# Pharmaceuticals and Medical Devices Safety Information

## No. 358 November 2018

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

Available information is listed here

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

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

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# Pharmaceuticals and Medical Devices Safety Information

**No. 358 November 2018**

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


## [Outline of Information]



*E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries*

**Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of providers of medical care and pharmaceutical products.**

If providers of medical care and pharmaceutical products 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 providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

## Abbreviations

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| BRCA | Breast cancer susceptibility gene |
| CRP | C-reactive protein |
| CK | Creatine kinase |
| CPK | Creatine phosphokinase |
| CT | Computed tomography |
| DI | Drug information |
| EPPV | Early Post-marketing Phase Vigilance |
| FY | Fiscal year |
| HER | Human epidermal growth factor receptor |
| LDH | Lactate dehydrogenase |
| MAH | Marketing authorization holder |
| MHLW | Ministry of Health, Labour and Welfare |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PMDSI | Pharmaceuticals and Medical Devices Safety Information |
| PSEHB | Pharmaceutical Safety and Environmental Health Bureau |
| RMP | Risk management plan |
| PSD | Pharmaceutical Safety Division |
| WBC | White blood cell |

# 1

# Safety Measures for Influenza Antiviral Drugs

## 1. Introduction

In 2007, healthcare providers were alerted that abnormal behaviour may occur in patients following administration of Tamiflu on the basis of 2 events widely reported by media that junior high school students who had taken Tamiflu later fell to their deaths, although the existence of a causal relationship between the students' symptoms and use of Tamiflu remained unclear. In addition, as a preventive measure, a statement was added to the Warnings section of the Tamiflu package insert recommending that, as a general rule, Tamiflu should not be administered to teenage patients except when the patient is believed to be at higher risk. In addition, a Dear Healthcare Professional Letters of Emergent Safety Communication (Yellow Letter) was distributed to medical institutions, etc.

Afterward, the causal relationship between administration of Tamiflu and abnormal behaviour was investigated by the Subcommittee on Drug Safety of the Committee on Drug Safety in Pharmaceutical Affairs and Food Sanitation Council (herein after referred to as the Subcommittee on Drug Safety), and working groups, which were established under the Subcommittee on Drug Safety, on the basis of nonclinical studies, epidemiological surveys, and clinical studies, etc. These groups compiled a report on their findings in 2009.

The report stated that as it was difficult to draw any clear conclusions about the causal relationship between Tamiflu and abnormal behaviour, it would be appropriate to continue the current safety measures, including recommending that healthcare professionals generally refrain from the use of Tamiflu in teenage patients.

The Tamiflu safety measure recommending adherence to a general rule of refraining from use in teenage patients was not implemented for other influenza antiviral drugs and a precaution concerning the potential for abnormal behaviour was mentioned in the Important Precautions section of their respective package inserts. Meanwhile, the Subcommittee on Drug Safety conducted annual reviews of this safety measure based on data such as adverse drug reaction (ADR) reports related to abnormal behaviour submitted during the previous year's flu season and the results of epidemiological surveys. Until 2017, the Subcommittee on Drug Safety had concluded that it would be appropriate to continue the safety measure, including refraining from administering Tamiflu to teenage patients. However, the necessity of more comprehensive discussion on the safety measure for influenza antiviral drugs has been pointed out in light of the fact that there was approximately 10 years of accumulated knowledge.

On this backdrop, the Subcommittee on Drug Safety reviewed the way safety measures should be with respect to influenza antiviral drugs on May 16 and July 13, 2018. This section will provide the details of the revision of package inserts of influenza antiviral drugs and information leaflets regarding abnormal behaviour when infected with influenza, based on the results of the discussion by the Subcommittee on Drug Safety.

## 2. Discussion by the Subcommittee on Drug Safety

The Subcommittee on Drug Safety confirmed that a clear causal relationship between abnormal behaviour and use of Tamiflu specifically could not be established, after summarizing the results of nonclinical studies since 2009, approximately 10 years of accumulated scientific knowledge of epidemiological studies, and the following observations:

(1) Abnormal behaviour has been reported in patients infected with influenza, regardless of whether influenza antiviral drugs are given or the specific type of drug prescribed.
(2) There is no clear difference in the occurrence of the abnormal behaviour between teenage patients and those under age 10, both with Tamiflu and other influenza antiviral drugs.

Based on these findings and considering the points mentioned below, the Subcommittee on Drug

Safety confirmed that there is no warranted need for such proactive measure only for Tamiflu as placing a general rule to refrain from use in teenage patients, and instead, the alert should be consistent to all influenza antiviral drugs.

(1) The situation in which a strong precaution is only provided to Tamiflu to refrain from using in teenage patients as a general rule may lead to a misunderstanding that other influenza antiviral drugs are safer than Tamiflu. There was a concern that the precaution to abnormal behaviour in patients infected with influenza including those who taking other influenza antiviral drugs can be undermined, as well.
(2) The guidelines of academic associations also pointed out the necessity of administrating Tamiflu to teenagers if they are severely ill or otherwise warranted, hence another concern was by refraining from using Tamiflu in teenage patients as a preventive measure may lose treatment opportunities of those patients.

As abnormal behaviour has been reported in patients infected with influenza regardless of whether influenza antiviral drugs are given or the specific type of drug prescribed, the necessity of calling further attention to healthcare professionals and caregivers regarding abnormal behaviour in patients infected with influenza was pointed out.

## 3. Revision of the Package Inserts of Influenza Antiviral Drugs

Based on these discussions, a notification of revisions of precautions to the package inserts of influenza antiviral drugs was issued by MHLW on August 21, 2018. The outlines of these revisions are as follows.

(1) From the Warning section of the package insert of Tamiflu, the language concerning the general rule to refrain from using this drug in teenage patients was deleted.
(2) In the Important Precautions section of the package inserts of all the influenza antiviral drugs, language was added stating that abnormal behaviour may occur in patients infected with influenza, regardless of whether influenza antiviral drugs are given or the specific type of drug prescribed, and patients and/or their families must be made aware of the following precautionary points:
    a. Abnormal behaviour may occur.
    b. Caregivers etc. should take preventive measures for accidents including falls at least for 2 days after patients develop pyrexia if they are treated at home.

    Additionally, language stating that severe abnormal behaviour potentially leading to accidents such as falls is known to have been reported to occur with greater frequency in male school-age children/adolescents, and within 2 days after patients develop pyrexia, was added.
(3) In the Clinically Significant Adverse Reactions section of the package inserts of influenza antiviral drugs, language concerning abnormal behaviour that may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and these drugs is currently unclear, was added.

## 4. Precautions Regarding Abnormal Behaviour when Infected with Influenza

Information leaflets for healthcare professionals and for patients etc. have been prepared in cooperation with the Japan Pediatric Society and the Japan Pediatric Association etc., as displayed in Figure 1 below.


Figure 1: Information leaflets for healthcare professionals and for patients etc. (only in Japanese)

## 5. Closing Remarks

The revision of the package inserts of influenza antiviral drugs this time revised the previous action to place a general rule to refrain from administering Tamiflu to teenage patients. Patients and/or their families must nonetheless be aware of these precautionary points, in light of the fact that abnormal behaviour has been reported in patients infected with influenza, regardless of whether influenza antiviral drugs are given or the specific type of drug prescribed. Healthcare professionals are also asked to understand the main purpose of the present revision and to offer their ongoing cooperation to ensure that patients remain properly advised when infected with influenza.

## 6. References


- Materials of the 1st Subcommittee on Drug Safety of the Committee on Drug Safety in Pharmaceutical Affairs and Food Sanitation Council in 2018 (held on May 16, 2018) http://www.mhlw.go.jp/stf/shingi2/0000206683.html (only in Japanese)
- Materials of the 4th Subcommittee on Drug Safety of the Committee on Drug Safety in Pharmaceutical Affairs and Food Sanitation Council in 2018 (held on July 13, 2018) http://www.mhlw.go.jp/stf/shingi2/0000213222_00001.html (only in Japanese)
- Revision of Precautions (Pharmaceutical Safety and Environmental Health Bureau [PSEHB]/ Safety Division [PSD] Notification No. 0821-1, dated August 21, 2018) https://www.mhlw.go.jp/content/11120000/000345399.pdf (only in Japanese)

# 2

# Results of a Survey Investigating Access, Communication, and Utilization of Drug Safety Information at Hospitals and Pharmacies and Desirable Directions

## 1. Introduction

MHLW and the PMDA collaborate to implement safety measures in order to ensure the proper use of pharmaceuticals and medical devices. Such regulatory safety measures include revisions of Precautions of the package inserts of drug products based on the information accumulated in adverse drug reaction (ADR) reports or other sources. Safety information related to these measures is provided to medical institutions by MHLW, PMDA, and pharmaceutical companies through various routes. It is essential that the latest information available is communicated to and utilized by healthcare professionals at clinical settings in an appropriate manner.

PMDA established an expert review committee in 2010 and has since conducted surveys to explore measures to promote the utilization of safety information by the relevant medical institutions by monitoring the access, communication, and utilization of the safety information at medical institutions to ensure the implementation of its regulatory measures whereby to enhance patients' safety.

This section will introduce the results of the survey that PMDA conducted in Fiscal Year (FY) 2017 and the desirable directions of action as indicated by the survey results.

## 2. Survey in Fiscal Year 2017 (hospital and pharmacy surveys)

### (1) Survey method and topics

Table 1 shows the period and major questions in the survey conducted in FY 2017 in hospitals (Hospital survey) and in pharmacies (Pharmacy survey). Questions regarding the handling of drug safety information were included.

The survey was conducted and its results have been compiled in consultation with the Expert Review Committee concerning the Survey Investigating Access, Communication, and Utilization of Drug Safety Information established by PMDA and comprised of experts in medical and pharmaceutical practices and drug information.

Table 1 Survey Outline

| | Hospital survey | Pharmacy survey |
|---|---|---|
| Survey period | Survey period: January 9 to February 16, 2018 | |
| Survey subjects | 10% of hospitals across the country (844 facilities) | 5% of health insurance pharmacies across the country (2 934 facilities) |
| Survey procedure | Survey forms were sent by post to the pharmaceutical safety management supervisors. | Survey forms were sent by post to the supervising pharmacists. |
| | Facilities responded by completing the web survey form or returning the completed survey form by post. | |
| Respondents | Pharmaceutical safety management supervisors | Supervising pharmacists or pharmacists responsible for drug information (DI) management |
| Survey questions | ・ How drug safety information is obtained and communicated in the institution<br>・ Awareness and utilization of risk communication tools such as the Risk | |

| | |
|---|---|
| | Management Plan (RMP), Manuals for Management of Various Serious Adverse Drug Reactions<br>・ Utilization of the internet, the PMDA Medi-navi etc.<br>・ Awareness of the Drugs and Medical Devices Safety Information Reporting System, the Relief System for Adverse Drug Reactions, the PMDA website.<br>・ Sample cases of access to, communication and utilization of information |

**(2) Summary of responding facilities**

373 facilities (44.2%) and 1,647 facilities (56.3%) responded to the hospital and pharmacy surveys, respectively.

Responding facilities are summarized in Figures 1 and 2.

Figure 1:
Number of beds [hospitals]

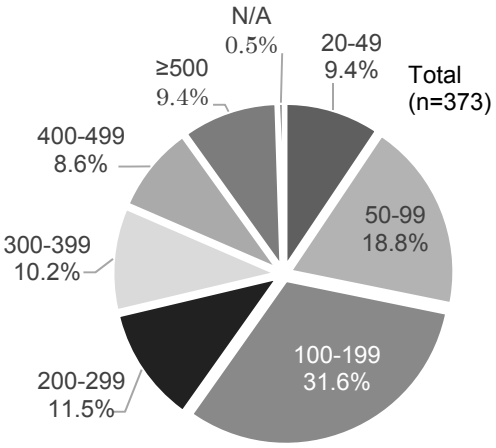
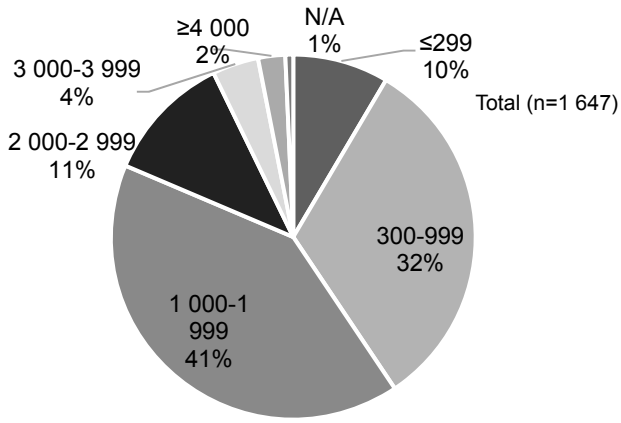



Figure 2: Number of prescriptions filled [pharmacies]
*In December 2017 or for one month preceding response




**(3) Main points of survey results and desirable directions**

This section introduces the Risk Communication Tools namely RMP, Active Utilization of Materials for Additional Risk Minimization Activities, Comprehensive Access to Critical Information, Utilization of the PMDA Medi-navi, (information access and provision) in relation to the survey results and indicated desirable directions.

**1) Active utilization of risk communication tools namely RMP and materials of additional risk minimization activities**

| |
|---|
| Understanding of RMP and use of materials prepared as additional risk minimization activities are required. |

Active utilization of risk communication tools provided by the administration agencies and pharmaceutical companies, etc. is important to share risk information concerning drugs among medical professionals, pharmaceutical companies, administrative agencies, and patients (risk communication). An RMP, one of such communication tools, is a document that compiles information on risks or lack of information identified in the review process of the application for marketing authorization of a drug, as well as activities for mitigation and avoidance of such risks. Preparation and implementation of a RMP are conditions for granting marketing authorization of a drug. Considering properties of individual drugs, materials prepared and distributed as additional risk minimization activities compile information to communicate to medical professionals and patients in addition to usual risk minimization for the purpose of safety measures.

The percentage of facilities that understood RMP was 48.2% among hospital respondents, an increase from the previous survey (22.2%), whereas, however, the percentage was 17.4% in pharmacies, not a significant increase from the previous survey (13.7%) (Fig. 3).

To the question if RMP had been actually utilized or not asked to the facilities that responded as understanding RMP to the preceding question, 50.6% answered that they had utilized RMP in hospitals, an increase from the previous survey (34.0%). The percentage was 39.4% in pharmacies, also an increase from the previous survey (33.6%) (Fig. 4). In both hospitals and pharmacies, the percentage of facilities responding as having utilized RMP was higher among facilities that answered “Fully understand” than among facilities that answered “Understand to some extent” to the preceding question (Fig. 4).

Whereas, 16.5% and 14.3% of the hospitals respectively, and 13.3% and 5.3% (Fig. 5) of the pharmacies respectively, had utilized materials prepared and distributed based on RMP as part of additional risk minimization activities for medication guidance to patients or for information provision to other medical professionals.

Figure 3: Awareness of RMP [hospitals and pharmacies]

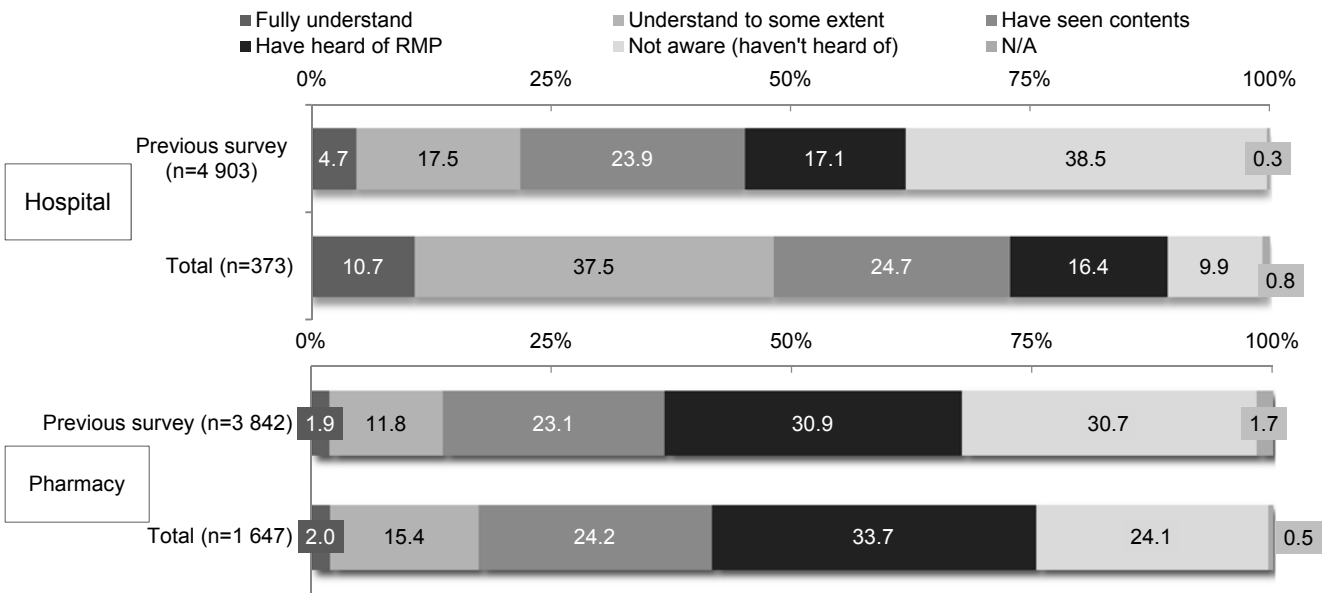


Figure 4: Utilization of RMP [hospitals and pharmacies]
<by awareness of RMP>
(facilities that responded as “Fully understand” or “Understand to some extent” RMP)

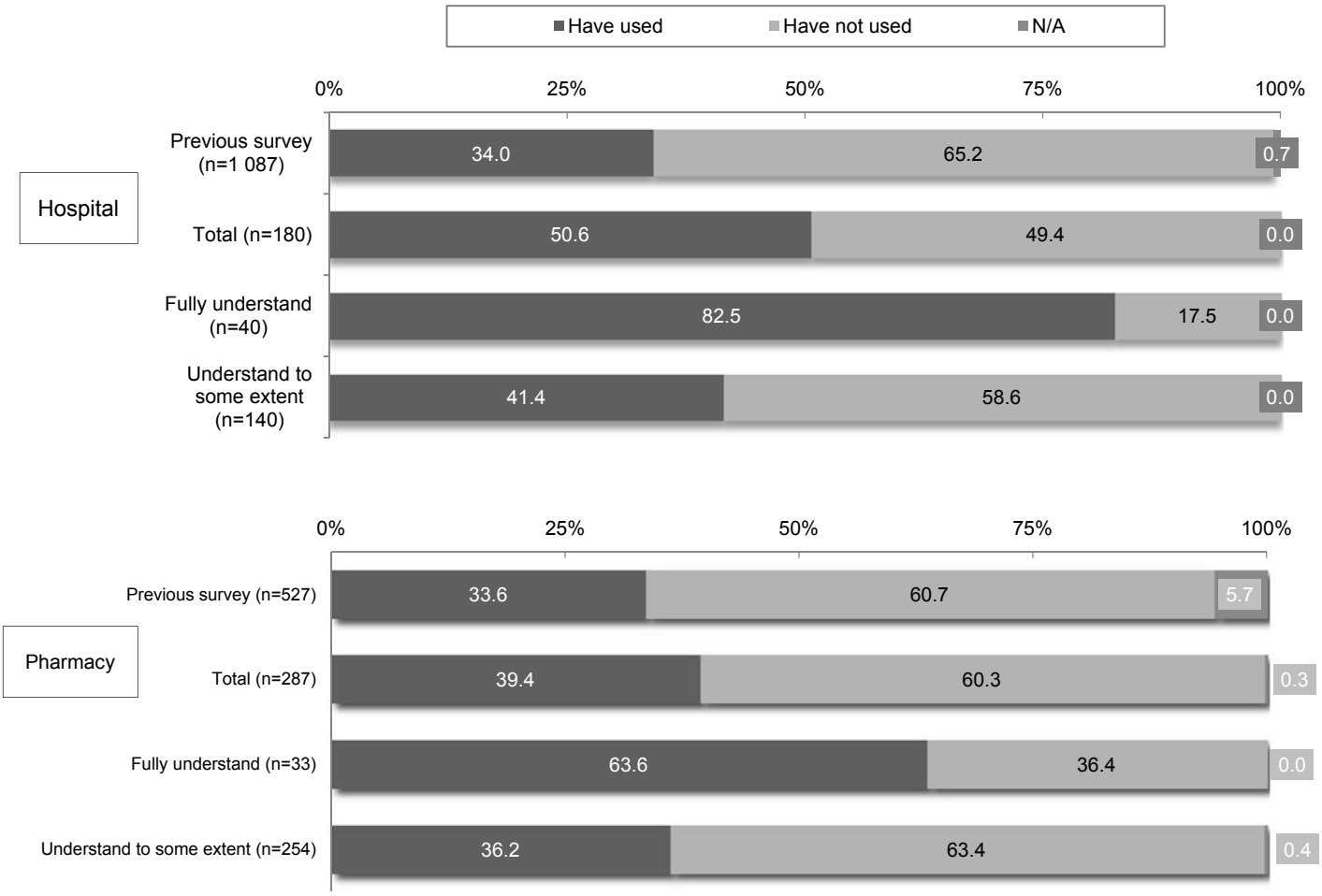
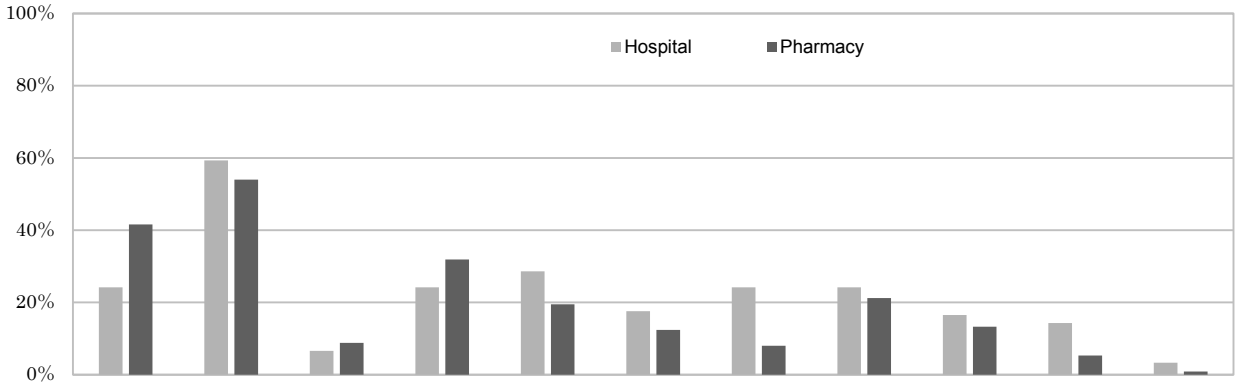


Figure 5: Sample cases of utilization of materials based on Additional Risk Minimization Activities and percentage of response [hospitals and pharmacies]
(facilities that responded as “Fully understand” or “Understand to some extent”, AND “Have used” RMP)




| | Total (n) | Used the RMP outline sheet to gain an understanding of safety specifications, pharmacovigilance and risk minimization plans | Used RMP as an information source to gain an understanding of possible risks when adopting new drugs. | Used RMP to an understanding of the scheduling of post-marketing surveillance , etc. | Used RMP for assessment of drugs linked to onset of adverse drug reactions | Used RMP to respond to inquiries from physicians (hospitals/clinics), etc. | Used RMP to prepare an adverse reaction monitoring plan | Used RMP in the preparation of internal news for pharmacies, etc. | Used RMP as reference for study meetings and workshops | Used materials for patients based on the additional risk minimization activities for medication guidance to patients | Used materials based for healthcare professionals on the additional risk minimization activities to share information within pharmacies or with other professions. | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hospital | 91 | 24.2 | 59.3 | 6.6 | 24.2 | 28.6 | 17.6 | 24.2 | 24.2 | 16.5 | 14.3 | 3.3 |
| Pharmacy | 113 | 41.6 | 54.0 | 8.8 | 31.9 | 19.5 | 12.4 | 8.0 | 21.2 | 13.3 | 5.3 | 0.9 |

<Desirable directions>
Lack of information, ongoing information gathering activities, and required modes of risk minimization activities including information provision can be identified by checking RMPs.
It is particularly important with respect to effective implementation of the safety measure cycle that pharmacists check the contents of RMPs and cooperate with the collection of missing information by MAHs through adverse drug reaction reports, use results surveys, and other sources. It is also important for pharmacists to be involved in risk minimization activities by delivering information to patients using available material.

Considering the correlation between higher levels of understanding and higher rates of utilization of RMPs, PMDA will continue its efforts to enhance understanding of RMP in medical professionals. Medical professionals are also encouraged to actively use the materials with RMP Marking*, which has been launched in order to facilitate utilization of relevant materials and are expected to increase, as well as materials prepared and distributed as part of the additional risk minimization activities which will be available on the PMDA website from FY 2019.

*See Administrative Notice: Marking to Materials Prepared and Distributed for Additional Risk Minimization Activities in the Risk Management Plan of Pharmaceuticals, dated June 8, 2017

**2) Comprehensive access to critical information**

Reliable access to critical information such as Blue Letters and Alerts for Proper Use should be ensured regardless of availability (dealing) of the products at the facilities.

PMDA Alert for Proper Use of Drugs publications are an important source of information that can eventually lead to issuance of a Dear Healthcare Professional Letter of Emergent Safety Communications (Yellow Letter) or a Dear Healthcare Professional Letter of Rapid Safety Communications (Blue Letter). 63.3% of all hospital respondents were aware of the release of MAH Alert for Proper Use of Drugs regarding fulminant type 1 diabetes mellitus associated with Opdivo Intravenous Infusion (dated January 29, 2016). While 98.5% of hospital respondents at which the product was used at the time of the release of the alert were aware of the alert's existence, only 51.7% of hospitals respondents at which the product was not used at that time were aware of the same (Fig. 6).

Among outpatient pharmacies where Opdivo Intravenous Infusion products are not available, 44.1% were aware of the alert (Fig. 7).

Figure 6: Awareness of MAH Alert for Proper Use of Drugs regarding fulminant type 1 diabetes mellitus associated with Opdivo Intravenous Infusion [hospitals]

<by usage>

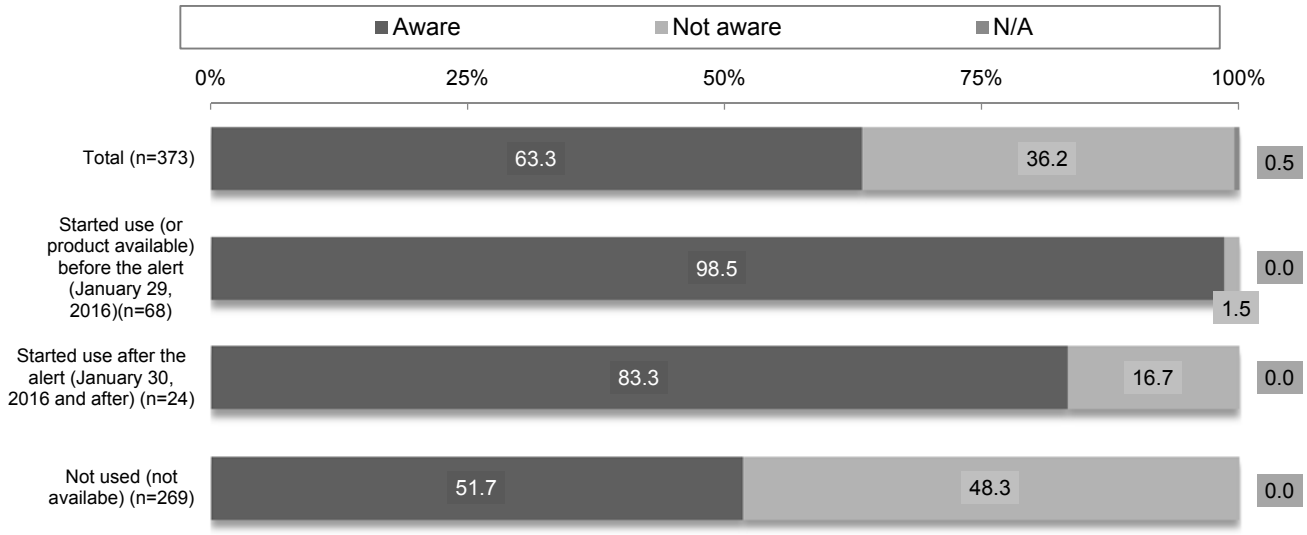
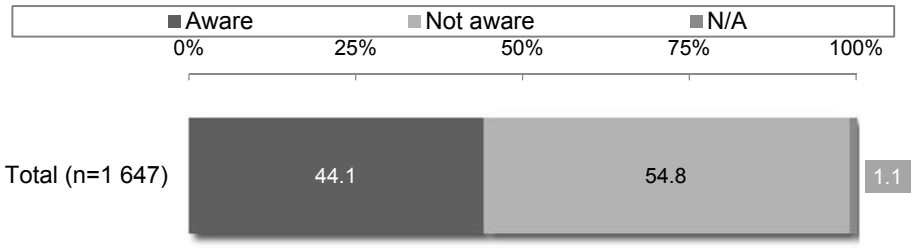



Figure 7: Awareness of MAH Alert for Proper Use of Drugs regarding fulminant type 1 diabetes mellitus associated with Opdivo Intravenous Infusion [pharmacies]




<Desirable directions>

In order to provide safer patient care including follow-up on adverse drug reactions and other undesirable events, understanding the importance and reliable access to information considered critical should be ensured such as Blue Letters and PMDA Alerts for Proper Use of drugs regardless of availability of the relevant products at facilities.

The PMDA Medi-navi identifies all such information by labeling the e-mail subject header to all subscribers as “IMPORTANT”. In this respect as well, use of the PMDA Medi-navi is encouraged for comprehensive access to critical information for proper use of drug products.

**3) Utilization of the PMDA Medi-navi (collection and provision of information)**

- ✓ Utilization of the PMDA Medi-navi is very effective for quick access to information regardless of the size of facilities.
- ✓ Sharing and provision of information delivered by the PMDA Medi-navi is important.

PMDA releases the latest safety information on its website and the PMDA Medi-navi. The survey revealed that 82.0% of hospitals subscribed to the PMDA Medi-navi, an increase from the previous survey (77.3%). Whereas, subscriptions tended to be lower among hospitals with smaller numbers of beds (Fig. 8). Among pharmacies, 67.5% subscribed to the PMDA Medi-navi, also an increase from the previous survey (44.1%) (Fig. 9).

The percentage of pharmacies at which information delivered from the PMDA Medi-navi was shared inside and pharmacies at which such information was provided to patients and other professions was both approximately 85% (Fig. 10).

Figure 8: Subscription to the PMDA Medi-navi [hospitals]
<by number of beds>

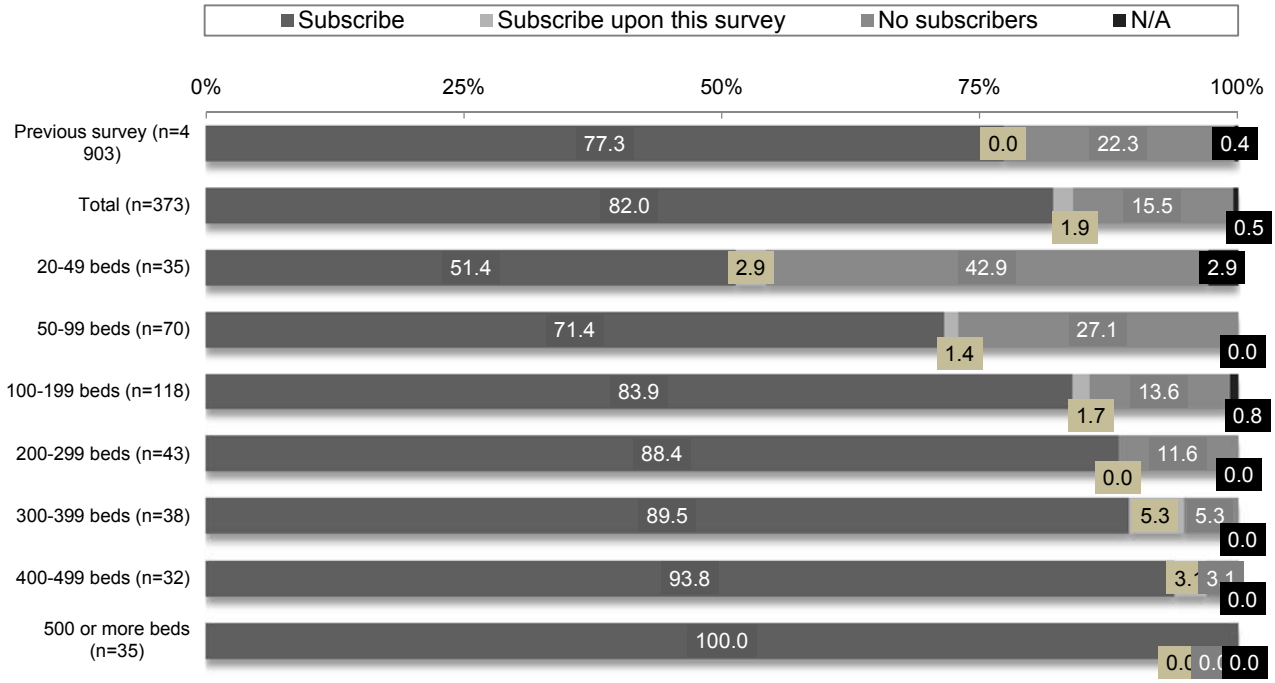



Figure 9: Subscription to the PMDA Medi-navi [pharmacies]

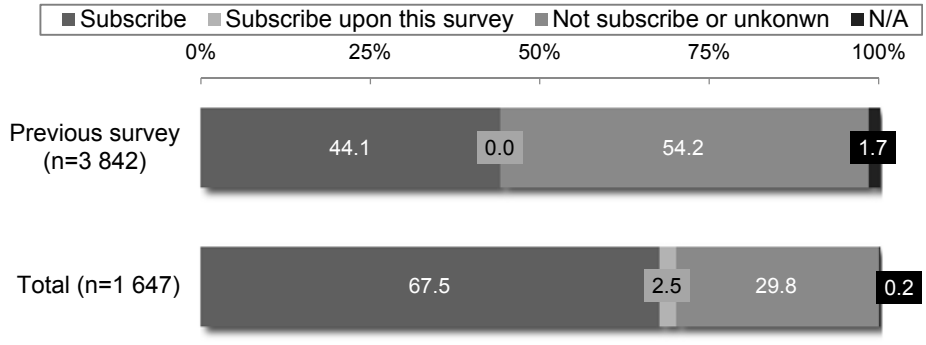
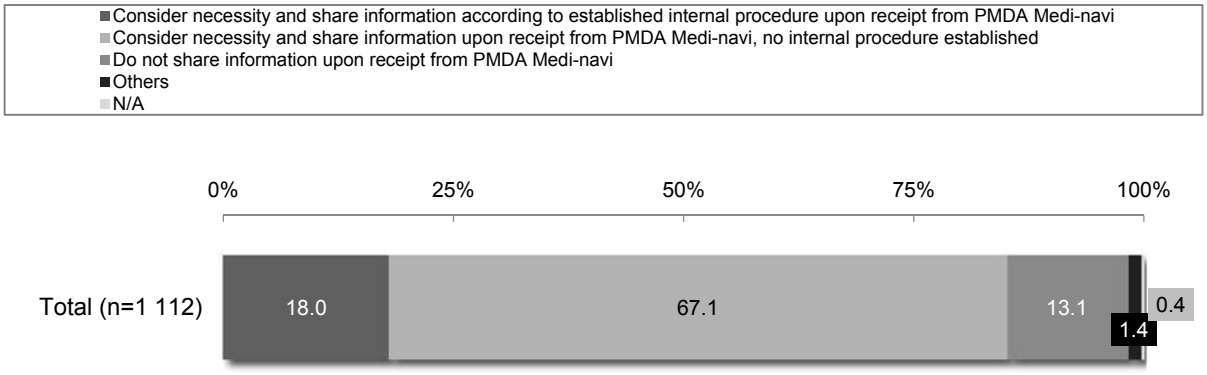
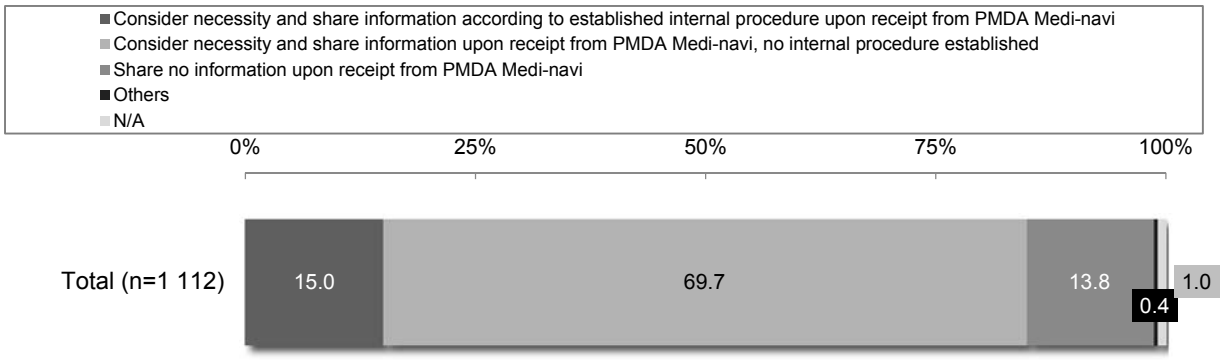


Figure 10: Sharing and provision of information delivered from the PMDA Medi-navi [pharmacies] (pharmacies that answered that there are people who “Subscribe” to the PMDA Medi-navi in the facility.)

<Sharing information inside the pharmacy upon receipt from PMDA Medi-navi>




<Provision of information to patients or other professions upon receipt from the PMDA Medi-navi>




<Desirable directions >

The PMDA Medi-navi is a useful tool to communicate safety information of critical importance concerning pharmaceuticals or medical devices upon its release. Hospitals of smaller bed numbers presumably tend to go without a DI office or full time DI office pharmacists. Under such circumstances, the Medi-navi can be found highly useful in terms of information collection as quick as in hospitals of larger bed numbers. In this respect, active utilization of the tool is all the more encouraged in smaller hospitals.

Among pharmacies, 80% or more shared information delivered by the PMDA Medi-navi as indicated in Figure 10. Continued use of the PMDA Medi-navi is encouraged among pharmacies as well.

## 3. Closing Remarks

The risk communication tools including RMPs addressed in this survey are all available from the pages of the PMDA website listed below. These tools are provided to aid your institution in safety management for pharmaceuticals when adopting drugs into the hospital formulary or providing medication guidance to patients.

[RMP：Risk Management Plan]
http://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0002.html
(only in Japanese)
[Drug Guides for Patients]

http://www.pmda.go.jp/safety/info-services/drugs/items-information/guide-for-patients/0001.html (only in Japanese)
[Manuals for Management of Various Serious Adverse Drug Reactions (for healthcare professionals)]
http://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html (only in Japanese)

Subscription to the Medi-navi is available on the following webpage.
[PMDA Medi-navi]
http://www.pmda.go.jp/safety/info-services/medi-navi/0007.html (only in Japanese)

This section have only introduced part of the results of the survey conducted in FY 2017. Summary of survey results and detailed reports are available on the PMDA website.

Healthcare professionals are expected to make good use of the results of this survey and desirable directions for the proper access, communication and utilization of drug safety information.

[The current survey: Survey on Access, Communication and Utilization of Drug Safety Information in Medical Institutions]
http://www.pmda.go.jp/safety/surveillance-analysis/0010.html (only in Japanese)

<Hospital Survey>

- Desirable Directions (2-page edition): http://www.pmda.go.jp/files/000225903.pdf (only in Japanese)
- Main Points of Survey Results and Desirable Directions: http://www.pmda.go.jp/files/000225904.pdf (only in Japanese)
- Report on Survey Results (full results) : http://www.pmda.go.jp/files/000225905.pdf (only in Japanese)

<Pharmacy Survey>

- Desirable Directions (2-page edition): http://www.pmda.go.jp/files/000225906.pdf (only in Japanese)
- Main Points of Surveillance Results and Desirable Directions: http://www.pmda.go.jp/files/000225907.pdf (only in Japanese)
- Report on Surveillance Results (full results): http://www.pmda.go.jp/files/000225908.pdf (only in Japanese)

# 3

# Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated October 23, 2018, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

## 1 Secukinumab (genetical recombination)

| | |
|---|---|
| **Branded name (name of company)** | Cosentyx for s.c. injection 150 mg syringe, Cosentyx for s.c. injection 150 mg pen (Novartis Pharma K.K.) |
| **Therapeutic category** | Miscellaneous metabolism agents-Miscellaneous |
| **Indications** | The following diseases in patients who were not sufficiently responsive to conventional therapies:<br>Psoriasis vulgaris, psoriatic arthritis, and pustular psoriasis |

**PRECAUTIONS (revised language is underlined)**

**Careful Administration**

Patients with <u>inflammatory bowel disease</u>

**Adverse reactions (clinically significant adverse reactions)**

**<u>Inflammatory bowel disease</u>**:
<u>Inflammatory bowel disease may occur. Patients should be carefully monitored, and if inflammatory bowel disease is suspected, appropriate measures should be taken.</u>

**Reference information**

Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported in approximately the previous 3 years and 4 months (April 2015 to August 2018).
Cases involving inflammatory bowel disease: 6 (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 2 600

Launched in Japan:
Cosentyx for s.c. injection 150 mg syringe: February 2015
Cosentyx for s.c. injection 150 mg pen: November 2016

## Case summary

| No. | Patient | | Daily dose/Treatment duration | Adverse reactions | |
|---|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 1 | Female 40s | Psoriasis vulgaris | 300 mg 200 days | **Inflammatory bowel disease** | |
| | | | | Approx. 2 years before administration | Administration of ustekinumab initiated.<br>Administration of ustekinumab completed. |
| | | | | 12 days before administration | CRP 0.054 mg/dL. |
| | | | | Day 1 of administration | Administration of secukinumab started at a dosage of 300 mg/week. |
| | | | | Day 57 of administration | Secukinumab dosage changed to 300 mg for 4 weeks. |
| | | | | Approx. 5th months of administration ( day 123 to 153 of administration) | The patient developed mucous and blood-rich stools. Ulcerative colitis affecting the left hemicolon accompanied by severe erosion and ulcer was confirmed via colonoscopy at the gastroenterological medicine department at Hospital A. The patient was admitted to the hospital.<br>· Sigmoid colon: No visible vascular pattern because of oedema and redness. Bleeding tendency, map-patterned erosion and ulceration were observed.<br>· Rectal: Same findings as those made in sigmoid colon. |
| | | | | Day 193 of administration | Lower gastrointestinal haemorrhage/occult blood and abdominal pain/stabbing pain were developed. Slight symptom improvement was observed following treatment with mesalazine at a dosage of 2 400 mg/day, but no further improvement was seen afterward. |
| | | | | Day 200 of administration | The last dosage of secukinumab was 300 mg. This dosage was administered for 4 weeks. |
| | | | | 11 days after the last administration | CRP 1.671 mg/dL. |
| | | | | 14 days after the last administration | The patient visited a dermatology clinic of Hospital B and diagnosed that secukinumab may be the cause of the symptoms, and the drug was discontinued. |
| | | | | 44 days after the last administration | CRP 0.525 mg/dL. |
| | | | | 53 days after the last administration | Administration of adalimumab initiated to treat inflammatory bowel disease and psoriasis. |
| | | | | 56 days after the last administration | Once daily administration of mesalazine enema 1% preparation initiated. |
| | | | | 105 days after the last administration | The patient experienced bloody stools. |
| | | | | 114 days after the last administration | CRP 0.085 mg/dL. |
| | | | | 238 days after | CRP 0.055 mg/dL. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | the last administration | |
| | | | | 329 days after the last administration | The patient no longer experienced bloody stools or abdominal pain. Inflammatory bowel disease symptoms improved. Administration of mesalazine and adalimumab continued. |
| | Concomitant medications: no information | | | | |

## 2 Lamotrigine

| | |
|---|---|
| **Branded name (name of company)** | [1] Lamictal Tablets 25 mg, 100 mg (Glaxo Smith Kline K.K.), and the others<br>[2] Lamictal Tablets for Pediatric 2 mg, 5 mg (Glaxo Smith Kline K.K.), and the others |
| **Therapeutic category** | Antiepileptics, psychotropics |
| **Indications** | [1] · Monotherapy for the following types of seizures in epileptic patients:<br>Partial seizures (including secondary generalized seizures), tonic-clonic seizures, typical absence seizures<br>・Concomitant therapy with antiepileptics for the following types of seizures in epileptic patients who were not sufficiently responsive to other antiepileptics:<br>Partial seizures (including secondary generalized seizures), tonic-clonic seizures, generalized seizures associated with Lennox-Gastaut syndrome<br>・Suppression of recurrent/relapsed mood episodes in patients with bipolar disorder<br>[2] · Monotherapy for the following types of seizures in epileptic patients:<br>Typical absence seizures<br>· Concomitant therapy with antiepileptics for the following types of seizures in epileptic patients who were not sufficiently responsive to other antiepileptics:<br>Partial seizures (including secondary generalized seizures), tonic-clonic seizures, generalized seizures associated with Lennox-Gastaut syndrome |

**PRECAUTIONS (revised language is underlined)**

| | |
|---|---|
| **Adverse reactions (clinically significant adverse reactions)** | **Haemophagocytic syndrome**:<br>Haemophagocytic syndrome may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. |
| **Reference information** | Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported in approximately the previous 3 years and 3 months (April 2015 to July 2018).<br>Cases involving haemophagocytic syndrome: 1 (no patient mortalities)<br><br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 196 000<br><br>Launched in Japan: December 2008 |

## Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/ Age</th><th>Reason for use (complications)</th><th>Clinical course and therapeutic measures</th></tr>
<tr><td>1</td><td>Female 20s</td><td>Bipolar disorder (none)</td><td>25 mg 42 days (incl. 3 days drug discontinuation)</td><td>Haemophagocytic syndrome, neutropenia, cytopenia, high serum lactate dehydrogenase (LDH), high serum ferritin, skin eruption, hyperthermia/pyrexia, hepatic disorder, malaise, and elevated hepatic deviation enzyme level<br>Day 1 of administration: Administration of lamotrigine was initiated at a dosage of 25 mg taken once daily by the previous physician for the treatment of bipolar disorder.<br>After the administration: After the initiation of administration (2 weeks before the occurrence of haemophagocytic syndrome), the patient began experiencing transient mild skin eruptions. Symptoms improved after suspension of administration for 3 days, after which treatment was resumed.<br>42 days after administration (Day of discontinuation): The patient visited an emergency outpatient unit due to hyperthermia/pyrexia and malaise persisting for 2 weeks. Neutropenia and hepatic disorder were found. Blood test showed neutropenia and elevated hepatic enzymes. The patient tested negative on a microbial culture test, and no findings suggestive of other infection. CT imaging revealed abnormal shadows at the early arterial phase in liver, and a low-density area could be observed proximal to the portal vein tract. Haemophagocytic syndrome was suspected based on high blood LDH and high serum ferritin. Bone marrow aspiration confirmed haemophagocytosis. The diagnostic criteria was met and the patient was diagnosed as haemophagocytic syndrome. Lamotrigine was discontinued. Methylprednisolone 1 g/day was administered for 3 days, and the treatment was switched to prednisolone 50 mg and tapered off.<br>After discontinuation: Later, a drug lymphocyte stimulation test was performed and the patient tested positive for lamotrigine. Cytopenia and hepatic disorder improved within 2 weeks, and no relapse occurred during the following 6 months.</td></tr>
<tr><td colspan="5">Laboratory Examination
<table>
<tr><th></th><th>Day 42 of administration</th><th>1 day after discontinuation</th></tr>
<tr><td>WBC (/mcl)</td><td>1 200</td><td>–</td></tr>
<tr><td>Neutrophil count (/mcl)</td><td>0</td><td>–</td></tr>
<tr><td>Blood lactate dehydrogenase (IU/l)</td><td>6 335</td><td>–</td></tr>
<tr><td>Serum ferritin (ng/ml)</td><td>–</td><td>28 035</td></tr>
<tr><td>sIL-2R (U/ml)</td><td>–</td><td>4 430</td></tr>
</table></td></tr>
<tr><td colspan="5">Suspected concomitant medications: None</td></tr>
<tr><td colspan="5">Concomitant medications: None</td></tr>
<tr><td colspan="5">Notes: Company report</td></tr>
</table>

# 3 Lenvatinib mesilate

| | |
|---|---|
| **Branded name (name of company)** | Lenvima Capsules 4 mg, 10 mg (Eisai Co., Ltd.) |
| **Therapeutic category** | Antineoplastics-Miscellaneous |
| **Indications** | Unresectable thyroid cancer, unresectable hepatocellular carcinoma |

**PRECAUTIONS (revised language is underlined)**

| | |
|---|---|
| **Careful Administration** | Patients with lung metastasis |
| **Adverse reactions (clinically significant adverse reactions)** | **Gastrointestinal perforation, fistula formation, and pneumothorax**:<br>Intestinal perforation, anal fistula, enterovesical fistula, and pneumothorax, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. |
| **Reference information** | Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported in approximately the previous 3 years and 3 months (April 2015 to July 2018).<br>Cases involving pneumothorax: 10 (no patient mortalities)<br><br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 4 200<br><br>Launched in Japan: May 2015 |

## Case summary

| No. | Patient | | Daily dose/Treatment duration | Adverse reactions | |
|---|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 1 | Female 60s | Anaplastic thyroid cancer (hypertension) | 24 mg<br>35 days<br>↓<br>20 mg<br>99 days<br>↓<br>14 mg<br>122 days<br>↓<br>10 mg<br>18 days | **Pneumothorax** | |
| | | | | Before administration | The patient visited a local hospital with a chief complain of neck swelling and difficult swallowing. Ultrasonography revealed a mass lesion in left lobe of the thyroid gland and the patient was subsequently referred to the reporter's hospital. Cytodiagnosis was performed and the patient's condition diagnosed as anaplastic thyroid cancer.<br>Multiple metastases to the lungs (subpleural, and proximal to the bronchi, etc.) were observed. No pulmonary bullae or blebs were found. The patient had no history of pneumothorax. |
| | | | | Day 1 of administration | Administration of lenvatinib mesilate was initiated at a dosage of 24 mg/day. |
| | | | | Day 15 of administration | Hypertension was detected. Administration of olmesartan medoxomil at a dosage of 20 mg was added to the patient's treatment regimen.<br>Proteinuria was observed. (this symptom persisted until the patient's death. However, the lenvatinib mesilate dosage had previously been reduced due to ADR onset) |
| | | | | Day 19 of administration | The patient's hypertension normalized. |
| | | | | Day 29 of administration | A CT examination was performed after 1 month of lenvatinib mesilate administration that revealed shrinkage of the primary carcinoma, as well as shrinkage and cavitation of the pulmonary metastases. |
| | | | | Day 36 of administration | Hand and foot syndrome occurred (the patient experienced mild pain in her fingers and plantar regions). The dosage of lenvatinib mesilate was reduced to 20 mg/day. |
| | | | | Day 43 of administration | The patient recovered from hand and foot syndrome. |
| | | | | Day 118 of administration | Cavitation of the pulmonary metastases was observed. |
| | | | | Day 135 of administration | The dosage of lenvatinib mesilate was reduced to 14 mg/day due to onset of proteinuria. |
| | | | | Day 148 of administration | Pneumothorax occurred. A CT examination confirmed the development of right pneumothorax and the patient was hospitalized on an emergency basis.<br>Thoracic cavity drainage was performed and pneumothorax promptly improved. The patient was discharged from the hospital on day 158 of administration, but pneumothorax relapsed on day 162 of administration.<br>A total of 4 instances of right pneumothorax (on days 148, 162, 204, and 237 of administration) and 1 instance of left pneumothorax (on day 240 of administration) occurred and were treated. |
| | | | | Day 257 of administration | The dosage of lenvatinib mesilate was reduced to 10 mg/day due to inappetence and queasy. |
| | | | | Day 275 of | Administration of lenvatinib mesilate was discontinued. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | administration (Day of discontinuation)<br>1 day after the last administration | A refractory lesion was identified during treatment of the right refractory pneumothorax. The patient died of left carcinomatous pleurisy. The cause of death was determined to have been the inability to control the primary disease due to the reduction of the lenvatinib mesilate dosage from 14 mg/day to 10 mg/day.<br>The patient did not recover from pneumothorax. |
| | Concomitant medications: amlodipine besylate | | | | |

| No. | Patient | | Daily dose/Treatment duration | Adverse reactions | |
|---|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 2 | Male 50s | Anaplastic thyroid cancer (hypertension) | 24 mg 57 days ↓ discontinued ↓ 20 mg 15 days | **Pneumothorax** | |
| | | | | Before administration | The patient was referred from another medical institution. Anaplastic thyroid cancer and multiple pulmonary metastases were observed. There were small widespread metastases throughout the lungs and confirming their locations and sizes was difficult. |
| | | | | Day 1 of administration | Administration of lenvatinib mesilate was initiated at a dosage of 24 mg/day. |
| | | | | Day 54 of administration | The patient visited the hospital with a complaint of dyspnea and chest pain. Pneumothorax in the upper left lung was observed. Thoracic cavity drainage was performed. |
| | | | | Day 58 of administration (Day of discontinuation) | Thoracic cavity drainage was performed but the patient showed poor recovery. Administration of lenvatinib mesilate was discontinued as a precaution. During hospitalization, the patient wore an oxygen mask supplying oxygen at a rate of 2-3 L/min. Oxygen saturation ($SpO_2$) reduced to 90%, and no further decreases were observed. |
| | | | | 5 days after the discontinuation | Pleurodesis was performed by the thoracic surgery department. |
| | | | | 8 days after the discontinuation (Day of resumed administration) | Administration of lenvatinib mesilate was resumed at a dosage of 20 mg/day. |
| | | | | Day 2 of resumed administration | The thoracic drain was removed after pneumothorax went into remission. |
| | | | | Day 7 of resumed administration | The patient was discharged from the hospital. |
| | | | | Day 16 of resumed administration (Day of discontinuation of resumed administration) | The patient visited the hospital with a complaint of dyspnea. Lenvatinib mesilate was not readministered. The patient's condition was diagnosed as right pneumothorax based on a chest x-ray. Thoracic cavity drainage was performed and the right pneumothorax went into remission. |
| | Concomitant medications: amlodipine besylate | | | | |

# 4

# Revision of Precautions (No. 298)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated October 16 and 23, 2018.

1 **Hyperlipidaemia agents, Cardiovascular agents-Miscellaneous**

## [1] Atorvastatin calcium hydrate
## [2] Ezetimibe/atorvastatin calcium hydrate
## [3] Pravastatin sodium
## [4] Amlodipine basilate/atorvastatin calcium hydrate

| | |
|---|---|
| **Branded name** | [1] Lipitor Tablets 5 mg, 10 mg (Astellas Pharma Inc.), and the others<br>[2] Atozet Combination Tablets LD, HD (MSD K.K.)<br>[3] Mevalotin Tablets 5, 10, Mevalotin Fine Granules 0.5%, 1% (Daiichi Sankyo Propharma Co., Ltd.), and the others<br>[4] Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban (Pfizer Japan Inc.), and the others |
| **Important precautions** | This drug should be co-administered with fibrates in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with fibrates is unavoidable, clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately. |

2 **Hyperlipidaemia agents**

## Clinofibrate

| | |
|---|---|
| **Branded name** | Lipoclin Tablets 200 (Sumitomo Dainippon Pharma Co., Ltd.) |
| **Careful administration** | Patients receiving HMG-CoA reductase inhibitors (e.g., pravastatin sodium, simvastatin, fluvastatin sodium) |
| **Important precautions** | This drug should be co-administered with HMG-CoA reductase inhibitors in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with HMG-CoA reductase inhibitors is unavoidable, initiation of treatment with this drug should begin at a low dose and clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately. |

3 **Hyperlipidaemia agents**

## Clofibrate

| | |
|---|---|
| **Branded name** | Clofibrate Capsules 250 mg [Tsuruhara] (Tsuruhara Pharmaceutical Co., Ltd.) |
| **Careful administration** | Patients receiving HMG-CoA reductase inhibitors (e.g., pravastatin sodium, simvastatin, fluvastatin sodium) |
| **Important precautions** | This drug should be co-administered with HMG-CoA reductase inhibitors in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with HMG-CoA reductase inhibitors is unavoidable, initiation of treatment with this drug should begin at a low dose and clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately. |
| **Precautions for Co-administration** | HMG-CoA reductase inhibitors (e.g., pravastatin sodium, simvastatin, fluvastatin sodium) |

4 **Hyperlipidaemia agents**

## Simvastatin

| | |
|---|---|
| **Branded name** | Lipovas Tablets 5, 10, 20 (MSD K.K.), and the others |
| **Careful administration** | Patients receiving fibrates (e.g., bezafibrate) |
| **Important precautions** | This drug should be co-administered with fibrates in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment; the dosage of this drug should not exceed 10 mg/day. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with fibrates is unavoidable, clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately. |

5 **Hyperlipidaemia agents**

## Pitavastatin calcium hydrate

| | |
|---|---|
| **Branded name** | Livalo Tab. 1 mg, 2 mg, 4 mg, Livalo OD Tab. 1 mg, 2 mg, 4 mg (Kowa Company, Ltd.), and the others |
| **Important precautions** | This drug should be co-administered with fibrates in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with fibrates is unavoidable, clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately. |

6 **Hyperlipidaemia agents**

## [1] Fenofibrate
## [2] Bezafibrate

**Branded name**

[1] Tricor Tablets 53.3 mg, 80 mg (Mylan EPD G.K.), Lipidil Tablets 53.3 mg, 80 mg (Aska Pharmaceutical. Co., Ltd.), and the others
[2] Bezatol SR Tab. 100 mg, 200 mg (Kissei Pharmaceutical Co., Ltd.), and the others

**Important precautions**

This drug should be co-administered with HMG-CoA reductase inhibitors in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with HMG-CoA reductase inhibitors is unavoidable, initiation of treatment with this drug should begin at a low dose and clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately.

7 **Hyperlipidaemia agents**

## Fluvastatin sodium

**Branded name**

Lochol Tablets 10 mg, 20 mg, 30 mg (Sun Pharma Japan Limited), and the others

**Careful administration**

Patients receiving fibrates (e.g., bezafibrate)

**Important precautions**

This drug should be co-administered with fibrates in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with fibrates is unavoidable, clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately.

8 **Hyperlipidaemia agents**

## Pemafibrate

| | |
|---|---|
| **Branded name** | Parmodia Tab. 0.1mg (Kowa Company, Ltd.) |
| **Important precautions** | This drug should be co-administered with HMG-CoA reductase inhibitors in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with HMG-CoA reductase inhibitors is unavoidable, initiation of treatment with this drug should begin at a low dose and clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine levels is observed, administration of this drug combination should be discontinued immediately. |
| **Precautions for Co-administration** | HMG-CoA reductase inhibitors (e.g., pravastatin sodium, simvastatin, fluvastatin sodium) |

9 **Hyperlipidaemia agents**

## Rosuvastatin calcium

| | |
|---|---|
| **Branded name** | Crestor Tablets 2.5 mg, 5 mg, Crestor OD Tablets 2.5 mg, 5 mg (AstraZeneca K.K.), and the others |
| **Important precautions** | This drug should be co-administered with fibrates in patients with abnormal renal function values only when such use is deemed to be absolutely necessary for treatment. Rhabdomyolysis accompanied by rapid deterioration of renal function tends to occur. When administration of this drug in combination with fibrates is unavoidable, clinical laboratory tests examining renal function should be performed periodically. If appearance of subjective symptoms (myalgia, feeling of weakness), increased CK (CPK) level, increased blood or urine myoglobin level, or signs of diminished renal function such as increased serum creatinine level is observed, administration of this drug combination should be discontinued immediately. |

10 **Antiepileptics, Psychotropics**

## Lamotrigine

| | |
|---|---|
| **Branded name** | [1] Lamictal Tablets 25 mg, 100 mg (Glaxo Smith Kline K.K.), and the others<br>[2] Lamictal Tablets for Pediatric 2 mg, 5 mg (Glaxo Smith Kline K.K.), and the others |
| **Adverse reactions (clinically significant adverse reactions)** | **Haemophagocytic syndrome**:<br>Haemophagocytic syndrome may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. |

11 **Miscellaneous metabolism agents-Miscellaneous**

## Secukinumab (genetical recombination)

| | |
|---|---|
| **Branded name** | Cosentyx for s.c. injection 150 mg syringe, Cosentyx for s.c. injection 150 mg pen (Novartis Pharma K.K.) |
| **Careful administration** | Patients with inflammatory bowel disease |
| **Adverse reactions (clinically significant adverse reactions)** | **Inflammatory bowel disease**:<br>Inflammatory bowel disease may occur. Patients should be carefully monitored, and if inflammatory bowel disease is suspected, appropriate measures should be taken. |

12 **Antineoplastics-Miscellaneous**

## Lenvatinib mesilate

| | |
|---|---|
| **Branded name** | Lenvima Capsules 4 mg, 10 mg (Eisai Co., Ltd.) |
| **Careful administration** | Patients with lung metastasis |
| **Adverse reactions (clinically significant adverse reactions)** | **Gastrointestinal perforation, fistula formation, and pneumothorax**:<br>Intestinal perforation, anal fistula, enterovesical fistula, and pneumothorax, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. |

# 5

# List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of October 31, 2018)
◎: Products for which EPPV was initiated after September 1, 2018

| | Nonproprietary name<br>Branded name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | Levonorgestrel/ethinylestradiol<br>Jemina Tablets | Nobelpharma Co., Ltd. | October 4, 2018 |
| ◎ | Spiramycin<br>Spiramycin 1.5M IU Tablets [Sanofi] | Sanofi K.K. | September 25, 2018 |
| ◎ | Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate<br>Odefsey Combination Tablets | Janssen Pharmaceutical K.K. | September 20, 2018 |
| ◎ | Fidaxomicin<br>Dafclir Tablets 200 mg | Astellas Pharma Inc. | September 18, 2018 |
| | Obinutuzumab (genetical recombination)<br>Gazyva Intravenous Infusion 1000 mg | Chugai Pharmaceutical Co., Ltd. | August 29, 2018 |
| | Durvalumab (genetical recombination)<br>Imfinzi Injection 120 mg, 500 mg | AstraZeneca K.K. | August 29, 2018 |
| | Ipilimumab (genetical recombination) *1<br>Yervoy Injection 50 mg | Bristol-Myers Squibb K.K. | August 21, 2018 |
| | Nivolumab (genetical recombination) *2<br>Opdivo I.V. Infusion 20 mg, 100 mg | Ono Pharmaceutical Co., Ltd. | August 21, 2018 |
| | Tedizolid phosphate<br>Sivextro Tablets 200 mg, Sivextro for iv infusion 200 mg | Bayer Yakuhin, Ltd. | August 21, 2018 |
| | Condoliase<br>Hernicore 1.25 Units for Intradiscal Inj. | Seikagaku Corporation | August 1, 2018 |
| | Fosravuconazole L-lysine ethanolate<br>Nailin Capsules 100 mg | Sato Pharmaceutical Co., Ltd. | July 27, 2018 |
| | Canakinumab (genetical recombination) *3<br>Ilaris for S.C. Injection 150 mg, Ilaris Solution for S.C. Injection 150 mg | Novartis Pharma K.K. | July 2, 2018 |
| | Olaparib*4<br>Lynparza Tablets 100 mg, 150 mg | AstraZeneca K.K. | July 2, 2018 |

| Nonproprietary name<br>Branded name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| Japanese cedar pollen extract<br>Cedarcure Japanese Cedar Pollen Sublingual Tablets 2,000 JAU, 5,000 JAU | Torii Pharmaceutical Co., Ltd. | June 29, 2018 |
| Ibuprofen L-lysine<br>Ibulief I.V. Injection 20 mg | Senju Pharmaceutical Co., Ltd. | June 14, 2018 |
| Rasagiline mesilate<br>Azilect Tablets 0.5 mg, 1 mg | Takeda Pharmaceutical Company Limited. | June 11, 2018 |
| Sirolimus<br>Rapalimus Gel 0.2% | Nobelpharma Co., Ltd. | June 6, 2018 |
| Pemafibrate<br>Parmodia Tab. 0.1 mg | Kowa Company, Ltd. | June 1, 2018 |
| Migalastat hydrochloride<br>Galafold Capsules 123 mg | Amicus Therapeutics, Inc. | May 30, 2018 |
| Letermovir<br>Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg | MSD K.K. | May 28, 2018 |
| Mepolizumab (genetical recombination) *5<br>Nucala for S.C. Injection 100 mg | GlaxoSmithKline K.K. | May 25, 2018 |
| Ipilimumab (genetical recombination)<br>Yervoy Injection 50 mg | Bristol-Myers Squibb K.K. | May 25, 2018 |
| Nivolumab (genetical recombination)<br>Opdivo I.V. Infusion 20 mg, 100 mg | Ono Pharmaceutical Co., Ltd. | May 25, 2018 |
| Botulinum toxin type A*6<br>Botox for Injection 50 Units, 100 Units | GlaxoSmithKline K.K. | May 25, 2018 |
| Tofacitinib citrate*7<br>Xeljanz Tablets 5 mg | Pfizer Japan Inc. | May 25, 2018 |
| Emicizumab (genetical recombination)<br>Hemlibra Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg | Chugai Pharmaceutical Co., Ltd. | May 22, 2018 |
| Guselkumab (genetical recombination)<br>Tremfya Subcutaneous Injection 100 mg Syringe | Janssen Pharmaceutical K.K. | May 22, 2018 |
| Evocalcet<br>Orkedia Tablets 1 mg, 2 mg | Kyowa Hakko Kirin Co., Ltd. | May 22, 2018 |
| Hydromorphone hydrochloride<br>Naruvein Injection 2 mg, 20 mg | Daiichi Sankyo Propharma Co., Ltd. | May 16, 2018 |
| Bedaquiline fumarate<br>Sirturo Tablets 100 mg | Janssen Pharmaceutical K.K. | May 8, 2018 |

*1 Radically unresectable or metastatic renal cell carcinoma

*2 Radically unresectable or metastatic renal cell carcinoma

*3 Systemic-onset juvenile idiopathic arthritis that does not adequately respond to existing treatments

*4 Unresectable or recurrent germline *BRCA*-mutated, HER2-negative metastatic breast cancer previously treated with chemotherapy

*5 Eosinophilic granulomatosis with polyangiitis that does not adequately respond to existing treatments

*6 Spasmodic dysphonia

*7 Remission induction or maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who were not sufficiently responsive to conventional treatments)