Pharmaceuticals and Medical Devices Safety Information

No. 360 February 2019

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

Available information is listed here

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

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

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Pharmaceuticals and Medical Devices Safety Information

No. 360 February 2019

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

[Outline of Information]

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2	**Important Safety Information**	*P* *C*	Nusinersen sodium (and 1 other): Regarding the revision of the Precautions in package inserts of drugs in accordance with the Notification dated January 10, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.	7
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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

ADEM	Acute disseminated encephalomyelitis
ADR	Adverse Drug Reaction
AMED	Japan Agency for Medical Research and Development
BRCA	Breast cancer susceptibility gene
CRP	C-reactive protein
CT	Computed tomography
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HER	Human epidermal growth factor receptor
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PML	Progressive multifocal leukoencephalopathy
SD	Standard deviation
VP	Ventriculoperitoneal
WBC	White blood cell

1

Package Inserts of Prescription Drugs under the Revised Instructions

1. Introduction

New instructions regarding language used in package inserts for prescription drug products were issued in June 2017. Package inserts for prescription drugs will be revised in line with the new instructions (hereinafter, the "Revised Instructions") to begin the process of replacing package inserts in the old format in April 2019. The revision of the instructions was outlined in the Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 344 (issued June 2017). This issue of the PMDSI will describe the main content of the revision with specific examples.

Please note that examples of package insert language included in this section do not substitute the real package inserts for specific drug products. Please also refer to package inserts attached to actual products or those available on the PMDA website to confirm the precautions or other information of specific products.

2. Features of Package Inserts under the Revised Instructions

(1) Format

It was decided to assign inherent numbers to sections of the package inserts under the Revised Instructions. Any sections required to fill under the Revised Instructions will be left blank when they are not applicable or relevant and the section numbers will be skipped. Subsections immediately under the sections mentioned above will be presented in the form of 1.1 or the like. Then sub-subsections under the subsections will be presented as 1.1.1.

Examples of new package insert language:
4. INDICATIONS
・Cough suppression and sedation in various
・Analgesia in pain
・Improvement of severe diarrhea

Section 5 is skipped, with no applicable information for PRECAUTIONS CONCERNING INDICATIONS

6. DOSAGE AND ADMINISTRATION
The usual adult dosage is 60 mg of Drug name daily administered orally in 3 divided doses.
The dose may be adjusted according to the pati

Section 7 is skipped, with no applicable information to PRECAUTION CONCERNING DOSAGE AND ADMINISTRATION.

8. IMPORTANT PRECAUTIONS
8.1 Drug dependence may occur due to prol efully monitored and caution should be exercised whe
8.2 Somnolence and dizziness may occur. Pati tioned regarding operating hazardous machine such as driving a car.

(2) Abolishing of the Relative Contraindications section and new addition of the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section

The Relative Contraindications and Careful Administration sections will be removed and information contained in these sections will be moved to a newly added PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section.

Example of current package insert language:	Examples of new package insert language:
Careful Administration	9. PRECAUTIONS CONCERNING

(This drug should be administered with care in patients as follows) 1. Patients with past or present arrhythmia (Cases of extrasystoles etc. have been reported. Symptoms of arrhythmia may be exacerbated or recur.) 2. Patients with past or present hepatic disorder [Since this drug metabolized mostly in the liver, patients may be susceptible to adverse reactions to this drug.]	PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with complication or history of diseases, etc. 9.1.1 Patients with complication or history of diseases, etc. 9.3 Patients with hepatic impairment 9.3.1 Patients with past or present hepatic disorder Since this drug metabolized mostly in the liver, patients may be susceptible to adverse reactions to this drug.

(3) Abolishing of the Geriatric Use, Use during Pregnancy, Delivery or Breastfeeding, and Pediatric Use sections

These sections currently present in package inserts will be abolished and information contained in these sections will be integrated under the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section. Regarding precautions for breastfeeding, the observation of excretion of the drug in breast milk alone should not warrant the language “should be counseled to avoid breastfeeding” in the new package inserts. The language “safety of the drug has not been established” should be replaced with statements on whether relevant studies have been conducted.

Examples of current package insert language: Use during Pregnancy, Delivery, or Breastfeeding 1. Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. (Fetal transfer (with a fetal concentration similar to the maternal blood concentration) was reported in an animal study in which rats were administered this drug orally.) 2. Administration to breast-feeding women should preferably be avoided. If administration of this drug is absolutely necessary, breast-feeding women should be instructed to avoid the practice. (Human milk transfer has been reported)	Examples of new package insert language: 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women 9.5.1 Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Fetal transfer (with a fetal concentration similar to the maternal blood concentration) was reported in an animal study in which rats were administered this drug orally. 9.6 Breast-feeding Women The potential therapeutic benefits of the drug and the nutritional benefits of breastfeeding should be weighed to decide to continue or discontinue breastfeeding. Human milk transfer has been reported.
Pediatric Use Safety of this drug in low birth weight babies, newborns, babies, infants, or children has not been established. [No clinical experience]	9.7 Pediatric Use 9.7.1 No clinical studies have been conducted specifically for the safety and effectiveness of this drug in pediatric patients.
Geriatric Use Careful administration is required in geriatric patients who generally have diminished physiological function.	9.8 Geriatric Use Geriatric patients generally have diminished physiological function.

(4) Adverse Reactions

New package inserts will no longer include a summary of observed adverse reactions. The Other Adverse Reactions section should present information in tabular forms. Onset frequencies of adverse reactions should be noted in the text or the tables. The rates of occurrence in clinical studies should be included in the 17. CLINICAL STUDIES section.

Examples of current package insert language:

Adverse Reactions

Summary of occurrence of adverse reactions

In a total of ( ) cases investigated prior to approval, adverse reactions (including abnormal laboratory findings) had been reported in X (Y %) cases. The most frequently reported adverse reactions included (snip).

Clinically significant Adverse Reactions

1. Shock or anaphylaxis (frequency unknown) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2. Disturbed consciousness (frequency unknown) such as decreased level of consciousness and/or loss of consciousness may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Other Adverse Reactions

Appropriate measures should be taken according to the patients' symptoms when adverse reactions listed below occur.

1. Blood

   0.5 to below 5%

   Anemia

2. Blood

   Frequency unknown

   Haemoglobin decreased

3.…

Examples of new package insert language:

11. ADVER

Summary of occurrence will not be presented.

The language "Patients should be carefully monitored *snip* and appropriate measures should be taken" will be placed at the beginning of the ADVERSE REACTIONS section and will not be repeated for individual adverse reactions listed.

Adverse reaction[illegible]lows may occur. Patients should be c[illegible]ully monitored and if any abnormalities are observed, administration of this drug should be discontinued or other appropriate measures should be taken.

11.1 Clinically Significant Adverse Reactions

11.1.1 Shock, anaphylaxis (both with an unknown frequency)

11.1.2 Disturbed consciousness (frequency unknown)

Disturbed consciousness such as (frequency unknown) such as decreased level of consciousness and/or loss of consciousness may occur.

11.2 Other Adverse Reactions

Type/frequency	1% or higher	0.1 to below 1%	Below 0.1%	Frequency Unknown
Blood		Anemia		Haemoglobin decreased
…				

The Other Adverse Reactions section should be presented in tabular forms.

3. Closing Remarks

Consultation sessions are currently underway concerning these revisions to the current package inserts in line with the new package insert requirements under the Revised Instructions. Revision of package insert pursuant to the Revised Instructions will start in April 2019. As MHLW has designated a transition period regarding compliance with the Revised Instruction extending through March 2024, healthcare professionals should be informed that package inserts conforming to either the former or Revised Instructions will exist in the interim.

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Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated January 10, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Nusinersen sodium

Branded name (name of company)	Spinraza Intrathecal Injection 12 mg (Biogen Japan Ltd)
Therapeutic category	Central nervous system agents-miscellaneous
Indications	Spinal muscular atrophy

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Hydrocephalus:** Hydrocephalus may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 42-month period (April 2015 to September 2018). Cases involving hydrocephalus: 1 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 300 Japanese market launch: August 2017

Case summary

No.	Patient		Daily dose/Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male under 1 year old	Spinal muscular atrophy (cerebral ventriculomegaly, mild brain stem atrophy)	4 ml (1st dose) 4.3 ml (2nd dose) 4.3 ml (3rd dose)	**Hydrocephalus**	
				14 days before administration	The patient's head circumference was + 0.6 standard deviation (SD).
				Day 1 of administration	Administration of nusinersen sodium was initiated.
				16 days after administration	The patient received the second dose of nusinersen sodium.
				30 days after administration	The patient received the third dose of nusinersen sodium.
				32 days after administration	Increased head circumference was observed. (+ 2.4 SD)
				35 days after administration	Cranial ultrasonography revealed marked cerebral ventriculomegaly. The patient was diagnosed with hydrocephalus. Discontinuation of nusinersen sodium for Week 9 and later of the start of administration was decided.
				42 days after administration	Head magnetic resonance imaging (MRI) revealed marked cerebral ventriculomegaly and patency of the cerebral aqueduct. The patient was diagnosed with communicating hydrocephalus.
				46 days after administration	Transient disturbance of lateral gaze and sunset phenomenon were observed.
				50 days after administration	A ventriculoperitoneal (VP) shunt procedure was performed.
				51 days after administration	Improvement in cerebral ventriculomegaly was observed. Disturbance of lateral gaze and sunset phenomenon disappeared. Patient exhibited improved feeding capacity.
				56 days after administration	The patient's head circumference was + 2.3 SD. Improvement in eye movement disorder was observed. Some decline in feeding capacity remained.
				77 days after administration	Eye movement disorder disappeared. Decrease in head circumference was observed (+ 1.8 SD).
	Suspected concomitant medications: none Concomitant medications: none				

2 Axitinib

Branded name (name of company)	Inlyta Tablets 1 mg, 5 mg (Pfizer Japan Inc.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Unresectable or metastatic renal cell carcinoma

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Interstitial lung disease:** Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 42-month period (April 2015 to September 2018). Cases involving interstitial lung disease: 2 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 2 000 Japanese market launch: August 2012

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/ Age</th><th>Reason for use (complications)</th><th>Clinical course and therapeutic measures</th></tr>
<tr><td>1</td><td>Male 70s</td><td>Metastatic renal (cancer pulmonary fibrosis, hyperlipidaemia, hypertension)</td><td>10 mg 918 days</td><td>Interstitial lung disease

Medical history: former smoker, interstitial lung disease, lung metastasis
Past treatment: interferon Alfa, sunitinib malate, sorafenib tosilate

Day 1 of administration: Administration of axitinib was initiated at a dosage of 5 mg taken twice daily.

Around Day 875 of administration: Dyspnea exacerbated and axitinib was intermittently suspended based on the patient’s wishes.

Day 918 of administration (Day of onset) (Day of discontinuation): Exacerbation of interstitial shadows was pointed out when the patient visited the urology department. The patient was admitted to the hospital. A chest x-ray revealed a decrease in pulmonary basilar permeability, and further loss of volume in the left residual lung. A chest computed tomography (CT) examination revealed increased nodule presence in the apical portion and middle lobe of the right lung, as well as exacerbation of interstitial shadows.

3 days after discontinuation: Administration of prednisolone was initiated at a dosage of 30 mg daily.
Dyspnea promptly improved after that.

32 days after discontinuation: Interstitial lung disease remitted.</td></tr>
<tr><td colspan="5">Laboratory Examination
<table><tr><th></th><th>Before administration (date unknown)</th><th>1 day after discontinuation (1 day after onset)</th><th>4 days after discontinuation</th><th>119 days after discontinuation</th></tr><tr><td>WBC (cells/mm^3)</td><td>—</td><td>6 600</td><td>—</td><td>—</td></tr><tr><td>LDH (IU/L)</td><td>—</td><td>277</td><td>—</td><td>—</td></tr><tr><td>SpO_2 (%)</td><td>98</td><td>87</td><td>85</td><td>96</td></tr><tr><td>SP-D (ng/mL)</td><td>—</td><td>381</td><td>401</td><td>85.1</td></tr><tr><td>β-D glucan (pg/mL)</td><td>—</td><td>≦ 5.0</td><td>—</td><td>—</td></tr><tr><td>CRP (mg/dL)</td><td>—</td><td>3.1</td><td>—</td><td>—</td></tr></table></td></tr>
<tr><td colspan="5">Concomitant medications: valsartan, codeine phosphate hydrate, magnesium oxide, omega-3 fatty acid ethyl esters</td></tr>
</table>

3

Revision of Precautions (No. 300)

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 10, 2019.

1 Central nervous system agents-miscellaneous

Nusinersen sodium

Branded name	Spinraza Intrathecal Injection 12 mg (Biogen Japan Ltd)
Adverse reactions (clinically significant adverse reactions)	**Hydrocephalus:** Hydrocephalus may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.

2 Antineoplastics-miscellaneous

Axitinib

Branded name	Inlyta Tablets 1 mg, 5 mg (Pfizer Japan Inc.)
Adverse reactions (clinically significant adverse reactions)	**Interstitial lung disease:** Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

3 Antineoplastics-miscellaneous

Lenalidomide hydrate

Branded name	Revlimid Capsules 2.5 mg, 5 mg (Celgene 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 the administration of this drug. If symptoms such as disturbed consciousness, cognitive disorder, symptoms of paralysis (hemiplegia or quadriplegia), or disorders related to linguistic capacity are observed, administration of this drug should be discontinued, diagnostic assessment using MRI and cerebrospinal fluid tests should be performed, and other measures should be taken as appropriate.

4 **Synthetic antibacterials**

[1] Ofloxacin (oral dosage form)
[2] Garenoxacin mesilate hydrate
[3] Ciprofloxacin
[4] Tosufloxacin tosilate hydrate (oral preparations with dosage and administration for pediatric use)
[5] Pazufloxacin mesilate
[6] Moxifloxacin hydrochloride (oral dosage form)
[7] Levofloxacin hydrate (oral and injectable dosage forms)
[8] Lomefloxacin hydrochloride (oral dosage form)

Branded name	[1] Tarivid Tablets 100 mg (Daiichi Sankyo Co., Ltd.), and the others [2] Geninax Tablets 200 mg (Fuji Film Toyama Chemical Co., Ltd.) [3] Ciproxan-I.V. 200, 400 (Bayer Yakuhin, Ltd.), and the others [4] Ozex fine granules 15% for pediatric, Ozex Tab. 60 mg for pediatric (Fuji Film Toyama Chemical Co., Ltd.), and the others [5] Pasil Intravenous Drip Infusion 300 mg, 500 mg, 1000 mg (Fuji Film Toyama Chemical Co., Ltd.), Pazucross Injection 300 mg, 500 mg, 1000 mg (Mitsubishi Tanabe Pharma Corporation [6] Avelox Tablets 400 mg (Bayer Yakuhin, Ltd.) [7] Cravit Tablets 250 mg, 500 mg, Cravit Fine Granules 10%, Cravit Intravenous Drip Infusion Bag 500 mg/100 mL, Cravit Intravenous Drip Infusion 500 mg/20 mL (Daiichi Sankyo Co., Ltd.), and the others [8] Bareon Capsule 100 mg, Bareon Tablets 200 mg (Mylan EPD G.K.)
Careful Administration	Patients complicated with aortic aneurysm or aortic dissection, or patients who have a previous history, a family history or risk factors (Marfan's syndrome, etc.) of aortic aneurysm or aortic dissection
Important precautions	Aortic aneurysm or aortic dissection may occur. Patients should be carefully monitored and instructed to seek medical attention immediately if they experience symptoms such as pain in the abdomen, chest, or back. Imaging assessment should be considered if necessary, for patients complicated with aortic aneurysm or aortic dissection, or patients who have a previous history, a family history, or risk factors of aortic aneurysm or aortic dissection.
Adverse reactions (clinically significant adverse reactions)	**Aortic aneurysm, aortic dissection:** Aortic aneurysm or aortic dissection may occur. If any abnormalities are observed, appropriate measures should be taken.

5 **Synthetic antibacterials**

[1] Sitafloxacin hydrate
[2] Ciprofloxacin hydrochloride hydrate
[3] Tosufloxacin tosilate hydrate (oral preparations without dosage and administration for pediatric use)
[4] Norfloxacin (oral dosage form)
[5] Prulifloxacin

Branded name	[1] Gracevit Tablets 50 mg, Gracevit Fine Granules 10% (Daiichi Sankyo Co., Ltd.), and the others [2] Ciproxan Tablets 100, 200 (Bayer Yakuhin, Ltd.), and the others [3] Ozex Tab. 75, 150 (Fuji Film Toyama Chemical Co., Ltd.), Tosuxacin Tablets 75 mg, 150 mg (Mylan EPD G.K), and the others [4] Baccidal Tablets 100 mg, 200 mg, Baccidal Tablets for Children 50 mg (Kyorin Pharmaceutical Co., Ltd.), and the others [5] Sword Tablets 100 (Meiji Seika Pharma Co., Ltd.)
Careful Administration	Patients complicated with aortic aneurysm or aortic dissection, or patients who have a previous history, a family history, or risk factors (Marfan's syndrome, etc.) of aortic aneurysm or aortic dissection
Important precautions	Aortic aneurysm or aortic dissection may occur. Patients should be carefully monitored and instructed to seek medical attention immediately if they experience symptoms such as pain in the abdomen, chest, or back. Imaging assessment should be considered if necessary for patients complicated with aortic aneurysm or aortic dissection, or patients who have a previous history, a family history, or risk factors of aortic aneurysm or aortic dissection.
Adverse reactions (clinically significant adverse reactions)	**Aortic aneurysm, aortic dissection:** Aortic aneurysm or aortic dissection may occur. If any abnormalities are observed, appropriate measures should be taken.

6 **Antivirals**

[1] Asunaprevir
[2] Daclatasvir hydrochloride
[3] Daclatasvir hydrochloride/asunaprevir/beclabuvir hydrochloride

Branded name	[1] Sunvepra Capsules 100 mg (Bristol-Myers Squibb Company) [2] Daklinza Tablets 60 mg (Bristol-Myers Squibb Company) [3] Ximency Combination Tablets (Bristol-Myers Squibb Company)
Important precautions	Renal impairment such as acute kidney injury may occur. Patients should be carefully monitored through methods such as periodic renal function tests.
Adverse reactions	**Renal impairment:**

(clinically significant adverse reactions)	Renal impairment such as acute kidney injury may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration 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 December 31, 2018)
◎: Products for which EPPV was initiated after December 1, 2018

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Secukinumab (genetical recombination) *1 Cosentyx for s.c. injection 150 mg syringe	Novartis Pharma K.K.	December 21, 2018
◎	Ipragliflozin L–proline *2 Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	December 21 2018
◎	Dolutegravir sodium/rilpivirine hydrochloride Juluca Combination Tablets	Viiv Healthcare K.K.	December 20, 2018
◎	Gilteritinib fumarate Xospata Tablets 40 mg	Astellas Pharma Inc.	December 3, 2018
	Abemaciclib Verzenio Tablets 50 mg, 100 mg, 150 mg	Eli Lilly Japan K.K.	November 30, 2018
	Dexmedetomidine hydrochloride a. Precedex Intravenous Solution 200 μg [Pfizer], b. Precedex Intravenous Solution 200 μg/50 mL syringe [Pfizer], c. Precedex Intravenous Solution 200 μg [Maruishi], d. Precedex Intravenous Solution 200 μg/50 mL syringe [Maruishi]	a, b Pfizer Japan Inc. c, d Maruishi Pharmaceutical Co., Ltd.	November 29, 2018
	Macrogol 4000/sodium chloride/sodium bicarbonate/potassium chloride Movicol Combination Powder	EA Pharma Co., Ltd.	November 29, 2018
	Omidenepag isopropyl Eybelis Ophthalmic Solution 0.002%	Santen Pharmaceutical Co., Ltd.	November 27, 2018
	Vibegron Beova Tablets 50 mg	Kyorin Pharmaceutical Co.,Ltd.	November 27, 2018
	Blinatumomab (genetical recombination) Blincyto I.V. Infusion 35 μg	Amgen Astellas BiPharma K.K.	November 27, 2018
	Lorlatinib Lorbrena Tablets 25 mg, 100 mg	Pfizer Japan Inc.	November 20, 2018
	Icatibant acetate Firazyr subcutaneous injection 30 mg syringe	Shire Japan KK	November 20, 2018
	Vedolizumab (genetical recombination) Entyvio for I.V. Infusion 300 mg	Takeda Pharmaceutical Company Limited.	November 7, 2018

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Nonacog beta pegol (genetical recombination) Refixia I.V. Injection 500, 1000, 2000	Novo Nordisk Pharma Ltd.	November 1, 2018
Levonorgestrel/ethinylestradiol Jemina Tablets	Nobelpharma Co., Ltd.	October 4, 2018
Spiramycin Spiramycin 1.5M IU Tablets [Sanofi]	Sanofi K.K.	September 25, 2018
Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate Odefsey Combination Tablets	Janssen Pharmaceutical K.K.	September 20, 2018
Fidaxomicin Dafclir Tablets 200 mg	Astellas Pharma Inc.	September 18, 2018
Obinutuzumab (genetical recombination) Gazyva Intravenous Infusion 1000 mg	Chugai Pharmaceutical Co., Ltd.	August 29, 2018
Durvalumab (genetical recombination) Imfinzi Injection 120 mg, 500 mg	AstraZeneca K.K.	August 29, 2018
Ipilimumab (genetical recombination) *3 Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	August 21, 2018
Nivolumab (genetical recombination) *4 Opdivo I.V. Infusion 20 mg, 100 mg, 240 mg	Ono Pharmaceutical Co., Ltd.	August 21, 2018
Tedizolid phosphate Sivextro Tablets 200 mg, Sivextro for iv infusion 200 mg	Bayer Yakuhin, Ltd.	August 21, 2018
Condoliase Hernicore 1.25 Units for Intradiscal Inj.	Seikagaku Corporation	August 1, 2018
Fosravuconazole L-lysine ethanolate Nailin Capsules 100 mg	Sato Pharmaceutical Co., Ltd.	July 27, 2018
Canakinumab (genetical recombination) *5 Ilaris for S.C. Injection 150 mg, Ilaris Solution for S.C. Injection 150 mg	Novartis Pharma K.K.	July 2, 2018
Olaparib*6 Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	July 2, 2018

*1 Ankylosing spondylitis that does not adequately respond to existing treatments

*2 Type 1 diabetes mellitus

*3 Radically unresectable or metastatic renal cell carcinoma

*4 Radically unresectable or metastatic renal cell carcinoma

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

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