda.go.jp/files/000205744.pdf
[Report on FY 2014 Surveillance Results]
http://www.pmda.go.jp/files/000205739.pdf

2
Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated July 7th, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Asunaprevir and Daclatasvir Hydrochloride

Brand name (name of company)	Asunaprevir: Sunvepra Capsules 100mg (Bristol-Myers K.K.) Daclatasvir Hydrochloride: Daklinza Tablets 60mg (Bristol-Myers K.K.)
Therapeutic category	Antivirals
Indications	Improvement of viremia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C

PRECAUTIONS (underlined parts are revised)

Important precautions

Hepatic function disorder and/or decreased hepatic residual function may occur and may result in hepatic failure. Hepatic failure should be assessed at least every 2 weeks until 12 weeks after the start of administration and every 4 weeks after 12 weeks. If deterioration in hepatic function is observed, hepatic function should be assessed more frequently, and appropriate measures such as discontinuation of administration should be adopted. In addition, regardless of increased hepatic enzyme levels, hepatic failure associated with jaundice, ascites, hepatic encephalopathy, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Adverse reactions (clinically significant adverse reactions)

Hepatic function disorder and hepatic failure:
Increased alanine aminotransferase (glutamate pyruvate transaminase) ALT (GPT) level, increased aspartate aminotransferase (glutamate oxaloacetate transaminase) AST (GOT) level, increased blood bilirubin level, prolonged prothrombin time (PT), decreased albumin (ALB) level, etc. may occur and may result in hepatic failure associated with jaundice, ascites, hepatic encephalopathy, etc. Hepatic function should be assessed at least every 2 weeks until 12 weeks after the start of administration and every 4 weeks after 12 weeks. If deterioration in hepatic function is observed, hepatic function should be assessed more frequently, and appropriate measures such as discontinuation of administration should be adopted. If ALT (GPT) increases ≥10 times the upper limit of normal, administration should be discontinued immediately and should not be re-administered.

Reference information

The number of reported adverse events (for which a causality to the drug could not be ruled out) for the past 8 months (from initial marketing to April 2015)
Cases of adverse events associated with decreased hepatic residual function: 21 cases* (1 fatal case)
*Cases of which causality to the combination therapy with daclatasvir hydrochloride and asunaprevir could not be ruled out.
The number of patients using these drugs estimated by the marketing authorization holder (MAH): Approximately 31 000 (from initial

marketing to April 2015)
Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Compensated cirrhosis type C (diabetes mellitus)	Daklinza Tablets 60mg and Sunvepra Capsules 200mg for 43 days	**Drug-induced liver injury, hepatic failure** No history of prior treatment. The patient had a medical history of oesophageal varices, hepatocellular carcinoma (after radiofrequency ablation), sclerotherapy for oesophageal varices, and oesophageal variceal ligation. Approximately 10 years before administration: Diagnosed as chronic hepatitis C. Day 1 of administration: Combination therapy with Daklinza Tablets 60mg once daily and Sunvepra Capsules 100mg twice daily was started. The patient had compensated cirrhosis with no ascites. The patient was administered spironolactone to prevent concomitant occurrence of portal hypertension. Day 43 of administration (day of discontinuation): AST level was 1 312 IU/L; ALT level was 1 082 IU/L; Lactate dehydrogenase (LDH) level was 540 IU/L; Alkaline phosphatase (ALP) level was 764 IU/L; and total bilirubin (T-Bil) level was 3.2 mg/dL. Hepatic function disorder was observed, and the patient was admitted to the hospital. The patient had no subjective symptom. Administration of Daklinza Tablets and Sunvepra Capsules was discontinued. 4 days after discontinuation: Half-dose steroid pulse therapy (methylprednisolone sodium succinate, 500 mg/day) was started (until 6 days after discontinuation). 7 days after discontinuation: Oral administration of prednisolone 30 mg/day was started. Hepatic function was recovering gradually. 12 days after discontinuation: The dose of prednisolone was decreased to 20 mg/day. 14 days after discontinuation: The patient developed pyrexia of 38.4°C. Chest and abdominal computed tomography (CT) scans showed infiltrative shadow associated with cavity in the left upper lobe. Onset of left lung abscess. Administration of sulbactam sodium/ampicillin sodium IV injection 6 g/day was started (until 24 days after discontinuation). 16 days after discontinuation: Due to complications of the left lung abscess, dose of prednisolone was decreased (10 mg/day). Ascites and oedema was controlled with ALB and diuretics (until 18 days after discontinuation). 19 days after discontinuation: Administration of prednisolone was terminated. Pyrexia and inflammatory response was recovering. 22 days after discontinuation: Chest CT showed slight increase of the infiltrative shadow associated with cavity. A new infiltrative shadow possibly due to inflammatory change appeared in the left lung.

				Ascites continued to increase. 30 days after discontinuation: Switched to administration of ALB + diuretics intravenous (IV) infusion since ascites was poorly controlled. Paracentesis was conducted for ascites as necessary. Beta-D-glucan was measured to further evaluate the infiltrative shadow of the lungs. Beta-D-glucan was 163 pg/mL, antigens for Aspergillus and Cryptococcus were negative, and cardiac echo showed no septic embolism. 36 days after discontinuation: Administration of micafungin sodium 150 mg IV infusion was started. Pyrexia did not recur, and inflammatory response decreased smoothly. 38 days after discontinuation: Body weight and ascites tended to increase. Administration of tolvaptan was started because there was no improvement in lower limb oedema. 42 days after discontinuation: Chest CT showed shrinking of the cavity shadow in the left upper lobe. No new lesions were found. 43 days after discontinuation: Switched diuretics to oral administration. 48 days after discontinuation: Improvement in AST and ALT levels, and improvement in lung abscess as well. The patient was discharged from the hospital upon request. Antifungal treatment was terminated. 51 days after discontinuation: Level of consciousness deteriorated. 53 days after discontinuation: Responsiveness decreased and the patient was emergently transported to the hospital. The patient was urgently admitted to the hospital due to deterioration of general conditions, mainly hepatic failure, was observed. Multidisciplinary treatment (initiating solution, amino acid formulations for hepatic failure, dopamine hydrochloride, and furosemide) was started. Consciousness on the Japan Coma Scale (JCS) was II-10/, ammonia (NH_3) was 154 μg/dL, and Electrocardiogram (at rest) showed normal sinus rhythm. Abdominal CT showed liver atrophy and massive ascites. Chest CT showed a cavity lesion in the left lung field (There were no signs of major pneumonia). 55 days after discontinuation: General conditions rapidly deteriorated and the patient died at 19:00. The cause of death was hepatic failure. Autopsy has not been conducted.

Laboratory examination

	102 days before administration	Day 1 of administration	Day 16 of administration	Day 29 of administration	Day 43 of administration (day of discontinuation)	7 days after discontinuation	16 days after discontinuation	31 days after discontinuation	46 days after discontinuation	53 days after discontinuation
AST (IU/L)	79	46	25	44	1 312	113	26	39	39	103
ALT (IU/L)	102	57	19	44	1 082	499	64	36	36	80
T-Bil (mg/dL)	0.9	0.8	0.8	1.1	3.2	4.0	4.1	3.5	4.1	6.2
D-Bil (mg/dL)	0.4	–	–	–	–	2.6	3.0	2.7	2.9	–
γ-GTP (IU/L)	23	20	19	43	59	55	30	18	13	–
ALP (IU/L)	496	622	363	456	764	685	458	423	534	382
LDH (IU/L)	191	192	176	195	540	236	254	203	314	373
ALB (g/dL)	3.5	3.4	3.2	3.0	3.0	2.8	2.2	2.9	2.3	–
Urea nitrogen (mg/dL)	15	–	–	–	–	32	40	28	30	56.2
s-Cr (mg/dL)	0.63	0.67	0.62	0.62	0.65	0.61	0.61	0.64	–	1.25
NH_3 (μg/dL)	–	36	–	–	–	22	20	31	44	154
CRP (mg/dL)	<=0.1	<=0.1	<=0.1	0.51	0.35	0.12	5.66	0.51	0.13	0.21
WBC (/mm^3)	3 430	3 210	3 260	5 350	6 320	11 600	25 190	8 870	11 610	13 960
RBC (×10^4/mm^3)	6.5	6.3	5.4	8.0	5.8	7.3	5.5	4.7	9.7	5.9
PT (%)	80	–	–	–	–	39	46	50	49	26.9
INR	1.15	–	–	–	–	2.04	1.77	1.64	1.68	2.25
HCV RNA (Log IU/mL)	–	4.5	ND	ND	–	–	ND	–	–	–

Concomitant medications: ursodeoxycholic acid, glimepiride, sitagliptin phosphate hydrate, metformin hydrochloride, cimetidine, spironolactone, loratadine, teprenone

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 80s	Compensated cirrhosis type C (hypertension, asthma, Hashimoto's thyroiditis)	Daklinza Tablets 60mg and Sunvepra Capsules 200mg for 90 days	**Ascites** The patient had a history of humerus fracture. Day 1 of administration: Combination therapy with Daklinza Tablets 60mg once daily and Sunvepra Capsules 100mg twice daily was started. Day 36 of administration: Onset of allergic liver disorder. Day 43 of administration: AST levels were 81, ALT levels were 65, and eosinophil was 8.5, and the patient's hepatic function was resolving. Approximately Day 51 of administration: The patient developed oedema in both lower limbs. Day 71 of administration: The patient developed generalised oedema, and oral administration of 1 tablet of furosemide and 0.5 tablets of spironolactone was started. Day 83 of administration: The patient was admitted to hospital due to severe ascites, mild pleural effusion, and respiratory disorder. Oxygen level was 2 L/minute. Oral administration of

				furosemide was terminated, and administration of furosemide injection 2 ante prandium was started. Day 84 of administration: ALB was 2.6 and urinary output was 4 540 mL/day. Administration of furosemide injection was discontinued, and oral administration of furosemide was restarted. Oral administration of spironolactone was discontinued, and administration of 1 tablet tolvaptan was started. Day 85 of administration: Urinary output decreased (840 mL/day). Administration of levothyroxine sodium hydrate 50 μg × 0.25 tablets was started for Hashimoto's thyroiditis. Day 86 of administration: Urinary output was 420 mL/day. Day 87 of administration: ALB level was 2.4. Human serum ALB 50 mL was administered intravenously for 5 days. Oxygen was 6 L/minute and arterial oxygen partial pressure (PaO_2) was 60.3. Day 89 of administration: The patient required oxygen mask at 8 L/minute and suffered from mild pleural effusion and atelectasis. Oral administration of furosemide was discontinued, and administration of furosemide injection (40 mg/24 hours) was started. Oral administration of 1 tablet of spironolactone was started. Day 90 of administration (day of discontinuation): Administration of Daklinza Tablets and Sunvepra Capsules was discontinued (A total of 12 weeks 6 days administration). Extracted 3 850 mL of ascites using paracentesis. Urinary output was 3 250 mL/day. PaO_2 was 58.5. Oxygen was 8 L (using an oxygen mask with a reservoir bag). 3 days after discontinuation: Temporary oxygen saturation was 91. Oxygen was 10 L/minute (using an oxygen mask with a reservoir bag). 4 days after discontinuation: Oxygen was 8 L/minute. 6 days after discontinuation: Administration of furosemide injection (30 mg/24 hours) was started. 7 days after discontinuation: Administration of furosemide injection was discontinued, and administration of furosemide tablet 40 mg and tolvaptan 7.5 mg was restarted. Oxygen was 5 L/minute. 8 days after discontinuation: Oxygen was 3 L/minute. 9 days after discontinuation: Administration of tolvaptan was discontinued. The dose of furosemide tablet was decreased to 20 mg. Administration of spironolactone was discontinued. Oxygen was 3 L/minute. 17 days after discontinuation: Ascites resolved. 21 days after discontinuation: Discontinued oxygen inhalation. Oedema was recovering. Respiratory failure and allergic liver disorder was resolved. Daklinza Tablets and Sunvepra Capsules were not re-administered.

Laboratory examination

	Day 28 of administration	Day 36 of administration	Day 83 of administration	Day 90 of administration (day of discontinuation)	20 days after discontinuation
AST (IU/L)	54	125	68	33	28
ALT (IU/L)	40	82	49	23	15
T-Bil (mg/dL)	1.4	2.0	3.1	1.8	1.3
γ-GTP (IU/L)	31	42	19	12	14
ALP (IU/L)	526	559	407	202	275
LDH (IU/L)	340	392	597	348	301
ALB (g/dL)	3.8	3.4	3.4	2.7	2.7
WBC (/mm^3)	4 300	4 400	6 200	3 800	2 300
Eosinophil (%)	–	14.0	2.8	12.0	4.8
Plt ($\times 10^4/mm^3$)	10.9	10.4	9.5	6.5	7.1
PT (%)	90.4	80.7	71.7	64.9	–
INR	1.06	1.11	1.18	1.24	–

Concomitant medications: candesartan cilexetil, rabeprazole sodium, ursodeoxycholic acid, nifedipine, brotizolam, etizolam, isoleucine/leucine/valine, montelukast sodium, salmeterol xinafoate/fluticasone propionate

2 Abiraterone Acetate

Brand name (name of company)	Zytiga Tablets 250 mg (Janssen Pharmaceutical K.K.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Castration-resistant prostate cancer

PRECAUTIONS (underlined parts are revised)

Important precautions

Fulminant hepatitis may occur. In addition, hepatic function disorder associated with increased levels of ALT (GPT), AST (GOT) and bilirubin, etc. may occur and may result in hepatic failure. Patients should be carefully monitored through periodic hepatic function tests during administration of the drug (particularly, liver function tests should be conducted frequently during the initial treatment stage).

Adverse reactions (clinically significant adverse reactions)

Fulminant hepatitis, hepatic failure, and hepatic function disorder: Fulminant hepatitis may occur. In addition, hepatic function disorder associated with increased levels of ALT (GPT), AST (GOT), and bilirubin, etc. may occur and may result in hepatic failure. Patients should be carefully monitored through periodic liver function tests during administration of the drug. If any abnormalities are observed, appropriate measures such as dose reduction, cessation of the drug, 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 9 months (from initial marketing to May 2015)
Cases of adverse events associated with fulminant hepatitis and/or hepatic failure: 5 cases (1 fatal case)
The number of patients using this drug estimated by MAH:
4 500 (from initial marketing to May 2015)
Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Castration-resistant prostate cancer (hypertension, benign prostatic hyperplasia, metastases to bone)	1 000 mg for 35 days	**Hepatic failure, hepatic encephalopathy** The patient had no history or complications of liver and/or biliary tract disease. Progression of primary disease: metastases to bone (ischium, vertebra, sternum) No metastases to liver. History of drinking was unknown. No history of enzalutamide or docetaxel administration No history of allergies. Consumption of herbs and dietary supplements was unknown. History of transfusion was unknown. 56 days before administration: AST was 30 IU/L, ALT was 36 IU/L, and T-Bil was 0.55 mg/dL. 28 days before administration AST was 33 IU/L, ALT was 41 IU/L, and T-Bil was 0.74 mg/dL. Day 1 of administration: Administration of Zytiga (1 000 mg/day) and prednisolone (10 mg/day) was started. No signs of

				hepatic encephalopathy nor ascites. AST was 42 IU/L, ALT was 47 IU/L, T-Bil was 0.61 mg/dL, and ALB was 3.5 g/dL. Day 29 of administration (day of onset): The patient had inarticulateness and consulted a nearby clinic due to physical disconditioning. Blood test was done. Onset of hepatic failure and hepatic encephalopathy (Grade I). There were no haemorrhage symptoms. AST was 1 215 IU/L and ALT was 877 IU/L. (Liver function test was conducted once every month after administration of Zytiga.) Day 31 of administration: Patient consulted the nearby clinic again. Day 35 of administration (day of discontinuation): The patient was referred to a different hospital due to hepatic function disorder and admitted to the hospital. Clinical symptoms such as pyrexia, malaise, anorexia, consciousness disturbed, and somnolence associated with hepatic disorder were observed. Administration of Zytiga and prednisolone was discontinued. Conservative treatment with plasma exchange (PE) was performed. CT scans showed no signs of cholelithiasis, liver tumor, or hepatomegaly. Hepatitis B surface antigen test was negative. Hepatitis C virus (HCV) antibody test was negative. Immunoglobulin M-Hepatitis A test was not conducted. Autoantibody tests were not conducted. AST was 1 025 IU/L, ALT was 1 785 IU/L, T-Bil was 3.25 mg/dL, direct bilirubin (D-Bil) was 2.11 mg/dL, and PT was 52%. 8 days after discontinuation: Patient had somnolence tendency. 10 days after discontinuation: CT scans showed signs of pleural effusion but no hepatomegaly or liver cancer. Onset of pleural effusion. Continuous hemodiafiltration (CHDF) was conducted. AST levels were recovering to 550 IU/L but still remained high and conditions were bad. Screening for hepatitis was conducted. Hepatitis B virus and HCV were both negative and HAV was not conducted. 11 days after discontinuation: The patient was still in the hospital. Although both AST and ALT levels were recovering, T-Bil was deteriorating. CHDF was conducted. AST was 437 IU/L, ALT was 424 IU/L, and T-Bil was 21.34 mg/dL. 12 days after discontinuation: PE was conducted. 13 days after discontinuation: CHDF + PE was conducted (for 3 days). 16 days after discontinuation: CHDF was conducted (for 2 days). 19 days after discontinuation: Onset of disseminated intravascular coagulation. There were no haemorrhage symptom or symptoms

				indicating organ disorder. Platelet count (Plt) was 4.6×10^4 /mm^3, AST was 35 IU/L, ALT was 29 IU/L, and T-Bil was 7.16 mg/dL. 21 days after discontinuation: AST was 54 IU/L, ALT was 61 IU/L, and T-Bil was 11.96 mg/dL. Level of consciousness was JCS II-10. CHDF was conducted. 22 days after discontinuation: CHDF was conducted. AST was 42 IU/L, ALT was 50 IU/L, and T-Bil was 7.92 mg/dL. 23 days after discontinuation: CHDF was conducted. 24 days after discontinuation: The patient died due to hepatic failure. The patient had hepatic encephalopathy (Grade I), pleural effusion, and outcomes of DIC were unknown. Zytiga was not re-administered.

Laboratory examination

	56 days before administ-ration	28 days before administ-ration	Day 1 of administ-ration	Day 29 of administ-ration (day of onset)	Day 35 of administ-ration (day of discontin-uation)	11 days after discontin-uation	19 days after discontin-uation	21 days after discontin-uation	22 days after discontin-uation
TP (g/dL)	6.3	–	5.9	–	5.6	–	5.4	–	4.8
ALB (g/dL)	3.6	4.0	3.5	–	3.1	2.8	3.4	3.5	2.5
T-Bil (mg/dL)	0.55	0.74	0.61	–	3.25	21.34	7.16	11.96	7.92
D-Bil (mg/dL)	–	–	–	–	2.11	–	–	–	–
ZTT (IU)	–	–	–	–	5.1	–	7.2	–	12.7
TTT (IU)	–	–	–	–	2.6	–	3.8	–	9.0
AST (IU/L)	30	33	42	1 215	1 025	437	35	54	42
ALT (IU/L)	36	41	47	877	1 785	424	29	61	50
ALP (IU/L)	308	298	283	–	341	491	275	461	394
LDH (IU/L)	219	252	242	–	606	359	320	499	450
γ-GTP (IU/L)	31	48	47	98	151	82	37	62	45
BUN (mg/dL)	18.1	–	22.2	–	23.4	–	42.7	–	61.6
Cr (mg/dL)	1.37	–	1.41	–	2.61	–	1.68	–	2.46
CRP (mg/dL)	–	–	–	–	3.28	–	1.02	–	2.23
WBC (/μL)	7 000	10 000	8 300	–	6 500	14 700	41 300	32 500	53 600
Plt ($\times10^4$/μL)	16.2	–	15.8	–	13.1	–	4.6	–	5.5
PT (seconds)	–	–	–	–	15.8	–	–	–	–
PT (%)	–	–	–	–	52.0	–	–	–	–
PT-INR	–	–	–	–	1.45	–	–	–	–
APTT (seconds)	–	–	–	–	44.6	–	–	–	–
Fibrinogen (mg/dL)	–	–	–	–	292	–	197	–	–
AT-III (%)	–	–	–	–	49	–	56	–	–
FDP (μg/mL)	–	–	–	–	6.0	–	>=160.0	–	–

Concomitant medications: prednisolone, nifedipine, famotidine, silodosin, goserelin acetate, zoledronic acid hydrate

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 80s	Castration-resistant prostate cancer (constipation, benign prostatic hyperplasia, urinary retention, metastases to lymph nodes)	1 000 mg for 25 days	**Fulminant hepatitis** The patient had no medical history or complications of liver and/or cholelith/biliary tract disease. No metastases to liver. No history of drinking. No history of allergies. Consumption of herbs and dietary supplements was unknown. No history of transfusions. Approximately 1 year before administration: The previous physician initiated prescription of silodosin for treatment of urinary retention. 56 days before administration: Administration of enzalutamide was started for the treatment of prostate cancer. AST was 34 IU/L, ALT was 24 IU/L, and T-Bil was 0.33 mg/dL. 28 days before administration: AST was 27 IU/L, ALT was 18 IU/L, and T-Bil was 0.55 mg/dL. Day 1 of administration: Administration of Zytiga (1 000 mg/day) and prednisolone (10 mg/day) was started. There were no sign of hepatic encephalopathy or ascites. AST was 37 IU/L, ALT was 33 IU/L, T-Bil was 0.26 mg/dL, and ALB was 3.8 g/dL. Day 15 of administration: No abnormalities in hepatic function were observed. AST was 24 IU/L, ALT was 17 IU/L, and T-Bil was 0.57 mg/dL. Day 22 of administration: The patient came for a consultation. There was no problem observed. Day 25 of administration (day of onset, day of discontinuation): The patient came for an emergency consultation due to pyrexia and consciousness disturbed. The patient was admitted to the hospital due to suspected drug-induced hepatitis. Onset of fulminant hepatitis. Grade IV hepatic encephalopathy. There were no haemorrhage symptoms. AST was 1 399 IU/L, ALT was 1 100 IUL, and T-Bil was 2.08 mg/dL. Administration of Zytiga and prednisolone was discontinued. Pyrexia over 39°C continued (for 2 days). The patient had a history of prostate cancer and was suspected to have developed urinary tract infection at that time. Blood cultures were negative in the emergency outpatient department, but *Staphylococcus epidermidis* and Corynebacterium were detected in the urine culture. However, it is unknown whether the patient suffered from urinary tract infection or not.

				Chest and abdominal CT scans were conducted. [Findings of chest and abdominal CT] Location tested: Cervix to pelvis Hepatic parenchyma was slightly enlarged, and oedematous changes of the portal area and gallbladder were observed. This suggests acute liver disorder or inflammation of the biliary tract. The patient also showed signs of slight ascites. There were no abnormalities seen in the pancreas, spleen, kidneys, or adrenal glands. The diffuse thickening of bladder wall is similar and suggests chronic cystitis. There was no active inflammation observed in the pulmonary field. The reticular shadow on the dorsal surface of the bilateral lungs suggested gravitational effects or mild interstitial changes. There were no marked changes in prostate cancer and metastases of paraaortic lymph nodes. Date unknown: Transfusion of fresh frozen plasma was started for treatment of fulminant hepatitis. Administration of meropenem was started for treatment of pyrexia. 1 day after discontinuation: AST and ALT both increased to 2 511 IU/L and 2 040 IU/L respectively; therefore, administration of menatetrenone and glycyrrhizin/glycine/L-cysteine was started. T-Bil was 2.53 mg/dL. Somnolence exacerbated during the night, and flapping tremor was also observed. Response to pain stimulus also decreased, and the physician on-call considered the patient to be in “Grade IV coma”; however, conditions were recovering to Grade II within an hour. 2 days after discontinuation: The blood test results showed PT to be 35%, and, based on the fact that PT was 40% or lower suggesting severe hepatic function disorder, the patient was diagnosed as acute hepatic failure. Administration of methylprednisolone sodium succinate 1 000 mg/day was started for treatment of fulminant hepatitis and consciousness disturbed. AST was 3 095 IU/L, ALT was 3 013 IU/L, and T-Bil was 3.88 mg/dL. 3 days after discontinuation: Steroid pulse therapy was discontinued due to request from patient’s family. Consciousness disturbed was recovering and pyrexia recovered. Head magnetic resonance imaging (MRI) was conducted. [Findings of MRI] Hyperintesity suggesting hepatic encephalopathy was not found, and it was not possible to determine whether the patient had hepatic encephalopathy or not. Cerebral white matter were interspersed with chronic ischemic changes. This is associated with mild cerebral atrophy. AST was 1 375 IU/L, ALT was 2 681 IU/L, and T-Bil was 3.32 mg/dL. 4 days after discontinuation: AST was 341 IU/L, ALT was 1 678 IU/L, and T-Bil was 2.40 mg/dL. 6 days after discontinuation:

				Hepatic function was recovering. AST was 131 IU/L, ALT was 839 IU/L, and T-Bil was 1.58 mg/dL. 8 days after discontinuation: AST was 119 IU/L, ALT was 546 IU/L, and T-Bil was 2.09 mg/dL. 10 days after discontinuation: The patient was discharged from the hospital. Fulminant hepatitis and pyrexia were recovering. Zytiga was not re-administered.

Laboratory examination

	56 days before adminis-tration	42 days before adminis-tration	28 days before adminis-tration	Day 1 of adminis-tration	Day 15 of adminis-tration	Day 25 of adminis-tration (Day of onset/ day of disconti-nuation)	1 day after disconti-nuation	2 days after disconti-nuation	3 days after disconti-nuation	4 days after disconti-nuation	6 days after disconti-nuation	8 days after disconti-nuation
AST (IU/L)	34	–	27	37	24	1 339	2 511	3 095	1 375	341	131	119
ALT (IU/L)	24	–	18	33	17	1 100	2 040	3 013	2 681	1 678	839	546
ALP (IU/L)	164	–	131	124	128	131	129	111	114	124	132	124
LDH (IU/L)	247	–	212	213	189	1 085	1 988	2 510	730	359	284	278
γ-GTP (IU/L)	–	–	–	–	–	57	59	56	53	49	53	50
Ch-E (IU/L)	–	–	–	–	–	–	218	182	186	204	188	168
CPK (IU/L)	193	–	140	129	120	6 060	7 235	6 393	2 710	1 092	216	129
TP (g/dL)	7.6	–	7.5	7.7	7.5	–	6.1	–	5.6	–	–	5.6
ALB (g/dL)	4.0	–	4.0	3.8	4.0	–	3.0	–	2.6	2.8	2.6	2.6
T-Bil (mg/dL)	0.33	–	0.55	0.26	0.57	2.08	2.53	3.88	3.32	2.40	1.58	2.09
D-Bil (mg/dL)	–	–	–	–	–	–	1.18	2.02	1.78	1.28	0.73	1.00
CRP (mg/dL)	0.07	–	0.05	0.19	0.03	9.84	18.58	23.08	18.82	9.63	2.75	3.66
NH3 (μg/dL)	–	–	–	–	–	–	64	100	74	62	61	76
WBC (/μL)	5 700	5 400	5 200	5 200	4 900	6 100	6 500	7 500	5 900	9 100	5 800	5 900
Neu (%)	–	–	–	–	–	81.5	90	–	90	91	57	44.2
Plt ($\times 10^4$/μL)	18.8	23.6	19.5	26.5	19.6	10.7	9.6	6.1	4.5	5.6	7.6	10.7
PT (%)	–	–	–	–	–	61	45	35	42	49	55	54
PT-INR	–	–	–	–	–	1.26	1.50	1.77	1.56	1.41	1.33	1.34

Concomitant medications: prednisolone, silodosin, rebamipide, bicalutamide, sennoside, flutamide, leuprorelin acetate

3 Indapamide

Brand name (name of company)	(1) Natrix Tablets 1 and 2 (Kyoto Pharmaceutical Industries, Ltd.) (2) Tenaxil Tablets 1 mg and 2 mg (Alfresa Pharma Corporation)
Therapeutic category	Antihypertensives
Indications	Essential hypertension

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and erythema multiforme exudativum:TEN, oculomucocutaneous syndrome, or erythema multiforme exudativum may occur. Patients should be carefully monitored. If any abnormalities such as erythema, pruritus, or enanthema are observed, administration of this drug should be discontinued, and 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 April 2015)
Cases of adverse events associated with TEN: 1 case (1 fatal case)
The number of patients using these drugs estimated by MAH:
(1) Approximately 260 000 (from April 2014 to March 2015)
(2) Approximately 7 000 (from April 2014 to March 2015)
Launched in Japan: (1) Tablet 1: February 1985, Tablet 2: December 1990; (2) Tablet 1 mg: December 1990, Tablet 2 mg: July 1992

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Hypertension (none)	2 mg for 19 days	TEN The patient was diagnosed with hypertension approximately 10 years before administration. Approximately 22 months before administration: Suffered from cardio-respiratory arrest due to myocardial infarction but resuscitated and implanted with a pacemaker. Day 1 of administration: Indapamide was added-on to current treatment. Day 17 of administration: Onset of pyrexia over 40°C and eye pruritus. Day 18 of administration: The patient became aware of oral mucosa erosion at night. Day 19 of administration (day of discontinuation): Small erythema appeared on trunk and rapidly increased. The patient consulted the emergency department in Hospital A early in the morning and after being seen by a dermatologist, was transferred emergently to Hospital B. The patient had mucosal lesions and skin lesions over 20% of his body, and steroid pulse therapy was started. The patient had hepatic disorder and renal disorder. 2 days after discontinuation: Cutaneous symptoms increased rapidly. (90% of the body) 3 days after discontinuation: PE therapy and IV administration of prednisolone sodium succinate 1 mg/kg was started. The patient had corneal erosion. (Until 4 days after discontinuation) 4 days after discontinuation:

Blood pressure dropped to <70 during PE therapy, and therefore therapy was discontinued.
5 days after discontinuation:
High-dose γ-globulin therapy + prednisolone sodium succinate IV 1 mg/kg was started but multi-organ failure progressed. (Until 9 days after discontinuation)
10 days after discontinuation:
The patient died.

<Results of Drug-induced Lymphocyte Stimulation Test>
Date conducted: 5 days after discontinuation
Results: Measured value was 310 cpm, and positive rate was 90% (normal value for positive rate is 179%)
(Reference values)
Negative control is 341 cpm
Positive control is (phytohejagglutinin) 4 760 cpm

Laboratory examination

	Approximately 20 months before administration	Day 19 of administration	3 days after discontinuation	6 days after discontinuation	7 days after discontinuation
WBC	3.8	10.9	3.0	10.8	12.1
AST (GOT)	36	392	344	537	1,119
ALT (GPT)	24	250	306	307	662
Urea nitrogen	9.2	29.7	71.3	138.9	157.2
s-Cr	0.73	1.60	2.34	10.57	14.63
CRP (mg/dL)	0.24	9.20	5.83	10.67	7.92
Body temperature	–	40.7	–	–	38.1

Concomitant medications: fixed-dose combination of aspirin/lansoprazole, fixed-dose combination of irbesartan/amlodipine besilate, bisoprolol fumarate

4 Influenza HA Vaccine

Brand name (name of company)	(1) Influenza HA Vaccine “KAKETSUKEN” (The Chemo-Sero-Therapeutic Research Institute) (2) Influenza HA Vaccine “Kitasatodaiichisankyo” Syringe 0.25 mL (Kitasato Daiichi Sankyo Vaccine Co., Ltd.) (3) Influenza HA Vaccine “Kitasatodaiichisankyo” Syringe 0.5 mL (Kitasato Daiichi Sankyo Vaccine Co., Ltd.) (4) Influenza HA Vaccine “Kitasatodaiichisankyo” 1 mL (Kitasato Daiichi Sankyo Vaccine Co., Ltd.) (5) Influenza HA Vaccine “SEIKEN” (Denka Seiken Co., Ltd.) (6) Flu-Syringe “SEIKEN” (Denka Seiken Co., Ltd.) (7) “BIKEN HA” (The Research Foundation for Microbial Diseases of Osaka University) (8) FLUBIK HA (The Research Foundation for Microbial Diseases of Osaka University) (9) FLUBIK HA Syringe (The Research Foundation for Microbial Diseases of Osaka University)
Therapeutic category	Vaccines
Indications	Prophylaxis of influenza

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Encephalitis/encephalopathy, myelitis, and optic neuritis:
Encephalitis/encephalopathy, myelitis, or optic neuritis may occur. Patients should be carefully monitored. If abnormalities are observed, patients should undergo MRI scans, etc., and 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 May 2015)
Cases of adverse events associated with optic neuritis: 3 cases (no fatal cases)
The number of patients using these drugs estimated by MAH:
Approximately 51 730 000 (from October 2013 to July 2014)
Launched in Japan: (1) October 1996, (2) October 2013, (3) October 2008, (4) October 1986, (5) September 1972, (6) October 2003, (7) September 1972, (8) September 2005, (9) December 2008

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 10s	Prophylaxis of influenza (none)	0.5 mL (once)	**Optic neuritis** The patient had a medical history of allergic rhinitis, atopic dermatitis, and bronchial asthma. The patient had an ADR history of eye pain (after influenza HA vaccine of last year). Day of vaccination: The patient received influenza HA vaccine at Clinic A. 2 days after vaccination: Pain occurred in the back of both eyes but predominantly in the left and caused reduced visual acuity. The patient consulted Clinic B. The results of CT and MRI showed no abnormalities. 5 days after vaccination: After being referred and consulting Hospital C, the patient was transferred to Hospital D. Further

				examination showed optic atrophy, and the patient was diagnosed with optic neuritis in both eyes. Visual acuity in the right eye was 0.1 (hand motion) while the left was tested using a light perception. Papilledema was confirmed. No paralysis or seizure was observed. Cerebrospinal fluid cell count was 16/3 μL, myelin basic protein (MBP) was <40 pg/mL, oligoclonal band was negative, serum anti-aquaporin (AQP)-4 antibody was negative, influenza antibody A/H1N1 was 40 times, A/H3N2 was 20 times, and B was 10 times. High intensity in bilateral optic nerve T2 was confirmed in the head MRI scans; however, cerebral and spinal lesions were not observed. The patient showed resistance to steroids and became almost completely blind. 7 months after vaccination: The patient recovered with sequelae (complete blindness).
	No concomitant medications			

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 10s	Prophylaxis of influenza (none)	0.3 mL for 1 day	**Optic neuritis** Day of vaccination: The patient's body temperature was 36.2°C before vaccination. The patient was vaccinated with the product. Nasal congestion developed. The patient was prescribed oral drugs (potassium clavulanate/amoxicillin hydrate, serrapeptase, ebastine). 2 days after vaccination: Ocular pain occurred during eye movement. The patient developed pyrexia in the 38.0°C range from the evening. 4 days after vaccination: The patient was prescribed influenza (-) and oral drugs (azithromycin hydrate, carbocisteine, sodium gualenate hydrate/L-glutamine, clemastine fumarate, acetaminophen). Pyrexia recovered; however, the patient suffered from dysuria and thighs pain from the afternoon, and was unable to place any pressure on his legs causing him to fall from steps. 5 days after vaccination: Oral administration was discontinued. 8 days after vaccination: Dysuria had disappeared. The patient started to realize reduced visual acuity in both eyes. 11 days after vaccination: Reduced visual acuity progressed and CT scans were conducted but no abnormalities were found. The patient had no problems walking. 12 days after vaccination: The patient was only able to distinguish light since the afternoon. 17 days after vaccination: Mild redness and swelling was observed in both optic discs in addition to reduced visual acuity, and the patient was diagnosed with optic neuritis.

				18 days after vaccination: The patient was admitted to hospital due to progression of reduced visual acuity. No abnormalities were found on the head imaging MRI and spinal imaging MRI. No abnormalities were observed in the spinal fluid tests. Oligoclonal bands for immunoglobulin G in spinal fluids were negative, MBP was <40, and AQP was negative. Visual acuity was 0.01 for the right and 0.01 for the left. First course of steroid pulse therapy (methylprednisolone 1 000 mg, 30 mg/kg/day, for 3 days) was started. 24 days after vaccination: Visual acuity was 0.09 for the right and 0.4 for the left. There were defects in the central vision. Improvement in flicker value was limited. 25 days after vaccination: Second course of steroid pulse therapy (methylprednisolone 1 000 mg, 30 mg/kg/day, for 3 days) was administered. 31 days after vaccination: Visual acuity was 0.6 for the right and 0.6 for the left. There were defects found in 1/2 of the central vision closer to the ear. Flicker values seemed to be recovering. Prednisolone 1 mg/kg/day was administered orally as after treatment, and the dose was reduced thereafter. 38 days after vaccination: Visual acuity was 1.0 for the right and 1.2 for the left. Defects in the central visual field vanished. 46 days after vaccination: The patient was discharged from the hospital after recovering. 60 days after vaccination: Optic neuritis recovered.
	No concomitant medications			

5 Interferon Beta-1a (Genetical recombination)

Brand name (name of company)	(1) Avonex IM Injection Syringe 30μg (Biogen Idec Japan Ltd.) (2) Avonex IM Injection Pen 30μg (Biogen Idec Japan Ltd.)
Therapeutic category	Biological preparations-Miscellaneous
Indications	Prophylaxis of multiple sclerosis relapse

PRECAUTIONS (underlined parts are revised)

Important precautions

Serious liver disorder such as fulminant hepatitis may occur. Prior to starting and during administration, patients should be carefully monitored by assessing hepatic function [AST [GOT], ALT [GPT], gamma-glutamyl transpeptidase (γ-GTP), etc.) periodically (every 1 to 3 months). If any abnormalities are observed, appropriate measures such as dose reduction or cessation of the drug should be adopted. Patients who have a history of hepatic function disorder are recommended to assess their hepatic function 1 to 2 weeks after the start of administration. In addition, liver disorder may occur if this drug is used in combination with other drugs reported to cause hepatic function disorder or with alcohol; therefore, great care should be exercised when using this drug in combination. In addition, if symptoms such as nausea and vomiting, malaise, inappetence, dark urine, or yellowing of the bulbar conjunctiva occur after the administration of this drug, patients should be instructed to contact a doctor.

Adverse reactions (clinically significant adverse reactions)

Fulminant hepatitis, hepatitis, and hepatic function disorder:
Serious liver disorder such as fulminant hepatitis, hepatitis, or hepatic function disorder may occur. Biochemical tests, including liver function tests, should be periodically performed. 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

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 May 2015)
Cases of adverse events associated with fulminant hepatitis: 1 case (1 fatal case)
The number of patients using these drugs estimated by MAH:
2 281 (as of 2014)
Launched in Japan: (1) November 2006, (2) June 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Multiple sclerosis (none)	7.5 μg (initial dose), 15 μg (second dose), 30 μg (third dose onwards) Administered once weekly for 73 days	**Fulminant hepatitis** 2 days before administration: The patient was admitted to a university hospital in order to initiate treatment with Avonex. Day 1 of administration: Administration of Avonex was started at 7.5 μg. Day 12 of administration: AST (GOT) was 31 U/L, ALT (GPT) was 32 U/L, ALP was 117 U/L, γ-GTP was 22 U/L, and T-Bil was 0.7 mg/dL. Day 15 of administration: Avonex 30 μg was administered (third dose). Day 17 of administration:

				The patient was discharged from the hospitals (with no adverse events). Day 26 of administration: The patient consulted a community hospital for follow-up. No new symptoms were observed. Avonex was prescribed. Day 54 of administration: Avonex was prescribed at the community hospital. Day 66 of administration: Avonex 30 μg was administered (10th dose). Day 69 of administration: The patient consulted a nearby clinic due to feeling queasy and general malaise. The patient was diagnosed with gastroenteritis, and was prescribed 1 week worth of saikokeishito extract and rebamipide. Symptoms such as jaundice were not noted at this time. Day 73 of administration (day of discontinuation): Avonex 30 μg was administered (11th and final dose). 1 day after discontinuation: The patient consulted the same clinic where the physician noted jaundice, after which the patient went to consult the community hospital. Although the patient was lucid, yellow coloring was observed in the whole body. Significant hepatic function disorder was confirmed through blood testing, and the patient was diagnosed as acute hepatitis and was admitted to the hospital. AST (GOT) was 1 398 U/L, ALT (GPT) was 1 780 U/L, ALP was 666 U/L, γ-GTP was 366 U/L, T-Bil was 19.3 mg/dL, and PT was 28.2 seconds 16%. 3 days after discontinuation: Onset of JCS-3 consciousness disturbed since middle of previous night. High levels of NH_3. The patient was unable to follow orders, suffered from Grade III hepatic encephalopathy, and was diagnosed with fulminant hepatitis. AST (GOT) was 1 156 U/L, ALT (GPT) was 1 446 U/L, ALP was 719 U/L, γ-GTP was 270 U/L, T-Bil was 17.9 mg/dL, PT was 34.3 seconds 11%, and NH_3 was 214 μg/dL. Transferred to a university hospital because higher medical care such as PE therapy was necessary. 4-9 days after discontinuation: Based on the test results, viral hepatitis and autoimmune hepatitis was ruled out. Although PE therapy was tried, general conditions did not recover and the patient died after developing multi-organ failure associated with fulminant hepatitis.

Laboratory examination

	Day 12 of administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	7 days after discontinuation	8 days after discontinuation
AST [GOT] (U/L)	31	1 398	1 244	1 156	80	69
ALT [GPT] (U/L)	32	1 780	1 597	1 446	62	32
ALP (U/L)	117	666	727	719	235	175
γ-GTP (U/L)	22	366	316	270	29	21
T-Bil (mg/dl)	0.7	19.3	16.8	17.9	10.8	6.7
D-Bil (mg/dl)	0.0	12.8	12.1	12.1	–	–
PT (seconds)	–	28.2	30.9	34.3	–	–
PT (%)	–	16	14	11	22	24
RBC ($\times 10^6$ μl)	4.82	4.98	4.71	4.81	3.92	1.65
WBC ($\times 10^3$ μl)	5.0	11.2	7.9	8.8	10.1	15.1
Plt ($\times 10^3$ μl)	289	155	163	177	67	41
Serum ALB (g/dl)	3.7	3.9	3.4	3.5	3.2	1.9
CRP (mg/dl)	0.02	–	–	0.51	0.64	–
NH3 (μg/dl)	–	–	–	214	–	–

Concomitant medications (suspected drugs): saikokeishito extract, rebamipide
Concomitant medications: loxoprofen sodium, magnesium oxide

3

Revision of Precautions (No. 266)

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 July 7, 2015.

1

Antipyretics and analgesics, anti-inflammatory agents

(1) Tramadol hydrochloride (OD tablets, Capsules, and Injection)

(2) Tramadol hydrochloride/acetaminophen

Brand name	(1) Tramal Injection 100, Tramal Capsules 25 mg and 50 mg, Tramal OD Tablets 25 mg and 50 mg (Nippon Shinyaku Co., Ltd.) (2) Tramcet Combination Tablets (Janssen Pharmaceutical K.K.)
Adverse reactions (clinically significant adverse reactions)	**Respiratory depression:** Respiratory depression 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.

2

Antidiabetic agents

Anagliptin

Brand name	Suiny Tablets 100 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
Careful administration	Patients who have a history of abdominal surgery or intestinal obstruction
Adverse reactions (clinically significant adverse reactions)	**Intestinal obstruction:** Intestinal obstruction may occur. Patients should be carefully monitored. If any abnormalities such as severe constipation, abdominal distention, sustained abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

3

Antivirals

Adefovir pivoxil

Brand name	Hepsera Tablets 10 mg (GlaxoSmithKline K.K.)
Important Precautions	Vigilance regarding the onset of renal impairment should be exercised by assessing renal function by measuring laboratory parameters such as serum creatinine (s-Cr) during administration of this drug. Osteomalacia and fracture caused by hypophosphatemia because of renal tubular disorder, including Fanconi syndrome, may occur. Prior to starting and during administration of this drug, levels of serum phosphorus, ALP, etc. should be measured, and the fluctuations should be periodically monitored. In addition, if hypophosphatemia is observed, appropriate

	measures such as phosphorus supplementation should be adopted. The administration of active vitamin D should be considered when supplementing phosphorus.
Adverse reactions (clinically significant adverse reactions)	**Osteomalacia and fractures:** Osteomalacia and fractures associated with bone pain, arthralgia, and muscular weakness caused by hypophosphatemia because of renal tubular disorder, including Fanconi syndrome, may occur as a result of long-term administration. If this drug is administered for a long-term, patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting the 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 June 30, 2015)
◎: Products for which EPPV was initiated after June 1, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	gadobutrol Gadovist IV Injection 1.0 mol/L Syringe 5mL, 1.0 mol/L Syringe 7.5 mL, 1.0 mol/L Syringe 10 mL	Bayer Yakuhin, Ltd.	June 30, 2015
◎	bortezomib Velcade Injection 3 mg[*1]	Janssen Pharmaceutical K.K.	June 26, 2015
◎	lidocaine/propitocaine EMLA Cream	Sato Pharmaceutical Co., Ltd.	June 26, 2015
◎	edaravone Radicut Injection 30 mg, Radicut Bag for I.V. Infusion 30 mg[*2]	Mitsubishi Tanabe Pharma Corporation	June 26, 2015
◎	botulinum toxin type A Botox for Injection 50 units, 100 units[*3]	GlaxoSmithKline K.K.	June 26, 2015
◎	tazobactam/piperacillin hydrate Zosyn IV Injection 2.25 and 4.5, Zosyn Fixed-dose Bag for I.V. Infusion 4.5[*4]	Taiho Pharmaceutical Co., Ltd.	June 26, 2015
◎	pitavastatin calcium hydrate Livalo Tablets 1 mg and 2mg, Livalo OD Tablets 1 mg and 2 mg[*5]	Kowa Company, Ltd.	June 26, 2015
◎	ramucirumab (genetical recombination) Cyramza Injection 100 mg, 500 mg	Eli Lilly Japan K.K.	June 22, 2015
◎	macitentan Opsumit Tablet 10 mg	Actelion Pharmaceuticals Japan Ltd.	June 9, 2015
◎	tramadol hydrochloride Onetram Tablets 100 mg	Nippon Shinyaku Co., Ltd.	June 2, 2015
	trelagliptin succinate Zafatek Tablets 50 mg, 100 mg	Takeda Pharmaceutical Company Limited	May 28, 2015
	peginterferon alfa-2b (genetical recombination) Peginteron Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL[*6]	MSD K.K.	May 26, 2015

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
ramosetron hydrochloride Irribow Tablets 2.5 μg and 5 μg[*7], Irribow OD Tablets 2.5 μg and 5 μg[*7]	Astellas Pharma Inc.	May 26, 2015
duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg[*8]	Shionogi & Co., Ltd.	May 26, 2015
nalfurafine hydrochloride Nopicor Capsules 2.5 μg[*9]	Toray Medical Co., Ltd.	May 26, 2015
aripiprazole hydrate Abilify prolonged release aqueous suspension for IM injection 300 mg and 400 mg, Abilify prolonged release aqueous suspension for IM injection 300 mg Syringe and 400 mg Syringe	Otsuka Pharmaceutical Co., Ltd.	May 25, 2015
colistin sodium methanesulfonate Aldreb for Injection 150 mg	GlaxoSmithKline K.K.	May 25, 2015
(1) sofosbuvir, (2) ribavirin (1) Sovaldi Tablets 400 mg, (2) Copegus Tablets 200 mg[*10]	(1) Gilead Sciences, Inc. (2) 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 Eklira 400 μg Genuair 30, 400 μg Genuair 60	Kyorin Pharmaceutical Co., Ltd.	May 20, 2015
4-strain meningococcal vaccine (diphtheria toxoid conjugate) Menactra intramuscular injection	Sanofi K.K.	May 18, 2015
metronidazole Rozex Gel 0.75%	Galderma S.A.	May 11, 2015
elosulfase alfa (genetical recombination) Vimizim I.V. Infusion 5 mg	BioMarin Pharmaceutical Japan Inc.	April 23, 2015
N/A Allergen Extract Mites 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

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
	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*11	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

*1 Mantle cell lymphoma
*2 Suppress progression of functional disorder associated to amyotrophic lateral sclerosis (ALS)
*3 Strabismus
*4 Febrile neutropenia (new pediatric dose)
*5 Familial hypercholesterolaemia (new pediatric dose)
*6 Postoperative adjuvant therapy for malignant melanoma
*7 Irritable bowel syndrome with diarrhea in females
*8 Pain associated with fibromyalgia
*9 Improvement of pruritus in patients with chronic liver disease
*10 Improvement in viraemia among serogroup 2 chronic hepatitis C or compensated cirrhosis type C by using it in combination with sofosbuvir
*11 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”