Pharmaceuticals and Medical Devices Safety Information

No. 370 February 2020

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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 (https://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. 370 February 2020

Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, 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
DLST	Drug-induced lymphocyte stimulation test
HER	Electronic health record
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
mPSL	Methylprednisolone
NCCHD	National Center for Child Health and Development
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PSL	Prednisolone

1

For the Promotion of Pediatric Clinical Development (development and safety measures) through Active Use of Medical Information Database

(Part 1) Maintaining the Pediatric Medical Data Collecting System and Examples of a Survey on the Drug Use in Children through Active Use of the System

1. Challenges related to pediatric drug therapy

An estimated 60-70% of the drugs commonly prescribed in the pediatric patients does not specify pediatric dosage and administration in their package inserts (prescriptions for "off-label use"[1)]). In the pediatric clinical settings consequently, dosage form alteration such as crushing tablets developed for adult patients is a routine practice. However, the scientific assessment of the safety and efficacy of such practice and stability of such preparations have not been sufficiently validated.

On the other hand, information on suspected adverse reactions to drugs are collected through the voluntary reporting or use results surveys performed by pharmaceutical companies and necessary safety measures are implemented. However, these surveys involve a significant cost and sometimes it is difficult to identify associations timely between the drug administered and events that subsequently occur, even if the events are detected.

Building a system that automatically and exhaustively collects and analyzes numerous cases including their controls enabling an initial assessment of adverse reactions is required as an approach to resolve these issues.

2. Creating and maintaining medical information database (Pediatric Medical Data Collecting System)

The Network Development Project for Collecting Data on Pediatric Drug Safety has established and been managing a system collecting and assessing safety information in pediatric population at the National Center for Child Health and Development (NCCHD) since Fiscal Year (FY) 2012. The database for collecting and centrally managing data on disease names, prescription of drugs, laboratory testing (specimen examinations), signs and symptoms in pediatric patients and the environment that facilitate the analysis of the collected data are created and maintained.

MHLW

Environmental Improvement Project for Drug Use to Promote Life Innovation

Network Development for Collecting Pediatric Drug Safety Data

Background

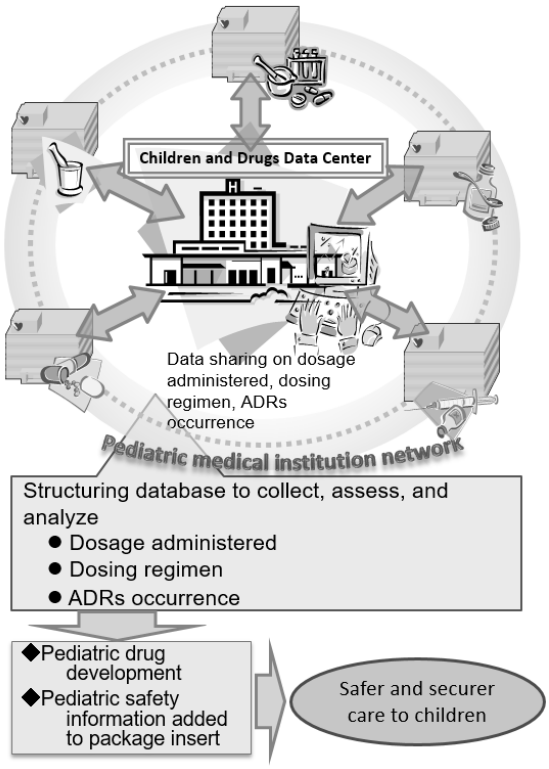
Drugs with no pediatric dosage specification are used for pediatric patients in practice by reducing the dose of drugs or making other alterations due to difficulties assessing safety and efficacy, conducting clinical trials, and getting enough return on investment. It is expected that the development and supply of new drugs will be driven by the promotion of life innovation, but it is important from the viewpoint of supporting the next-generation development to improve an environment in which drugs can be safely administered to children.

Overview

To establish **Children and Drugs Data Center**, develop necessary databases, and develop a system to collect ADRs information and dosage information, etc., by making use of a network consisting of pediatric medical institutions nationwide.

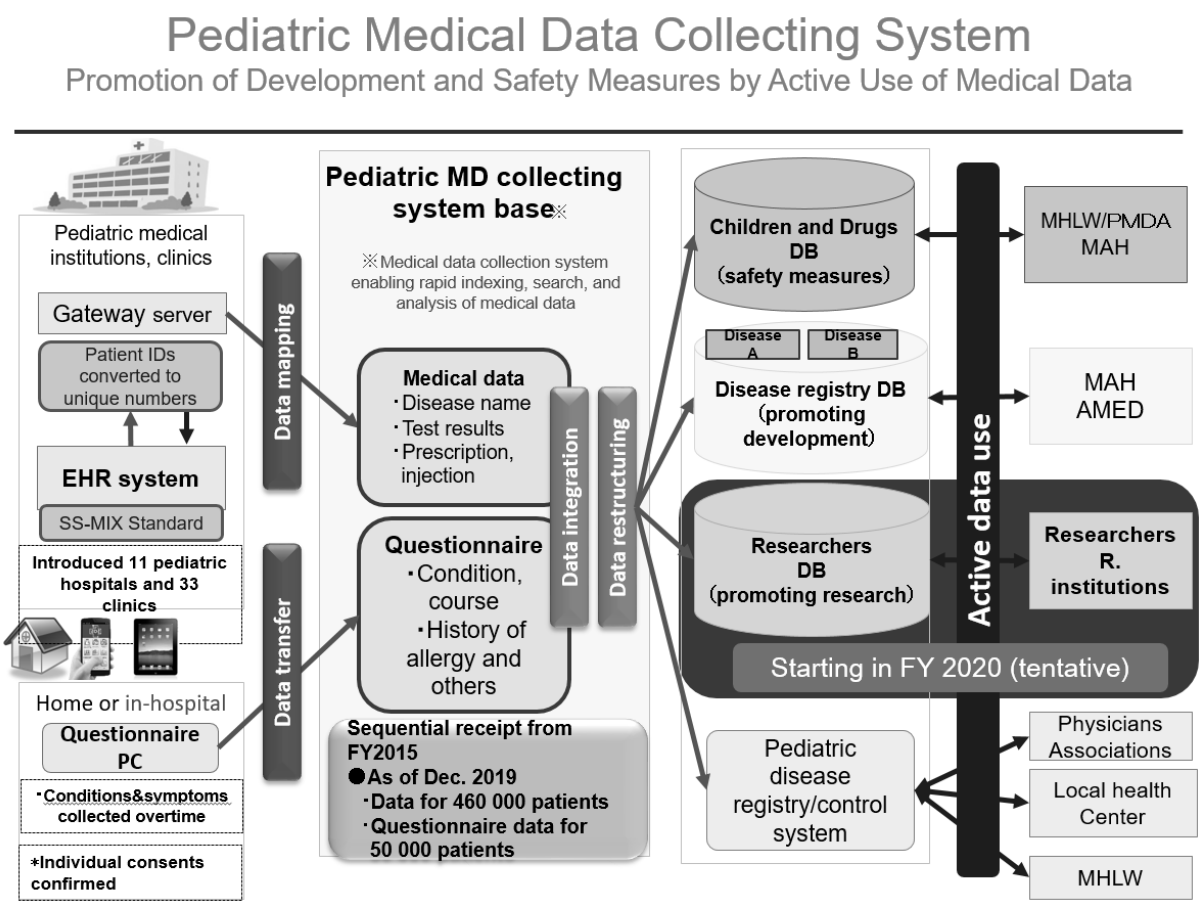
Goals

Aiming at improving the safety measures for pediatric drug use and contributing to the pediatric drug development by making use of the pediatric medical institution network to collect pediatric data on dosage administered, dosing regimen, ADRs occurrence while enhancing database for analyzing and assessing collected data.



This Network Development Project for Collecting Data concerning Pediatric Drug Safety (the System) collects the medical information (data concerning disease names, prescriptions and injections received, and results of specimen examinations, etc.) stored in the electronic health record (EHR) at pediatric medical facilities as well as data on questionnaire completed by consenting patients (or their proxies).

As of the end of December 2019, medical data of 460 000 patients and questionnaire data for 50 000 patients had been stored in this system and are updated daily. The System aims at improving clinical development in pediatric patients by more accurate safety evaluation as well as promoting development in pediatric population through analyzing and assessing the information collected by this system.



Patient confidentiality is strictly maintained in this system because of the nature of information handled. This system does not receive personal information of patients such as their names, addresses, postal codes, or telephone numbers. Actual patient IDs are not stored in the System either. On the NCCHD's end, the System is designed to analyze and assess received information as data not immediately linkable to personal information of patients.

3. Survey on the drug use in children by active use of Pediatric Medical Data Collecting System

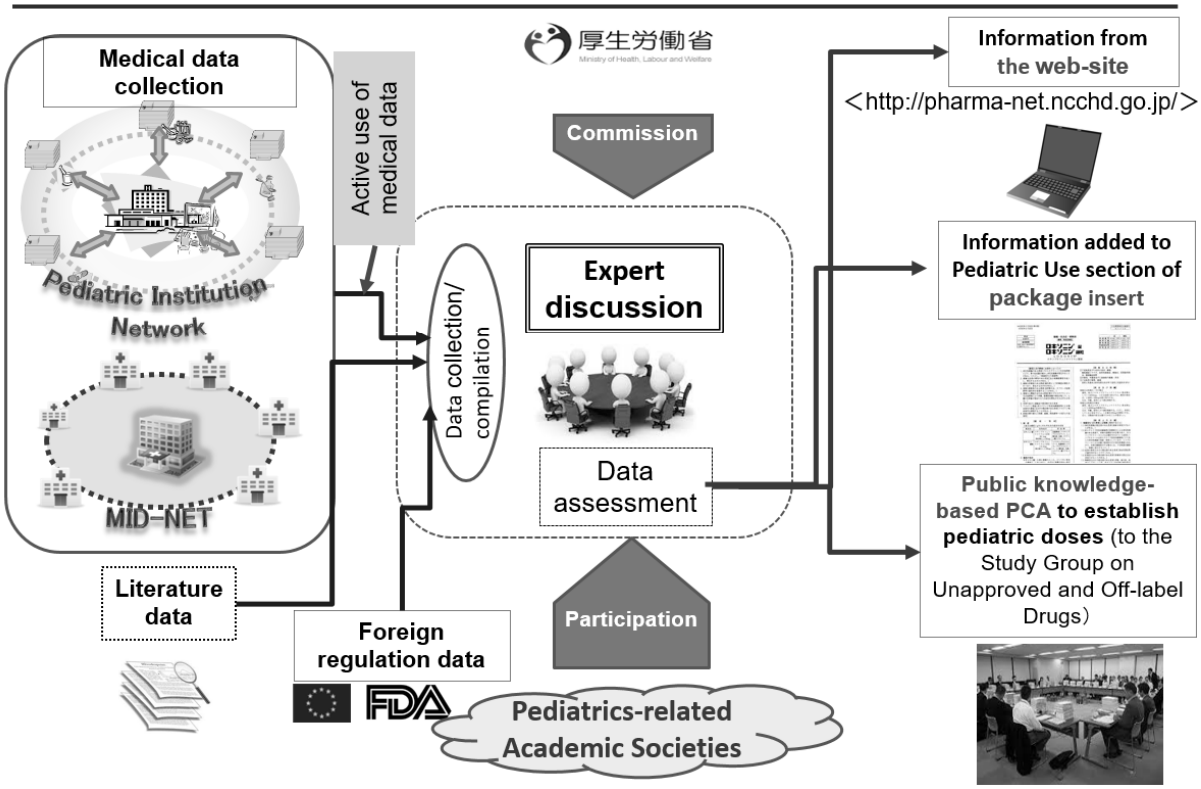
The Environmental Improvement Project for Pediatric Drug Treatments started in FY2017 for enhancing the promotion of proper use of drugs in pediatric patients by collecting and organizing the data acquired by the System and other information sources, evaluating such data in the expert review committees and providing information for proper use of drugs. Part of the cases investigated in the project is introduced below.

Famotidine, a H_2 receptor antagonist, is extensively prescribed in pediatric disciplines although its package insert does not specify pediatric dosage and administration. The current survey was conducted on roxatidine acetate hydrochloride which is a similar drug to famotidine and for which pediatric dosage and administration is specified in the package insert. The number of patients prescribed the drug and of prescriptions issued between April 2016 and March 2017 (1 year) was investigated using the System. Data are presented by age group (newborns younger than 28 days, nursing infants aged 28 days to prior to I year, toddlers and preschoolers 1 to 6 years, and school-age children 7 to 14 years) at the time of prescription to reflect the actual prescription practices.

Age group	Age	Number of patients		Number of prescriptions	
		Famotidine	Roxatidine acetate hydrochloride	Famotidine	Roxatidine acetate hydrochloride
Newborns・nursing infants	0	191	19	1 137	145
Toddlers and preschoolers	1	104	26	609	115
	2	112	17	609	80
	3	109	23	589	61
	4	129	13	515	37
	5	168	21	496	40
	6	156	19	447	47
School-age children	7	167	8	401	10
	8	154	14	474	18
	9	139	15	428	19
	10	131	15	487	22
	11	115	17	413	24
	12	127	22	738	43
	13	125	7	585	11
	14	130	15	517	28
Total		2 057	251	8 445	700

The package insert of famotidine prepared did not mention pediatric dosage and administration and under the Old instructions (Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997) the Pediatric Use section only noted that “Safety of this drug in low birth-weight infants, newborns, nursing infants, toddlers, and preschool or school-age children has not been established (scarce use experience) ”. The package insert of roxatidine acetate hydrochloride specifically mentioned pediatric dosage and administration and the Pediatric Use section stated that “Safety of this drug in low birth-weight infants, newborns, nursing infants, toddlers, and preschool or school-age children has not been established (no use experience in low birth-weight infants, newborns, nursing infants, toddlers and preschoolers)”.

Compared with these statements, prescription of famotidine turned out to be frequent in any age groups both in terms of the number of patients prescribed the drug, and the number of prescriptions. By making full use of this system, it became possible to quickly grasp the actual administration practice of drugs.



Results of investigation involved in this project since FY2017 are posted in the website of the Pediatric Medical Data Collecting System (https://pharma-net.ncchd.go.jp).

*The investigation of actual prescription practices has its limitation because it is an investigation that uses data of order information (prescription order), not dosage information. It is not possible to accurately confirm facts that patients actually took the drug and dosages that they actually took, and it cannot track prescriptions beyond existing data because all prescription discontinuation order information has not been collected.

4. Closing Comments

Next issue of Pharmaceuticals and Medical Devices Safety Information, No. 371, will introduce case examples of adverse event assessment and efforts focused on future utilization of the System in the Environmental Improvement Project for Pediatric Drug Treatments.

[References]

1) Shushi Morita, Actual Prescription Practices and Analysis of Package Insert Statements in Pediatric Drug Therapy, Ministry of Health Pharmaceutical Safety Project, FY 1999 Study.

2
Post-Marketing Information Collection and Malfunctions Report from Medical Institutions for Medical Devices

1. Introduction

Efficacy and safety of medical devices are guaranteed by the devices' own quality and their proper handling by users so that such devices can work for the daily diagnosis and treatment of diseases. In other words, medical devices should be supplied to the clinical settings with their quality as a product properly controlled and their proper use in the settings ensured in order to guarantee their efficacy and safety. Malfunction information related to such product quality and information on adverse events occurring in the clinical settings where the products are used should be collected by the marketing authorization holder (MAH) and medical professionals as post-marketing information for medical devices as stipulated by the relevant laws and regulations. This article explains the basic concept and structure of the system to take post-marketing safety measures for medical devices and the regulatory reporting required when malfunctions occur at medical institutions.

2. Post-marketing safety measures for medical devices and safety information collection

In Japan, the perception of the necessity of safety measures for medical devices, etc. until the 1990s was "Medical accidents are inconceivable and should be preventable with the careful attention of individual healthcare professionals." Meanwhile, the perception has changed since 2000 to recognizing medical accidents as something that can actually occur from various factors. Accordingly, medical institutions have established their safety system as an internal structure or a team and are working for the prevention of medical accidents.

The causes of medical accidents and incidents that occur in the clinical settings are related to poor quality of the medical devices themselves or improper maintenance of them, to human factors such as stress, assumption or level of understanding on the side of healthcare professionals, to environment such as labor environment or human relationship, and to the educational system in which healthcare professionals learn how to use the medical devices such as incomplete manuals.

To prevent recurrence of medical accidents, it is important to perform thorough cause analysis while considering the above-mentioned possibilities. As multiple factors often induce an accident in medical devices, it is necessary to collect information with composite factors taken into account and discuss the applicable safety measures.

For example, even if a malfunction of a medical device occurred due to a human error or mistakes in its use, comprehensive analysis of possible causes, examining whether medical professionals such as those using the medical device, properly informed of how to use the device as well as the safety of the device, or whether the device itself has any factors that may induce misuse in order to implement necessary and sufficient safety measures.

Therefore, information needs to be collected as widely as possible for discussing adequate safety measures. It is necessary to ensure complete information exchange between medical institutions who are the medical device users, and the marketing authorization holders, who are the manufacturers and distributors of the devices, as well as to fully provide information required for safe use.

Based on the above, it is important to establish the system where the MAHs of medical devices obtain information necessary related to safety such as how devices are actually used and for proper correction measures to be taken based on the obtained information to prevent the recurrence of a malfunction (damage, operational failure, or other untoward conditions in a broad sense) when medical devices are used.

3. Regulatory reporting system regarding malfunction and other related issues of medical devices

When a malfunction occurs in a medical device, the MAH of the device who received the malfunction report from the medical institution is supposed to carry out an investigation including

hearings from the institution or other parties concerned and a product recall so that they can find what caused the malfunction. The MAH investigates the manufacturing site that produced the medical device to see whether there have been problems in the quality of the product itself in the manufacturing process, etc. when necessary. The investigation performed by the MAH is extensive from the serial number of the device with the malfunction, how the device was used with respect to maintenance and other related issues, the manual technique or procedure when the malfunction occurred, to the primary disease of the patient for whom the device was used. Figure 1 shows the flow from the occurrence of malfunction to discussion for measures.

These information-collecting activities and information-provision activities to medical professionals by MAHs are stipulated in Article 68-2, Paragraph 1 of the Pharmaceutical and Medical Device Act (PMD Act). At the same time, the Article 68-2, Paragraph 2 of the Act also stipulates an obligation not subject to penalty of medical professionals including healthcare providers to cooperate in the information collection activities by MAHs.

Under the above-mentioned cooperation by medical professionals, the MAH collects information and performs an analysis for the cause of the malfunction of the medical device. When obtaining information on the occurrence of diseases, disorders, or deaths suspected to have been caused by use of a medical device, or the onset of an infection suspected to have been induced by use of the product in question, etc., the MAH is required to report them to the Pharmaceutical and Medical Devices Agency (PMDA) in accordance with Article 68-10, Paragraph 1 of the PMD Act, etc. Medical professionals are also obliged to report such a situation when considered necessary to prevent an occurrence of any damage in terms of sanitation and hygiene in accordance with Article 68-10, Paragraph 2 of the PMD Act.

As stated above, extensive regulatory reporting by MAHs and medical professionals regarding malfunctions of medical devices leads to safety measures to prevent recurrence of the malfunctions and subsequently the safety measures and precautions for other similar-product groups.

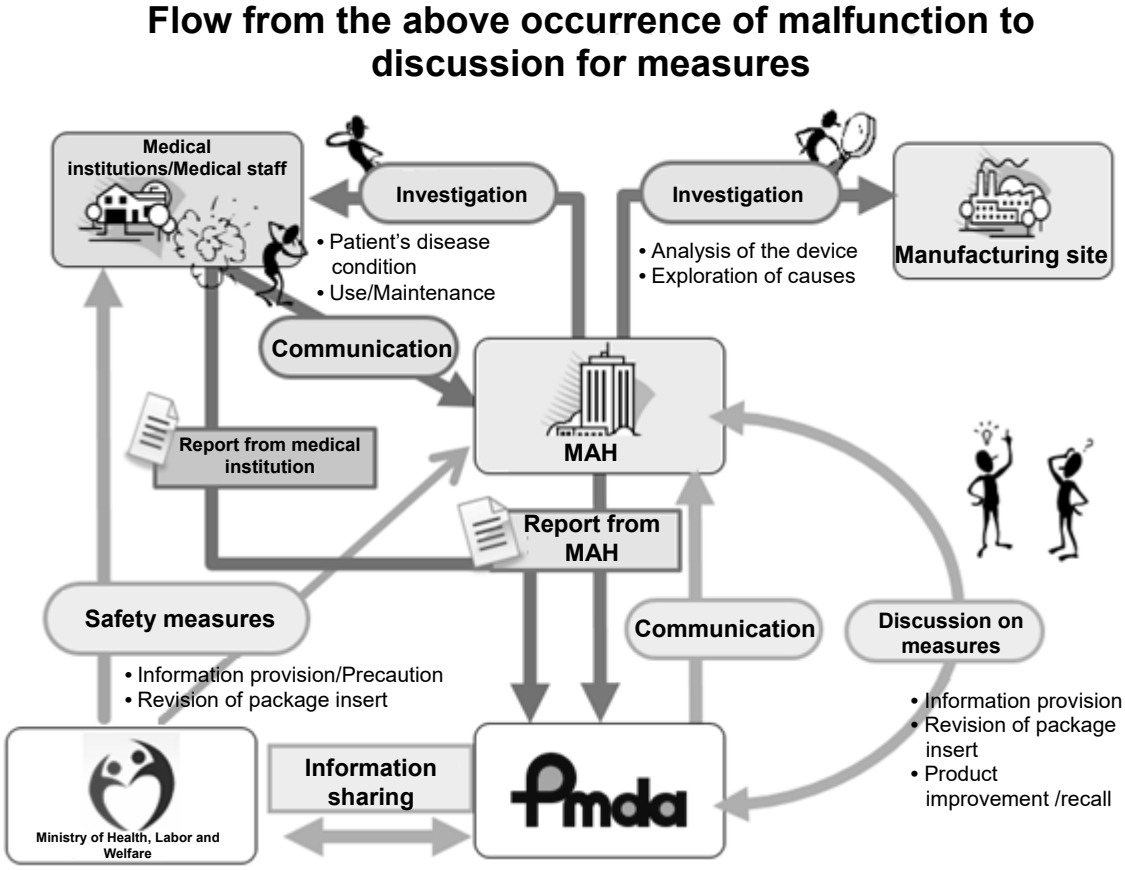


Figure 1 Flow from Occurrence of Malfunction to Discussion on Measures

4. Drugs and Medical Devices Safety Information Reporting System

As mentioned above, the MAH performs a cause analysis and takes safety measures to prevent the recurrence of malfunctions due to use of medical devices. Meanwhile, it is also important for the regulatory authorities to receive information on malfunctions that occur due to use of medical devices in the daily clinical settings from healthcare professionals, etc. and to recognize them without delay. When a malfunction that occurred in a medical institution may occur in other institutions, a swift discussion toward the prevention of recurrence of the malfunction can be expected by early regulatory reporting. For this purpose, a system has been in place where medical professionals including healthcare providers directly report to the regulatory authorities.

This system is called the Drugs and Medical Devices Safety Information Reporting System, in which when medical professionals working at a medical institution or pharmacy learn the occurrence of any adverse reactions or malfunction associated with use of a drug or a medical device, etc. for which a causal relationship with such use could not be ruled out, they shall report the occurrence to the Minister of Health, Labour and Welfare if the reporting is considered necessary in order to prevent the occurrence or spread of hazards in health and hygiene (Article 68-10, Paragraph 2)*1. The system aims to analyze and evaluate reported information from a professional perspective, take necessary safety measures, provide information to healthcare professionals widely, and secure post-marketing safety measures for drugs, medical devices and regenerative medicine products.

Figure 2 shows the form used for medical device reporting. Required fields are the information necessary to identify the medical device with a malfunction and the MAH (the name of medical device, approval no. and the name of MAH), a malfunction that occurred to patients, etc. (reportable cases include those where only a malfunction occurred with no health damage), and reporter's information. The form also includes the columns for comments on structural, material, or functional flaws of the medical device or for reporter's comment.

Cases subject to the Drugs and Medical Devices Safety Information Reporting System from medical professionals among the cases related to medical-device use include those with information

considered reportable in terms of prevention of occurrence or spread of hazards in health and hygiene.

It should be noted that even the cases for which the causal relationship with the relevant medical device is not necessarily clear are subject to reporting. This is aimed to widely collect and analyze the information on a malfunction for which the causal relationship with the medical device cannot be ruled out based on only 1 case using the device in the clinical settings. We hope that this approach will accelerate discussions on safety measures to be taken for reported events with unclear causality.

医療機器安全性情報報告書

☆医薬品医療機器法に基づいた報告制度です。記入前に裏面の「報告に際してのご注意」をお読みください。

患者ｲﾆｼｬﾙ / 不具合・健康被害発現年齢 歳 / 身長 cm / その他特記すべき事項 ☐飲酒 ( ) ☐喫煙 ( ) ☐ｱﾚﾙｷﾞｰ ( ) ☐その他 ( )

性別 ☐男 ・☐女 / 妊娠：☐無 ・☐有（妊娠 週）・☐不明 / 体重 kg

○不具合・健康被害の原因と考えられる医療機器（特定できない場合は複数記載していただいて結構です。）

製品名

製造販売業者名

承認番号 / ﾛｯﾄ番号・製造番号・JANｺｰﾄﾞ（任意）

○不具合・健康被害の状況
医療機器の不具合：☐無 ・☐有（内容： ）
患者等の健康被害：☐無 ：☐有（内容： ）

○医療機器の不具合・健康被害の発生経緯（不具合・健康被害が発生した日時とその後の発生）

使用開始日時 年 月 日 時 / 不具合発生日時 年 月 日 時 / その後の発生（再現性） 年 月 日 時 / 年 月 日 時

○医療機器の用途（使用目的、併用した医療機器／医薬品）

○医療機器の取扱者 ☐医師☐歯科医師☐臨床工学技士☐診療放射線技師☐看護師☐患者 ☐その他（ ）

○不具合・健康被害後の患者等の症状、処置等に関する経過及びコメント
年 月 日

○医療機器の構造的、材質的又は機能的欠陥に関するコメント

○報告者意見欄（再発防止の対処方法、類似した不具合・健康被害が発生する危

報告日： 年 月 日 （既に医薬品医療機器総合機構へ報告し
報告者 氏名： （職種：
施設名（所属部署まで）： （安全性情報受
住所：〒
電話： FAX：

○ 製造販売業者への情報提供の有無 ☐報告済 ・
○ 現品（医療機器）の製造販売業者への返却 ☐返却済 ・
※発生原因の追求、安全対策の検討のため、製造販売業者への情報提

生物由来製品等感染等被害救済制度について：☐患者が請求予定 ☐
☐制度対象外（生物由来
※生物由来製品を介した感染等による重篤な健康被害については、生物
は裏面）。

様式掲載ホームページへのリンク
医薬品・医療機器等安全性情報報告

5. Conclusion

In order to properly use medical devices and ensure the safety in the clinical settings, it is important for the MAH of medical devices to adequately collect the relevant post-marketing information under the cooperation with medical professionals including healthcare providers. As it is necessary to understand correctly the situation where a malfunction has occurred and to take adequate safety measures in view of post-occurrence recurrence prevention, medical professionals and other relevant parties are requested to acknowledge the above post-marketing information collection scheme and the regulatory reporting system for medical devices for continued cooperation.

[References]

*1 Revisions in practices of reporting ADR, infections, and malfunctions from medical institutions, etc. regarding drugs, medical devices, or regenerative medical products (PSEHB Notification No. 0325-4 by the Director of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated March 25, 2016) (only in Japanese)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated January 21, 2020, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Ipragliflozin L-proline

Branded name (name of company)	Suglat Tablets 25 mg, 50 mg (Astellas Pharma Inc.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus, Type 1 diabetes mellitus

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS Shock, anaphylaxis

11.1 Clinically Significant Adverse Reactions (newly added)

Reference information

Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 43-month period (April 2016 to October 2019)

Cases involving shock or anaphylaxis: 2 (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 370 000

Japanese market launch: April 2014

Case summary

No.	Patient		Daily dose and administration duration	Adverse reaction
	Sex/ age	Indication for use (complication)		Clinical course and treatment provided
1	Male 50s	Diabetes mellitus (none)	50 mg for 1 day	**Anaphylactic shock** History: hypertension, hyperlipidaemia Height: 174 cm Body weight: 84 kg Day 1 of administration (day of discontinuation): The patient regularly visited the internal medicine department of Hospital A. Diabetes mellitus was noted and fosravuconazole L-lysine ethanolate (50 mg once daily orally before breakfast) started. The patient took the prescribed drug the same day. Itching started over the whole body in the evening and the patient experiences nausea, and breathing difficulty, but was kept home to see his clinical course. Anaphylactic shock and nausea occurred. Fosravuconazole L-lysine ethanolate was discontinued (rechallenge: no). 1 day after discontinuation: The patient's conditions did not improve and he visited Hospital A on foot unaccompanied. Blood pressure was 86/61 mmHg, SpO2 was 95% (low). Laboured respiration and trunk redness were obvious. The patient was diagnosed with anaphylactic shock and admitted to the hospital. Adrenaline 0.25 mg was subcutaneously injected, hydrocortisone sodium succinate 500 mg was intravenously injected, and normal saline 100 mL was intravenously infused. The dermatology department was consulted and an olopatadine hydrochloride tablet 5 mg was administered twice daily (in the morning and evening after meal) for the trunk redness. Application of mixture of clobetasol Propionate ointment 0.05% 50 g and white petrolatum 50 g twice daily started. 2 days after discontinuation: The outcome of the nausea was recovery. Nausea dissolved. Redness and itchy feeling persisted. 3 days after discontinuation: Redness and itchy feeling persisted but were somewhat improving. 4 days after discontinuation: Redness and itchy feeling persisting but improving, discharge of the patient was decided. 9 days after discontinuation: The outcome of the anaphylatic shock was recovery.
	Concomitant drugs: benidipine hydrochloride, olmesartan medoxomil, rosuvastatin calcium, febuxostat, zolpidem tartrate			

2 Olmesartan medoxomil

Branded name (name of company)	Olmetec OD Tablets 5 mg, 10 mg, 20 mg, 40 mg (Daiichi Sankyo Co., Ltd.), and the others
Therapeutic category	Antihypertensives
Indications	Hypertension

PRECAUTIONS (revised language is underlined)

[Under old instructions]	
ADVERSE REACTIONS (Clinically Significant Adverse Reactions) (newly added)	**Interstitial pneumonia:** Interstitial pneumonia accompanied by pyrexia, cough, dyspnoea, or abnormal chest X-ray may occur. In such cases, administration of this drug should be discontinued and appropriate measures should be taken such as administration of corticosteroids.
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 43-month period (April 2016 to October 2019) Cases involving interstitial pneumonia: 2 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 450 000 Japanese market launch: December 2015

Case summary

No.	Patient		Daily dose and administration duration	Adverse reaction
	Sex/age	Indication for use (complication)		Clinical course and treatment provided
	Male 50s	Heart failure (right pneumothorax)	20 mg for 197 days	**Interstitial pneumonia** History: viral myocarditis, acute heart failure 173 days before administration: Carvedilol 5 mg/day started. Day 1 of administration: Olmesartan medoxomil 20 g/day started. Approximately Day 90 of administration: Worsening tendency appeared in the pulmonary interstitial shadow in the chest X ray. Day 146 of administration: KL-6 was 1 820（U/mL） Approximately Day 150 of administration: The patient experienced breathing discomfort with fever. Day 197 of administration (Day of discontinuation): Chest X ray revealed right pneumothorax. The finding could be an effect of the bronchoscopic examination 2 days prior. Right chest deaeration was performed for poor oxidation which was considered caused by pneumothorax. Results of the bronchoscopic examination indicated drug-induced interstitial pneumonia by lymphocyte count 69.2% and eosinophill count 18.0%. Olmesartan medoxomil and carvedilol were discontinued. 1 day after discontinuation: Pneumothorax was improving through deaeration. No particular problems were noted in chest x ray. 2 days after discontinuation: Methylprednisolone (mPSL) 500 mg/day started. 4 days after discontinuation: Methylprednisolone was increased to 1 mPSL/day. 5 days after discontinuation: Prednisolone (PSL) 60 mg/day started. KL-6 was 1 620 (U/mL). 8 days after discontinuation: Bisoprolol 0.625 mg/day started. 10 days after discontinuation: Bisoprolol was increased to 1.25 mg/day. With little improvement observed in oxydation, steroid pulse therapy started for 3 days. 13 days after discontinuation: PSL 60 mg/day started. 14 days after discontinuation: Bisoprolol was increased to 2.5 mg/day. Considering the $CHADS_2$ score 1, Anticoagulant rivaroxaban 15 mg/day started. 15 days after discontinuation: The patient tested olmesartan positive in DSLT. 19 days after: PSL was tapered down to 50

				discontinuation	mg/day.
				33 days after discontinuation	The patient had mild strange feeling of voice and pharyngeal region. KL-6 was 1 697 (U/mL).
				36 days after discontinuation	PSL was tapered down to 40 mg/day.
				43 days after discontinuation	PSL was tapered down to 35 mg/day.
				52 days after discontinuation	The patient was discharged from the hospital.

Laboratory test values

	Day 146 of administration	5 days after discontinuation	33 days after discontinuation
KL-6 (U/mL)	1 820	1 620	1 697

Suspect concomitant drugs: carvedilol

Concomitant drugs: no data available

3 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: Psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and ankylosing spondylitis

PRECAUTIONS (revised language is underlined)

[Under old instructions]
ADVERSE REACTIONS (Clinically Significant Adverse Reactions) (newly added)

Erythroderma (dermatitis exfoliative): Erythroderma (dermatitis exfoliative) may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing this drug should be taken.

[Under new instructions]
11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Erythroderma (dermatitis exfoliative)

Reference information

Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported in approximately the previous 44-month period (April 2016 to November 2019).
Cases involving Erythroderma (dermatitis exfoliative): 1 (no patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 3 000

Launched in Japan: February 2015

Case summary

No.	Patient		Daily dose administration duration	Adverse reaction	
1	Sex/age	Indication for use (complication)		Clinical course and treatment provided	
	Male 40s	Psoriatic arthritis (Pruritus)	300mg 4 doses every other week	**Erythroderma** 35 days before administration 1 day before administration Day 1 of administration Day 7 of administration Day 22 of administration (day of discontinuation) 3 days after last administration 4 days after last administration 5 days after last administration 14 days after last administration 21 days after last administration 34 days after last administration	Oral administration of apremilast for skin symptoms started. Apremilast was discontinued. Secukinumab 300 mg/week started. Olopatadine hydrochloride for itching started. The last dose of secukinumab was administered (a total of 4 doses had been administered.). Olopatadine hydrochloride was discontinued. Eosinophils increased markedly to 41.0%. Neutrophil count decreased to 1 597. Erythroderma state was observed. Hydrocortisone butyrate ointment and betamethasone butyrate propionate lotion started as psoriasis treatment. No marked changes noted in skin findings. Eosinophils decreased slightly to 25.1%. Skin biopsy was performed and 2 doses of ciclosporin 200 mg started. The results of biopsy did not contradict psoriasis: Erythema with mild scales over the whole body was observed extensively. Skin desquamation: Yes Mucosal lesion: No Systemic erythema showed a tendency for improvement from the body trunk. Eosinophils decreased to 0% Systemic erythema and psoriasis rash mostly disappeared, still persistent in parts. Eosinophils was 0.1%. (Erythroderma) Outcome: recovered. Continued administration of hydrocortisone butyrate ointment and betamethasone butyrate propionate was decided.
	Concomitant drugs: Fexofenadine hydrochloride, d-chlorpheniramine maleate, difluprednate, maxacalcitol				

4
Revision of Precautions (No.310)

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 January 21, 2020.

1 Antiparkinsonian agents

[1] Levodopa
[2] Levodopa/carbidopa hydrate
[3] Levodopa/benserazide hydrochloride

Branded name

[1] Dopaston Capsules 250 mg, Dopaston Powder 98.5%, Dopaston for Intravenous Use 25 mg, 50 mg (Ohara Pharmaceutical Co., Ltd.), Dopasol Tablets 200 mg (Alfresa Pharma Corporation)
[2] Neodopaston Combination Tablets L100, L250 (Daiichi Sankyo Co., Ltd.), Menesit Tablets 100, 250 (MSD K.K.), Duodopa enteral combination solution (AbbVie GK), and the others
[3] Neodopasol Combination Tablets (Alfresa Pharma Corporation), EC-Doparl Tablets (Kyowa Kirin Co., Ltd.), Madopar Combination Tablet (Taiyo Pharma Co., Ltd.)

[Under Old instructions]
Important Precautions

Impulse-control disorder such as pathological gambling (persistent and recurrent gambling behavior despite negative social consequences including ruined personal life), pathologically increased sexual urges, compulsive shopping, and binge eating have been reported following administration of levodopa or a dopamine receptor agonist. In addition to impulse-control disorder, dopamine dysregulation syndrome in which patients seek doses of levodopa in excess of those required also has been reported in patients receiving levodopa. Patients, their families, or other caregivers should be informed of these symptoms and reducing the dose or discontinuing the medicine, or other appropriate measures should be taken if such symptoms develop.

2 Antiparkinsonian agents

Levodopa/carbidopa hydrate/entacapone

Branded name

Stalevo Combination Tablets L50, L100 (Novartis Pharma K.K.)

[Under Old instructions]
Important Precautions

Impulse-control disorder such as pathological gambling (persistent and recurrent gambling behavior despite negative social consequences including ruined personal life), pathologically increased sexual urges, compulsive shopping, and binge eating have been reported in patients receiving levodopa or a dopamine receptor agonist. In addition to impulse-control disorder, dopamine dysregulation syndrome in which patients seek doses of levodopa in excess of those required also has been reported in patients receiving levodopa. Patients, their families, or other caregivers should be informed of these symptoms and reducing the dose or discontinuing the medicine, or other appropriate measures should be taken if such symptoms develop.

3 Antihypertensives

[1] Olmesartan medoxomil
[2] Olmesartan medoxomil/azelnidipine

Branded name
[1] Olmetec OD Tablets 5 mg, 10 mg, 20 mg, 40 mg (Daiichi Sankyo Co., Ltd.), and the others
[2] Rezaltas Combination Tablets LD, HD (Daiichi Sankyo Co., Ltd.)

[Under Old instructions]

Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)

Interstitial pneumonia:
Interstitial pneumonia accompanied by pyrexia, cough, dyspnoea, or abnormal chest X-ray may occur. In such cases, administration of this drug should be discontinued and appropriate measures should be taken such as administration of corticosteroids.

[Under New instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Interstitial pneumonia
Interstitial pneumonia accompanied by pyrexia, cough, dyspnoea, or abnormal chest X-ray may occur. In such cases, administration of this drug should be discontinued and appropriate measures should be taken such as administration of corticosteroids.

4 Antidiabetic agents

Ipragliflozin L-proline

Branded name
Suglat Tablets 25 mg, 50 mg (Astellas Pharma Inc.)

[Under New instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Shock, anaphylaxis

5 Antidiabetic agents

Sitagliptin phosphate hydrate/ipragliflozin L-proline

Branded name
Sujanu Combination Tablets (MSD K.K.)

[Under New instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions

Shock, anaphylaxis

6 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.)

[Under Old instructions]

Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)

Erythroderma (dermatitis exfoliative): Erythroderma (dermatitis exfoliative) may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing this drug should be taken.

[Under New instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Erythroderma (dermatitis exfoliative)

7 Antineoplastics-miscellaneous

Alemtuzumab (genetical recombination)

Branded name
MabCampath 30 mg I.V. Infusion (Sanofi K.K.)

[Under Old instructions]

Adverse Reactions

Cervicocephalic arterial dissection: Cervicocephalic arterial

(Clinically Significant Adverse Reactions) (newly added)	dissection such as carotid or vertebral artery dissection may occur and cases that led to ischaemic stroke have been reported. Patients should be carefully monitored and appropriate measures should be taken such as temporal discontinuation or discontinuation of this drug if any abnormalities are observed.
[Under New instructions] **11. ADVERSE REACTIONS** **11.1 Clinically Significant Adverse Reactions (newly added)**	Cervicocephalic arterial dissection Cervicocephalic arterial dissection such as carotid or vertebral artery dissection may occur and cases that led to ischaemic stroke have been reported.

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 adverse drug reactions (ADRs) 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 31 December, 2019)

◎: Products for which EPPV was initiated after December 1, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Nintedanib ethanesulfonate*1 Ofev capsules 100 mg, 150 mg	Boehringer Ingelheim Japan, Inc.	December 20, 2019
◎	Avelumab (genetical recombination)*2 Bavencio intravenous infusion 200 mg	Merck Biopharma Co., Ltd	December 20, 2019
◎	Ceftolozane sulfate/tazobactam sodium*3 Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	December 20, 2019
◎	Certolizumab pegol (genetical recombination) *4 Cimzia 200 mg Syringe for S.C. Injection, Cimzia 200 mg AutoClicks for S.C. Injection	UCB Japan Co. Ltd.	December 20, 2019
◎	Evocalcet*5 Orkedia Tablets 1 mg, 2 mg	Kyowa Kirin Co., Ltd.	December 20, 2019
◎	Botulinum toxin type A Botox for injection 50 units, 100 units	Glaxo Smith Kline K.K.	December 20, 2019
◎	Polyethylene glycol treated human normal immunoglobulin*6 Venoglobulin IH 5% I.V. 0.5 g/10 mL, 1g/20 mL, 2.5 g/50 mL, 5 g/100 mL, 10 g/200 mL, Venoglobulin IH 10% I.V. 0.5 g/5 mL, 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	Japan Blood Products Organization	December 20, 2019
◎	Freeze-dried sulfonated human normal immunoglobulin*7 Kenketsu Venilon- Ⅰ for Intravenous Injection 500 mg, 1000 mg, 2500 mg, 5000 mg	KM Biologics Co., Ltd.	December 20, 2019
◎	Ropinirole hydrochloride Haruropi Tape 8 mg, 16 mg, 24 mg, 32 mg, 40 mg	Hisamitsu Pharmaceutical Co., Inc.	December 17, 2019
◎	Omalizumab (genetical recombination) *8 Xolair for s.c. injection 75 mg, 150 mg, Xolair for s.c. injection syringe 75 mg, 150 mg	Novartis Pharma K.K.	December 11, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Trafermin (genetical recombination) Retympa 250 μg Set for Otology	Nobelpharma Co., Ltd.	December 9, 2019
◎	Burosumab (genetical recombination) Crysvita Subcutaneous Injection 10 mg, 20 mg, 30 mg	Kyowa Kirin Co., Ltd.	December 6, 2019
◎	Lisdexamfetamine mesilate Vyvanse Capsules 20 mg, 30 mg	Shionogi & Co., Ltd.	December 3, 2019
	Vortioxetine hydrobromide Trintellix Tablets 10 mg, 20 mg	Takeda Pharmaceutical Company Limited.	November 27, 2019
	Necitumumab (genetical recombination) Portrazza Injection 800 mg	Nippon Kayaku Co., Ltd.	November 22, 2019
	Ranibizumab (genetical recombination) *9 Lucentis solution for intravitreal injection 10mg/mL	Novartis Pharma K.K.	November 22, 2019
	Ixekizumab (genetical recombination) *10 Taltz Subcutaneous Injection Syringes 80 mg, Taltz Subcutaneous Injection Autoinjectors 80 mg	Eli Lilly Japan K.K.	November 22, 2019
	Venetoclax Venclexta Tablets 10 mg, 50 mg, 100 mg	AbbVie GK	November 22, 2019
	Safinamide mesilate Equfina Tablets 50 mg	Meiji Seika Pharma Co., Ltd.	November 20, 2019
	Roxadustat Evrenzo tablets 20 mg, 50 mg, 100 mg	Astellas Pharma Inc.	November 20, 2019
	Ivabradine hydrochloride Coralan Tablets 2.5 mg, 5 mg, 7.5 mg	Ono Pharmaceutical Co., Ltd.	November 19, 2019
	Quizartinib hydrochloride Vanflyta Tablets 17.7 mg, 26.5 mg	Daiichi Sankyo Co., Ltd.	October 10, 2019
	Insulin degludec (genetical recombination)/liraglutide (genetical recombination) Xultophy combination Injection FlexTouch	Novo Nordisk Pharma Ltd.	September 26, 2019
	Belimumab (genetical recombination) Benlysta for I.V. infusion 120 mg, 400 mg	Glaxo Smith Kline K.K.	September 20, 2019
	Apremilast*11 Otezla Tablets 10 mg, 20 mg, 30 mg	Celgene K.K.	September 20, 2019
	Desmopressin acetate hydrate*12 Minirinmelt OD Tablets 25 μg, 50 μg	Ferring Pharmaceuticals Co., Ltd.	September 20, 2019
	Azithromycin hydrate Azimycin Ophthalmic Solution 1%	Senju Pharmaceutical Co., Ltd.	September 11, 2019
	Blonanserin Lonasen Tape 20 mg, 30 mg, 40 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 10, 2019
	Patisiran sodium Onpattro infusion 2 mg/mL	Alnylam Pharmaceuticals, Inc.	September 9, 2019
	Glycopyrronium bromide/formoterol fumarate hydrate	AstraZeneca K.K.	September 4, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
	Bevespi Aerosphere 28 inhalations		
	Budesonide/glycopyrronium bromide/formoterol fumarate hydrate Breztri Aerosphere 56 inhalations	AstraZeneca K.K.	September 4, 2019
	Entrectinib Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	September 4, 2019
	Defibrotide sodium Defitelio Injection 200 mg	Nippon Shinyaku Co., Ltd.	September 4, 2019
	Ravulizumab (genetical recombination) Ultomiris Intravenous Infusion 300 mg	Alexion Pharmaceuticals, Inc.	September 4, 2019
	pH4-treated normal human immunoglobulin Privigen 10% I.V. Drip Infusion 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	CSL Behring K.K.	August 19, 2019
	Freeze-dried inactivated tissue culture rabies vaccine Rabipur for intramuscular injection	Glaxo Smith Kline K.K.	July 26, 2019
	Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate Symtuza Combination Tablets	Janssen Pharmaceutical K.K.	July 26, 2019
	Peficitinib hydrobromide Smyraf Tablets 50 mg, 100 mg	Astellas Pharma Inc.	July 10, 2019

*1 Systemic sclerosis-associated interstitial lung disease

*2 Unresectable or metastatic renal cell carcinoma

*3 <applicable microorganisms> Zerbaxa-susceptible serratia bizio and haemophilus influenzae <applicable conditions> pneumonia and sepsis

*4 Plaque psoriasis, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma for which existing treatment methods are not sufficiently effective

*5 Hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after parathyroidectomy

*6 Preoperative desensitization in renal transplantation with donor-specific antibodies

*7 Acute optic neuritis (when steroids are not sufficiently effective)

*8 With a new additional indication and a new dosage for seasonal allergic rhinitis (only in severe to the most severe cases inadequately controlled with existing treatment)

*9 Retinopathy of prematurity

*10 Ankylosing spondylitis with inadequate response to existing therapies

*11 Oral ulcers associated with Behçet's disease with inadequate response to local therapies

*12 Nocturia due to nocturnal polyuria in males