Pharmaceuticals and Medical Devices Safety Information

No. 353 May 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 available in Japanese language).

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. 353 May 2018

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

[Outline of Information]

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
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
CRP	C-reactive protein
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MID-NET	Medical Information Database NETwork
NCCHD	National Center for Child Health and Development
PCA	Partial change application
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
γ-GTP	Gamma-glutamyl transpeptidase

1

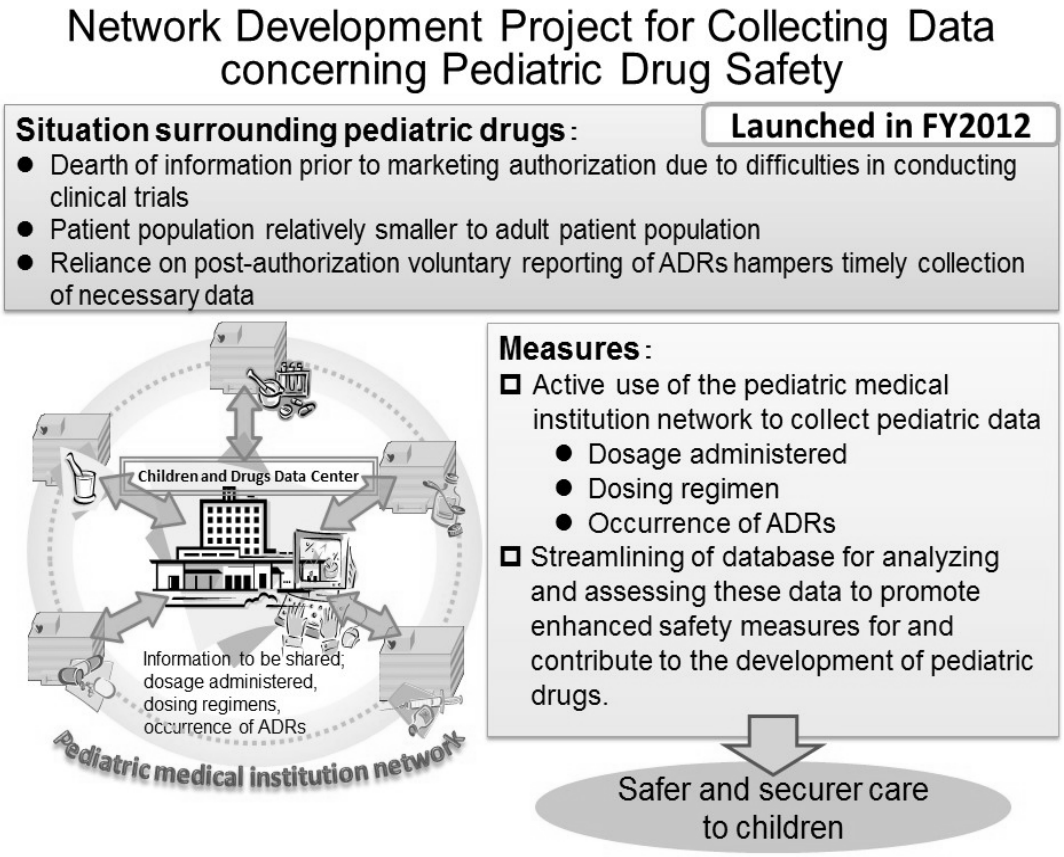
Initiative for the Compilation of Database-stored Data and Provision of Information concerning Pediatric Drugs

1. Challenges related to Pediatric Drugs

Pediatric drugs involve a number of challenges arising from the smaller size of relevant patient populations (number of indicated patients, total number of prescriptions) relative to those comprised of adult patients. Difficulties in conducting clinical trials prior to marketing authorization, as well as in the collection and assessment of data on safety and efficacy after marketing authorization are included among these challenges. Particularly during clinical trials to obtain marketing authorization, the lower profitability and the special considerations required for pediatric subjects can discourage pharmaceutical companies from actively conducting such trials. Medical institutions also reportedly face various difficulties in establishing an environment for conducting clinical trials involving pediatric subjects due to the small number of trials and eligible subjects. On this backdrop, it is estimated that approximately 60-70% of the drugs commonly prescribed in the pediatric disciplines do not specify the dosage and administration for pediatric patients in their package inserts.

2. Network Development Project for Collecting Data concerning Pediatric Drug Safety

In light of these challenges, a database was created at the National Center for Child Health and Development (NCCHD) in Fiscal year (FY) 2012 to facilitate collection and more centralized control of data concerning the total number of prescriptions of drugs administered to children, laboratory testing (specimen examinations), and signs and symptoms of patients in order to establish an integrated system for collecting and assessing data on the safety of drugs used in children. A data processing environment to facilitate the analysis of such data was also established as a component of the Pediatric Medical Data Collecting System. This system utilizes the network of institutions belonging to the Japanese Association of Children's Hospitals and Related Institutions as well as various other medical facilities.

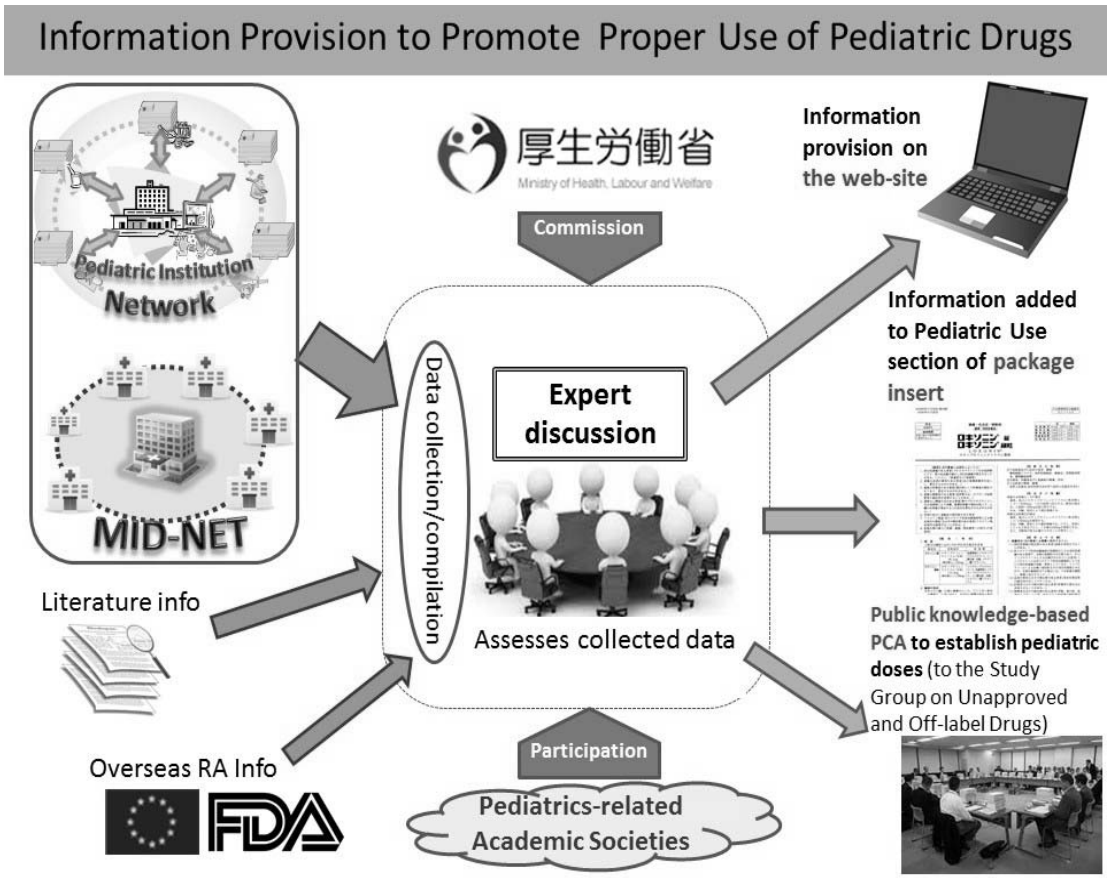


As of March 31, 2018, electronic medical records of approximately 250 000 patients (excluding patients with disease name data alone) and medical interview data of approximately 30 000 patients derived from 11 pediatric medical institutions and 37 clinics have accumulated. Search and extraction of such data have been enabled. Functions to analyze the data are also available in the data processing environment and accuracy of the search and analysis will be further enhanced.

Anticipating the start of trial use of the system within FY 2018, and preparations are ongoing. Details of the request for utilization of the system will be posted to the website* of the Pediatric Medical Data Collecting System.

3. Efforts of Data Collection and Organization coupled with Information Provision

To promote the proper use of pediatric drugs, a project started in 2017 to gather and organize the data by the Pediatric Medical Data Collecting System and other data so far collected for the information provision to promote proper use of pediatric drugs.



A group of experts (including pediatricians and pharmacists) discussed the project based on the data collected by the Pediatric Medical Data Collecting System and other information.

Prescription data were extracted from the data collected by the system and the numbers of prescriptions and patients specific to individual drugs were investigated. Ultimately, 3 types of drugs were selected as targets of their investigation among those drugs with a statement in their package inserts that safety has not been established for specific age groups of children. One of the reasons for their selection was that sufficient numbers of data could be expected for the age group or groups of unproven safety. With a drug frequently co-prescribed with the one of the 3 drugs added, spironolactone, furosemide, levetiracetam, and aspirin were finally subject to the investigation.

・Spironolactone, furosemide

Actual prescription practices were investigated for spironolactone and furosemide since they are widely used as diuretics, often co-prescribed with each other.

While only adult dosage is specified in their package inserts under a phrase of “the usual adult dose is…” the database has evidenced their widespread use in children as well. The investigation also revealed that spironolactone monotherapy is prescribed to only a small number of patients, whereas its co-administration[1] with furosemide and furosemide monotherapy are prescribed more frequently.

・Levetiracetam

Levetiracetam, as a relatively new drug therapy indicated for epilepsy, has in its package insert a pediatric dosage and administration specified for the treatment of epilepsy in children aged over 4 years.

The results of the investigation revealed that this drug is actually prescribed to patients under 4 years of age as well. A clinical investigation is currently underway in patients aged 1 month to 4 years.

[1] Co-administration is defined as one patient having prescription records of both drugs, regardless of the overlap in the time periods covered by the prescriptions.

・Aspirin

Aspirin has a pediatric dosage and administration for Kawasaki disease. Aspirin is known to exhibit inhibitory effect on platelet aggregation.

The investigation revealed that only 20% of patients were accompanied with a disease name of Kawasaki disease. Meanwhile, over 30% of those were not accompanied with a disease name of Kawasaki disease had other disease name(s) related to thrombosis.

The average daily dose prescribed tended to be higher during the early stages of the prescribed period in the group of infant patients accompanied with Kawasaki disease as disease name in the claim data[2].

Powder formulations were prescribed in children aged 3 years or younger while ratio of tablets increased for children aged 4 years or older, surpassing the ratio of powders as the age of patients approached 10 years of age.

4. Future Direction

Improvement of the accuracy of information used is intended for FY 2018 by (1) Expansion of the timeframe of investigation, (2) Use of body weight data, (3) More intensive collection of prescription dose data, and (4) Extraction of adverse event data to accelerate the promotion of proper use of pediatric drugs.

*Website of the Pediatric Medical Data Collecting System
http://pharma-net.ncchd.go.jp (only in Japanese)

<Reference>

Environmental Improvement Project for Pediatric Drug Treatments, Public Release of Information (FY 2018), Website of the Pediatric Medical Data Collecting System, NCCHD
http://pharma-net.ncchd.go.jp/wp-content/uploads/2018/04/Environment_Improvement_20180421.pdf (only in Japanese)

[2] Dosage and administration for Kawasaki disease: during the febrile stage in the acute phase, 30 to 50 mg/kg daily of aspirin is orally administered in 3 divided doses. During the convalescent phase after fever resolved to the chronic phase, 30 to 50 mg/kg of aspirin is orally administered once daily, which may be adjusted according to the patient's condition.

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated April 19, 2018, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Pembrolizumab (genetical recombination)

Brand name (name of company)	Keytruda Injection 20 mg, 100 mg (MSD K.K.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Treatment of unresectable melanoma Treatment of patients with PD-L1 positive, unresectable, recurrent or advanced non-small cell lung cancer Treatment of relapsed or refractory classical Hodgkin lymphoma Treatment of unresectable urothelial carcinoma which has progressed after cancer chemotherapy

PRECAUTIONS (revised language is underlined)

Important Precautions

Hepatic impairment or sclerosing cholangitis accompanied by increased levels of certain hepatic enzymes, such as AST (GOT), ALT (GPT), γ-GTP, ALP, as well as bilirubin, may occur. Patients should be closely monitored through periodic liver function tests.

Adverse reactions (clinically significant adverse reactions)

Hepatic impairment, hepatitis, sclerosing cholangitis: Hepatic impairment, hepatitis, or sclerosing cholangitis accompanied by increased levels of certain hepatic enzymes, such as AST (GOT), ALT (GPT), γ-GTP, ALP, as well as bilirubin, may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken such as discontinuation of this drug.

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 11 months (April 2014 to March 2018).
Cases associated with sclerosing cholangitis: 1 case (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 7 700

Launched in Japan: February 2017

Case summary

No.	Patient		Daily dose/Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 80s	Squamous cell carcinoma of lung (chronic renal impairment)	200mg 3 courses in 3-week intervals	**Sclerosing cholangitis**	
				Start of administration	The patient had no prior history of chemical therapy. Administration of pembrolizumab (genetical recombination) started.
				Day of completion of	The third cycle of Pembrolizumab was administered (last administration)

				administration	
				14 days after completion (day of onset)	The patient complained of back pain during a routine visit. Higher ALP and γGTP values were observed as a result of a blood test. The patient was to be referred to the gastrointestinal department. Intrahepatic bile duct dilation was observed during abdominal echography. The patient was prescribed levofloxacin hydrate and was released to return home.
				17 days after completion	Inflammatory responses increased and aggravation in AST, ALT, ALP, γGTP were observed. The patient was admitted to the gastrointestinal department. The patient was given nothing by mouth (NBM) and fluid replacement therapy. Administration of cefozopran hydrochloride was initiated.
				19 days after completion	Upper gastrointestinal tract endoscopy and endoscopic retrograde cholangiopancreatography (ERCP) were performed. Dilation of biliary/pancreatic duct dilatation were noted but smooth. No masses were observed.
				20 days after completion	Inflammatory reactions were observed to be improving and oral food intake resumed.
				24 days after completion	Increase in hepatobiliary enzymes were noted. Oral administration of ursodeoxycholic acid started.
				26 days after completion	Elevated ALP and γGTP were observed. ERCP was performed, and diffuse stenosis/sclerosis was observed, a finding consistent with sclerosing cholangitis. Bile cytodiagnosis was Class II. No metastasis to liver was detected. No gallstones were detected. No biopsy of bile duct wall was performed. Endoscopic nasobiliary drainage was indwelled in the right hepatic duct. Gradual improvements in hepatobiliary enzyme levels were observed.
				31 days after completion	Antinuclear antibody, IgE, IgG4 were negative. Improvement in inflammatory reactions was observed.
				35 days after completion	Methylprednisolone 500 mg/day was initiated.
				36 days after completion	Respiratory conditions became exacerbated since morning. Blood gas analysis detected respiratory acidosis. Disturbed consciousness due to CO_2 narcosis was observed.Noninvasive positive pressure ventilation (NPPV) was ineffective. A bag valve mask was also ineffective, and the patient died. The patient's condition was posthumously diagnosed as respiratory failure by acute exacerbation of COPD. The patient had not recovered from cholangitis (Grade 4) at the time of death.

Laboratory Examination

	Before Administration	14 days after completion	17 days after completion	20 days after completion	24 days after completion	26 days after completion	31 days after completion	35 days after completion
ALP (U/L)	-	1 693	2 545	1 640	3 712	3 880	4 716	3 619
γ-GTP (U/L)	-	603	934	672	-	1 370	1 378	1 099
AST (U/L)	17	201	405	53	-	313	112	149
ALT (U/L)	6	230	374	121	-	241	130	89
T-Bil (mg/dL)	-	0.6	1.2	0.4	1.4	1.2	2.2	0.9
D-Bil (mg/dL)	-	-	0.6	-	0.9	0.7	1.4	0.5
WBC (10^4 cells/μL)	-	1.12	1.12	0.65	-	1.10	0.76	0.69
CRP (mg/dL)	-	11.43	19.74	7.92	8.77	7.97	7.90	3.32

Autoimmune tests (31 days after completion)

IgG4 (TIA) : 36.8 mg/dL, IgE (RIST): 22 IU/mL, antinuclear antibody (ANA) : < 40×
PR3-ANCA : <1.0 U/mL, MPO-ANCA: <1.0 U/mL, anti-mitochondria M2 antibody: < 1.5

Concomitant medications: none

3

Revision of Precautions (No. 294)

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 April 19, 2018.

1 Antidiabetic agents

[1] Omarigliptin
[2] Saxagliptin hydrate
[3] Trelagliptin succinate

Brand name	[1] Marizev Tablets 12.5 mg, 25 mg (MSD K.K.) [2] Onglyza Tablets 2.5 mg, 5 mg (Kyowa Hakko Kirin Co., Ltd.) [3] Zafatek Tablets 50 mg, 100 mg (Takeda Pharmaceutical Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Pemphigoid:** Pemphigoid may occur. If blister, erosion, or other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate measures, such as discontinuation of administration, should be taken.

2 Antineoplastics-Miscellaneous

Cladribine

Brand name	Leustatin Injection 8 mg (Janssen Pharmaceutical K.K.)
Adverse reactions (clinically significant adverse reactions)	**Progressive multifocal leukoencephalopathy (PML)**: Progressive multifocal leukoencephalopathy (PML) may occur. Patients should be closely monitored during and after being treated with this drug. If symptoms such as disturbed consciousness, cognitive disorder, symptoms of paralysis (hemiplegia or quadriplegia), language disorder, or visual disturbance are observed, imaging diagnostic assessment using MRI and cerebrospinal fluid tests should be performed. In addition, administration of this drug should be discontinued, and appropriate measures should be taken.

3 Antineoplastics-Miscellaneous

Pembrolizumab (genetical recombination)

Brand name	Keytruda Injection 20 mg, 100 mg (MSD K.K.)
Important precautions	Hepatic impairment or sclerosing cholangitis accompanied by increased levels of certain hepatic enzymes, such as AST (GOT), ALT (GPT), γ-GTP, ALP, as well as bilirubin, may occur. Patients should be closely monitored through periodic liver function tests.
Adverse reactions (clinically significant adverse reactions)	**Hepatic impairment, hepatitis, sclerosing cholangitis:** Hepatic impairment, hepatitis, or sclerosing cholangitis accompanied by increased levels of certain hepatic enzymes, such as AST (GOT), ALT (GPT), γ-GTP, ALP, as well as bilirubin, may occur. Patients should be

carefully monitored, and if any abnormalities are observed, appropriate measures should be taken such as discontinuation of this drug.

4 **Synthetic antibacterials**

Tosufloxacin tosilate hydrate (for oral use)

Brand name	Ozex Tab. 75, 150, Ozex fine granules 15% for pediatric (Toyama Chemical Co., Ltd.), Tosuxacin Tablets 75 mg, 150 mg (Mylan EPD G.K) and the others
Adverse reactions (clinically significant adverse reactions)	**Acute kidney injury, interstitial nephritis, nephrogenic diabetes insipidus**: Serious renal impairments such as acute kidney injury, interstitial nephritis, or nephrogenic diabetes insipidus may occur. Patients should be carefully monitored through methods such as periodic examinations. If any abnormalities are observed, this drug should be discontinued and appropriate measures should be taken.

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 April 30, 2018)
◎: Products for which EPPV was initiated after March 1, 2018

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	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)[*1] 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
	Esomeprazole magnesium hydrate Nexium Capsules 10 mg, 20 mg, Nexium Granules for Suspension 10 mg, 20 mg	AstraZeneca K.K.	January 19, 2018
	Eculizumab (genetical recombination)[*2] Soliris for Intravenous Infusion 300 mg	Alexion Pharma G.K.	December 25, 2017

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
Aminolevulinic acid hydrochloride*3 Alaglio Divided Granules 1.5 g	SBI Pharmaceuticals Co., Ltd.	December 19, 2017
Palbociclib Ibrance Capsules 25 mg, 125 mg	Pfizer Japan Inc.	December 15, 2017
Belimumab (genetical recombination) Benlysta for I.V. Infusion 120 mg, 400 mg Benlysta for S.C. Injection 200 mg Autoinjector, 200 mg Syringe	GlaxoSmithKline K.K.	December 13, 2017
Bezlotoxumab (genetical recombination) Zinplava for Intravenous Drip Infusion 625 mg	MSD K.K.	December 8, 2017
Budesonide Rectabul 2 mg Rectal Foam 14 Doses	EA Pharma Co., Ltd.	December 7, 2017
Lonoctocog alfa (genetical recombination) Afstyla I.V. Injection 250, 500, 1000, 1500, 2000, 2500, 3000	CSL Behring K.K.	December 1, 2017
Glecaprevir hydrate/pibrentasvir Maviret Combination Tablets	AbbVie GK	November 27, 2017
Rupatadine fumarate Rupafin Tablets 10 mg	Teikoku Seiyaku Co., Ltd.	November 27, 2017
Avelumab (genetical recombination) Bavencio Intravenous Injection 200 mg	Merck Serono Co., Ltd.	November 22, 2017
Daratumumab (genetical recombination) Darzalex Intravenous Infusion 100 mg, 400 mg	Janssen Pharmaceutical K.K.	November 22, 2017
Flutemetamol (^{18}F) Vizamyl Intravenous Injectable	Nihon Medi-Physics Co., Ltd.	November 10, 2017

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

*2 Generalized myasthenia gravis (for use only in patients whose symptoms are difficult to control with high-dose intravenous immunoglobulin therapy or hemocatharsis)

*3 Visualization of tumor tissues of the non-muscle invasive bladder cancer in transurethral resection of bladder tumor