Pharmaceuticals and Medical Devices Safety Information

No. 356 September 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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Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by:
Pharmaceuticals and Medical Devices Agency

Office of Safety I,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan E-mail: safety.info@pmda.go.jp

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Pharmaceuticals and Medical Devices Safety Information

No. 356 September 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
BP	Blood pressure
BRCA	Breast cancer susceptibility gene
ECCJ	Electromagnetic Compatibility Conference Japan
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HER	Human epidermal growth factor receptor
LAN	Local area network
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MID-NET	Medical Information Database NETwork
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information

1

Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions

1. Introduction

Regarding measures to promote proper radio wave utilization taken to date, the Electromagnetic Compatibility Conference Japan (ECCJ, a conference that academic experts, related government agencies, and industry organizations constitute to discuss measures to prevent/eliminate interference of radio frequency with electronic devices and others) established in September 2015 the Radio Wave Utilization Promotion Committee for Medical Institutions and the committee has since continued to discuss the issue. The results of such discussions were published in April 2016 as the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions (the Guidance).The Guidance was followed by a video and e-learning teaching materials that excerpted its contents released for public awareness and education in April 2018. The Ministry of Internal Affairs and Communication requested dissemination of the release of the Guidance and the materials for public awareness and education from the Ministry of Health, Labour and Welfare, which then notified medical institutions accordingly. This section will introduce the excerpts of the respective contents of the Guidance and materials for public awareness and education of the Guidance.

2. Purpose of the Guidance

Radio wave-emitting devices such as mobile phones and wireless local area network (LAN) devices have increasingly become part of everyday life. Such devices are also used in medical institutions as critical tools for data collection by healthcare providers and for communication by inpatients and outpatients with their families or friends. Consequently, radio wave-emitting devices brought in by patients and other parties from outside are also present in medical institutions besides those under the supervision of the institution. In consideration of the anticipated increase in use of radio wave-emitting devices in medical institutions, problems could arise related to medical devices, etc. that utilize radio waves if appropriate care is not taken with regard to radio frequencies.

Under these circumstances, the Guidance is meant for healthcare professionals, marketing authorization holders of medical devices or of healthcare systems, and providers of wireless LAN network, mobile phones, or other communication devices with the purpose of providing basic information required for safe and secure use of radio waves in medical institutions in an easy-to-understand manner.

3. 3 principles for safe and secure radio wave utilization

To respond to the anticipated increase in opportunities to use radio wave-emitting devices in medical institutions, it is important to prepare an environment ensuring safe and secure use of radio wave-emitting devices and medical devices. It is also important to adhere to the following 3 principles when implementing required measures, while taking into account the required cost/human and other resources, as well as the current situations of individual medical institutions (see Fig. 1.)

3 Principles for Safe and Secure Radio Wave Utilization

Principle 1. Identify the actual state of radio wave-emitting device use at the institution, and consider potential risks and corresponding countermeasures.

Types of wave-emitting devices used, where they are used, potential problems involving them, and preventive and response measures for such problems should be acknowledged by relevant parties.

Principle 2. Complete a system for radio wave management.

A cross-sectional internal system should be built in medical institutions in order to share information concerning radio wave management throughout the facility, in addition to the management of radio wave-emitting devices in respective departments.

Principle 3. Explore and implement measures for managing radio wave utilization.

Based on the progress in actions in Principle 1 and 2, explore and implement measures required from the procurement and operation of devices to the occurrence of problems involving the devices as situation requires.

Figure 1. 3 principles for safe and secure utilization of radio wave
(excerpted from the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions)

(1) Identify the actual state of radio wave use at the institution, and consider potential risks and corresponding countermeasures.

Medical electrical devices (medical devices that are driven by electricity and equipped with electric circuits and/or sensors) currently marketed in Japan are assigned specific permissible intensities of radio waves as emitted from other radio wave-emitting devices. Consequently, it is critical to ensure a suitable radio wave environment with respect to the strength of the medical electrical devices being used inside an institution to withstand the radio frequencies emitted from other radio wave-emitting devices. Sufficient information regarding characteristics of radio wave-emitting devices and medical electrical devices being used inside the institution, problems that may arise from the use of such services and devices together with preventive measures to anticipate such problems or possible solutions when they actually occur should be collected from the provider(s) of services or devices and shared among the relevant parties within each medical institution.

Although a wide variety of radio wave-emitting devices and medical devices is used in medical institutions, the Guidance focuses on medical telemeters, wireless LAN (Wi-Fi), and mobile phones. It introduces basic information (system overview, method for checking the wireless settings, for the radio wave utilization state and others), types and details of problems that may arise, and their preventive measures and solutions.

With respect to medical telemeters for example, basic information such as an overview of the antenna system for wireless transmission and reception (see Fig. 2) and how to confirm the radio frequency bands allocated (to wireless devices) as well as wireless channel settings is introduced at the beginning. Examples of problems that actually occurred follow, including expired batteries, interference due to improper setting of channels for the wireless network, or to electromagnetic interference from other devices. Next, actions taken by each respective party (e.g., medical institutions, marketing authorization holders (MAHs) of medical telemeters, and other relevant entities are presented in a flow chart (see Fig. 3) to describe the items that must be implemented

or identified for respective components.

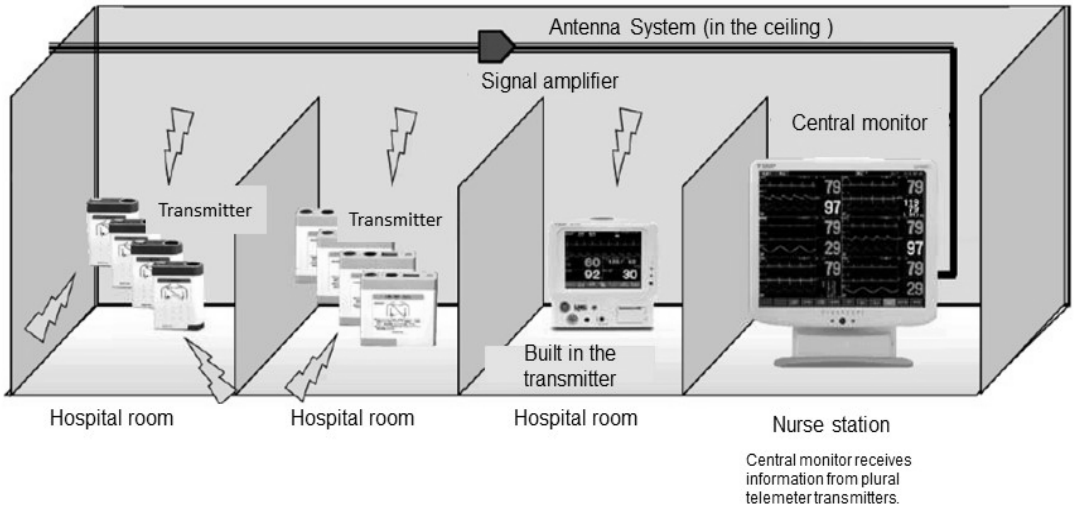

Figure 2. Drawing of a medical telemeter system
(excerpted from the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions)

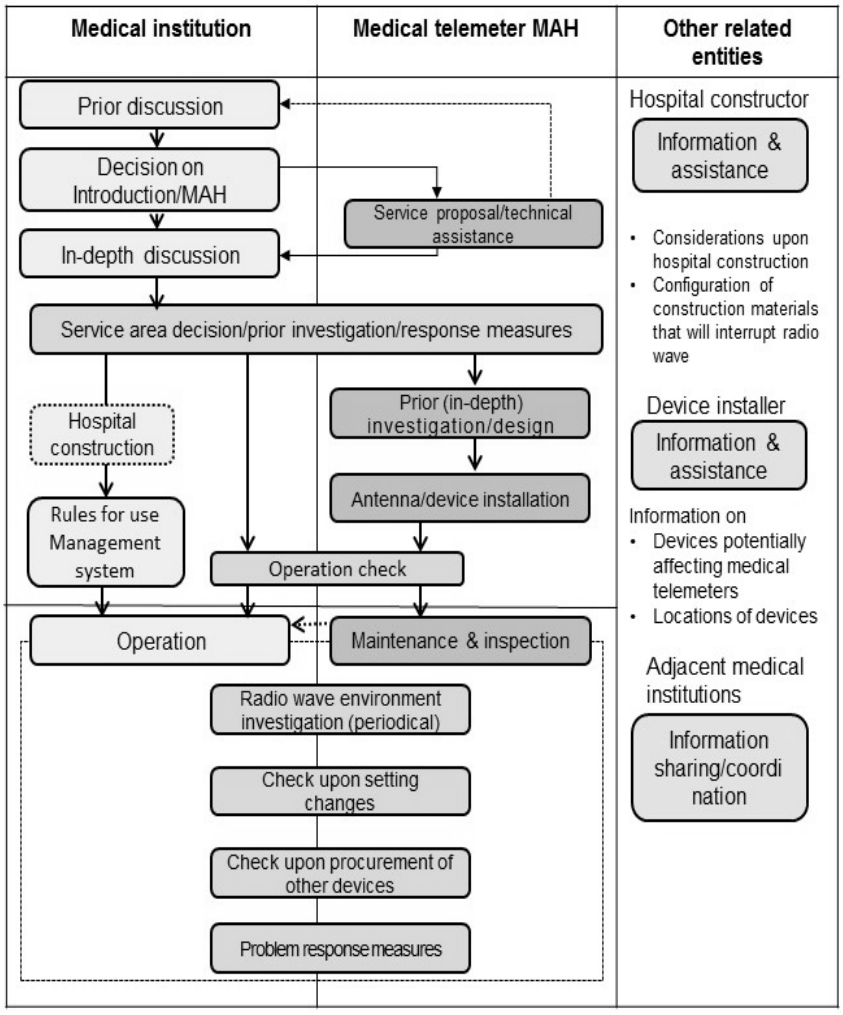

Figure 3 Preventative/solution measures against problems arising in medical telemeters
(excerpted from the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions)

(2) Complete a system for radio wave management

Internal radio wave management systems are indispensable for medical institutions to respond to the ever-increasing use of radio wave-emitting devices and medical electrical devices inside their facilities. An approach to optimizing the use of such systems that considers the needs of individual institutions (e.g., resource limitations, budget restrictions, etc.), incorporating the following actions should be taken when appropriate:

a. Secure resources tasked with radio wave management in each relevant department.
b. Establish a radio wave safety committee and designate a contact person (radio wave manager.)
c. Develop a coordination structure for procuring medical electrical devices, information devices/equipment/services.
d. Formulate rules concerning the management of radio wave environment.
e. Enhance literacy for radio wave management.
f. Allocate roles among related entities and clearly define responsibilities accepted by respective parties.

(3) Explore and implement measures for managing radio wave utilization

Medical institutions must, after acknowledging information regarding radio wave-emitting devices or medical electrical devices used in their facilities and structuring arrangements for the management of radio wave use, explore specific measures to take, and implement such measures that are appropriate considering their current situation. The Guidance specifies data to be identified regarding radio wave-emitting devices or medical electrical devices (changes to channels/output or their functions, recommended distances separating radio wave-remitting devices) or details to be recorded in 3 situations: (1) when procuring radio wave-emitting devices or medical electrical devices, (2) when operating or implementing such devices, and (3) when responding to problems that actually occur.

4. Materials for Public Awareness and education of the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions

A video and e-learning teaching materials to introduce the Guidance and to support in-depth study of it are available on the ECCJ website aiming for its dissemination and awareness. The video and e-leaning teaching materials are designed for users to learn basic knowledge of radio wave-emitting devices and medical electrical devices, examples of problems, and responses to problems that actually occur.

Furthermore, in addition to the Basic Course, in which physicians or medical nurses can learn basic knowledge and review examples of problems, the e-learning teaching materials also include an Advanced Course meant for clinical engineers and other expert healthcare providers with professional knowledge related to the maintenance and inspection of medical electrical devices to assist their in-depth learning of response measures for specific problems and others.

The Basic and Advanced Courses respectively introduce with illustrations examples of problems arising inside medical institutions that involve medical telemeters, wireless LAN, or mobile phones (see Fig. 4.) The 2 Courses both contain Knowledge Check tests (see Fig. 5) in which learners can check their own learning by reading the guidance provided after answering questions.

2.1 Examples of technical difficulties related to medical telemeters

- The following are examples of problems that actually occurred related to radio waves used by medical telemeters:
  - **Instances of areas with poor radio wave reception** due to expiration of the battery of the transmitting device, expired battery/poor signal transmission (e.g., transmitter is located far from device antenna system or signal transmission is impeded by objects such as metal doors or meal delivery carts used on hospital floors)
  - Signal crosstalk due to inappropriate *wireless channel settings
  - **Radio interference** from other devices (e.g., LED lighting appliances, wired delivery cables for in-hospital terrestrial digital broadcasting and satellite broadcasting systems, bed-exit sensors, in-hospital wireless LAN access points (AP), hospital nurse call aggregator systems, illuminated hallway patient name signs, security surveillance cameras, etc.)

Example problem: Radio signal not received

Example: There is too great a distance from the transmitter to the receiving antenna, a stable signal could not be transmitted to the central monitor, and **the patient's condition was not correctly displayed**.

Terminology: In wireless communication systems, usable radio frequency bands (usable spectrum) is divided in order to allow multiple devices to transmit information simultaneously.
Each band frequency division is called a ***wireless channel**.
Signal crosstalk can be prevented by separating wireless channels used by nearby equipment.

Figure 4. Examples of technical difficulties related to medical telemeters found in e-learning course content (Basic Course)
(excerpted from the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions public awareness and education material)

Knowledge Check

Q: Please select from the following choices the **correct statement** regarding wireless LAN (Wi-Fi) systems.

1. Radio waves used by wireless LAN systems are also used by various other devices, and radio interference is likely to occur.
2. Although wireless LAN is widely used in general, such systems has not yet entered common use in medical institutions.
3. Wireless LAN radio waves reception is favorable within a fixed distance regardless of the construction/structure of hospital buildings.
4. Equipment that uses wireless LAN networks (PCs, tablet devices, mobile phones, etc.) directly communicate with each other.

Figure 5. Example of a Knowledge Check test found in e-learning content (Basic Course)
(excerpted from the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions public awareness and education material)

・Related Notifications and Alerts

Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions prepared by the Electromagnetic Compatibility Conference Japan (Joint HPB/GAD Notification No. 0408-2 and PSEHB/SD No. 0408-1 by the Director of General Administration Division, Health Policy Bureau and by the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated April 8, 2016)
http://www.pmda.go.jp/files/000211546.pdf (only in Japanese)

Public Awareness Educational Materials for Safe and Secure Radio Wave Utilization in Medical Institutions prepared by the Electromagnetic Compatibility Conference Japan (Joint HPB/GAD/MSPO Notification No. 0511-1 and PSEHB/PSD No. 0511-1 by the Director of the Medical Safety Promotion Office, General Affairs Division, Health Policy Bureau and by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated May 11, 2018
http://www.pmda.go.jp/files/000224124.pdf (only in Japanese)

Announcement of Public Awareness Educational Materials for Safe and Secure Radio Wave Utilization in Medical Institutions by the Electromagnetic Compatibility Conference Japan
http://www.soumu.go.jp/main_sosiki/joho_tsusin/eng/Releases/Telecommunications/2018410_5.html

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated August 2, 2018, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Ceftriaxone sodium hydrate

Branded name (name of company)	Rocephin Intravenous 0.5 g, 1 g, Rocephin Infusion bag 1 g (TAIYO Pharma Co., Ltd.), and the others
Therapeutic category	Acting mainly on gram-positive and gram-negative bacteria
Indications	Applicable microorganisms: ・Ceftriaxone-susceptible strains of genus Staphylococcus, genus Streptococcus, Pneumococcus, Neisseria gonorrhoeae, Escherichia coli, genus Citrobacter, genus Klebsiella, genus Enterobacter, genus Serratia, genus Proteus, Morganella morganii, genus Providencia, Haemophilus influenzae, genus Peptostreptococcus, genus Bacteroides, and genus Prevotella species (except Prevotella bivia) Applicable conditions: ・Sepsis, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, lung abscess, pyothorax, infections secondary to chronic respiratory lesions, cystitis, pyelonephritis, epididymitis, urethritis, cervicitis, pelvic inflammatory disease, proctitis, peritonitis, intra-abdominal abscess, cholecystitis, cholangitis, bartholinitis, intrauterine infection, uterine adnexitis, parametritis, suppurative meningitis, keratitis (including corneal ulcer), otitis media, sinusitis, cellulitis around jawbone and jaw inflammation

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)

Neuropsychiatric symptoms:
Disturbed consciousness (loss of consciousness, decreased level of consciousness, etc.), convulsions, or involuntary movements (choreoathetosis, myoclonus, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken. These symptoms have been reported in numerous patients with severe renal disorder.

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 10 months (April 2015 to February 2018).
Cases involving neuropsychiatric symptoms: 11* (no patient mortalities)
*Including 4 cases that have no symptoms except disturbed consciousness.

Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 1 980 000

Launched in Japan: Rocephin Intravenous 0.5 g, 1 g: August 1986
Rocephin Infusion bag 1 g: June 2003

Case summary

No.	Patient		Daily dose/Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Cholangitis (chronic glomerulonephritis, pancreatic carcinoma)	2 g 6 days	**Choreiform movements** 1 day before administration: The patient was admitted to the hospital to receive chemotherapy for the treatment of pancreatic carcinoma, while on maintenance dialysis due to chronic glomerulonephritis Day 1 of administration: Pyrexia occurred and blood pressure (BP) decreased. Cholangitis was diagnosed and administration of ceftriaxone sodium hydrate was initiated. 6 days after administration: Choreiform movements occurred in the extremities. (Day of discontinuation): Ceftriaxone sodium hydrate administration was discontinued and treatment was switched to gentamicin sulfate. 1 day after discontinuation: Involuntary movements were observed. 2 days after discontinuation: Involuntary movements ceased.

Laboratory Examination

	Day 1 of discontinuation (before the administration on the day)	1 day after discontinuation	4 days after discontinuation	7 days after discontinuation
Serum concentrations of this drug (μg/mL)	450	488	428	195

Concomitant medications: no information

3

Revision of Precautions (No. 296)

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated August 2, 2018, this section will present the details of revisions and branded names involved in these revisions.

1 **Miscellaneous metabolism agents**

Apremilast

Branded name	Otezla Tablets 10 mg, 20 mg, 30 mg (Celgene K.K.)
Adverse reactions (clinically significant adverse reactions)	**Severe diarrhoea:** Severe diarrhoea may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

2 **Acting mainly on gram-positive and gram-negative bacteria**

Ceftriaxone sodium hydrate

Branded name	Rocephin Intravenous 0.5 g, 1 g, Rocephin Infusion bag 1 g (TAIYO Pharma Co., Ltd.), and the others
Adverse reactions (clinically significant adverse reactions)	Neuropsychiatric symptoms: Disturbed consciousness (loss of consciousness, decreased level of consciousness, etc.), convulsions, or involuntary movements (choreoathetosis, myoclonus, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken. These symptoms have been reported in numerous patients with severe renal disorder.

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 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 July 31, 2018)

◎: Products for which EPPV was initiated after July 1, 2018

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Fosravuconazole L-lysine ethanolate Nailin Capsules 100 mg	Sato Pharmaceutical Co., Ltd.	July 27 2018
◎	Canakinumab (genetical recombination) *1 Ilaris for S.C. Injection 150 mg, Ilaris Solution for S.C. Injection 150 mg	Novartis Pharma K.K.	July 2 2018
◎	Olaparib*2 Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	July 2 2018
	Japanese cedar pollen extract Cedarcure Japanese Cedar Pollen Sublingual Tablets 2,000 JAU, 5,000 JAU	Torii Pharmaceutical Co., Ltd.	June 29 2018
	Ibuprofen L-lysine Ibulief I.V. Injection 20 mg	Senju Pharmaceutical Co., Ltd.	June 14, 2018
	Rasagiline mesilate Azilect Tablets 0.5 mg, 1 mg	Takeda Pharmaceutical Company Limited.	June 11, 2018
	Sirolimus Rapalimus Gel 0.2%	Nobelpharma Co., Ltd.	June 6, 2018
	Pemafibrate Parmodia Tab. 0.1 mg	Kowa Company, Ltd.	June 1, 2018
	Migalastat hydrochloride Galafold Capsules 123 mg	Amicus Therapeutics, Inc.	May 30, 2018
	Letermovir Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 28, 2018
	Mepolizumab (genetical recombination) *3 Nucala for S.C. Injection 100 mg	GlaxoSmithKline K.K.	May 25, 2018
	Ipilimumab (genetical recombination) Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	May 25, 2018
	Nivolumab (genetical recombination) Opdivo I.V. Infusion 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	May 25, 2018
	Botulinum toxin type A*4 Botox for Injection 50 Units, 100 Units	GlaxoSmithKline K.K.	May 25, 2018

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Tofacitinib citrate[*5] Xeljanz Tablets 5 mg	Pfizer Japan Inc.	May 25, 2018
Emicizumab (genetical recombination) Hemlibra Subcutaneous Injection 30 mg, 60mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	May 22, 2018
Guselkumab (genetical recombination) Tremfya Subcutaneous Injection 100 mg Syringe	Janssen Pharmaceutical K.K.	May 22, 2018
Evocalcet Orkedia Tablets 1 mg, 2 mg	Kyowa Hakko Kirin Co., Ltd.	May 22, 2018
Hydromorphone hydrochloride Naruvein Injection 2 mg, 20 mg	Daiichi Sankyo Propharma Co., Ltd.	May 16, 2018
Bedaquiline fumarate Sirturo Tablets 100 mg	Janssen Pharmaceutical K.K.	May 8, 2018
Ezetimibe/atorvastatin calcium hydrate Atozet Combination Tablets LD, HD	MSD K.K.	April 23, 2018
Dupilumab (genetical recombination) Dupixent S.C. Injection 300 mg Syringe	Sanofi K.K.	April 23, 2018
Elobixibat hydrate Goofice Tablets 5 mg	EA Pharma Co., Ltd.	April 19, 2018
Olaparib Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	April 18, 2018
Inotuzumab ozogamicin (genetical recombination) Besponsa Injection 1mg	Pfizer Japan Inc.	April 18, 2018
Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	April 18, 2018
Brexpiprazole Rexulti Tablets 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	April 18, 2018
Atezolizumab (genetical recombination) Tecentriq I.V. Infusion 1200 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2018
Romidepsin Istodax Injection 10 mg	Celgene Corporation	April 18, 2018
Baloxavir marboxil Xofluza Tablets 10 mg, 20mg	Shionogi & Co., Ltd.	March 14, 2018
Abatacept (genetical recombination)[*6] Orencia for I.V. Infusion 250 mg	Bristol-Myers Squibb K.K.	February 23, 2018
Sarilumab (genetical recombination) Kevzara 150 mg, 200 mg Syringe for SC Injection	Sanofi K.K.	February 5, 2018

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

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

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

*4 Spasmodic dysphonia

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

*6 Polyarticular juvenile idiopathic arthritis that does not adequately respond to existing treatments