Pharmaceuticals and Medical Devices Safety Information

No. 379 January 2021

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.

Register here

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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
BRAF	V-Raf murine sarcoma viral oncogene homolog B
CYP3A	Cytochrome P450 3A
DAPT	dual anti-platelet therapy
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PCI	percutaneous coronary intervention
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information

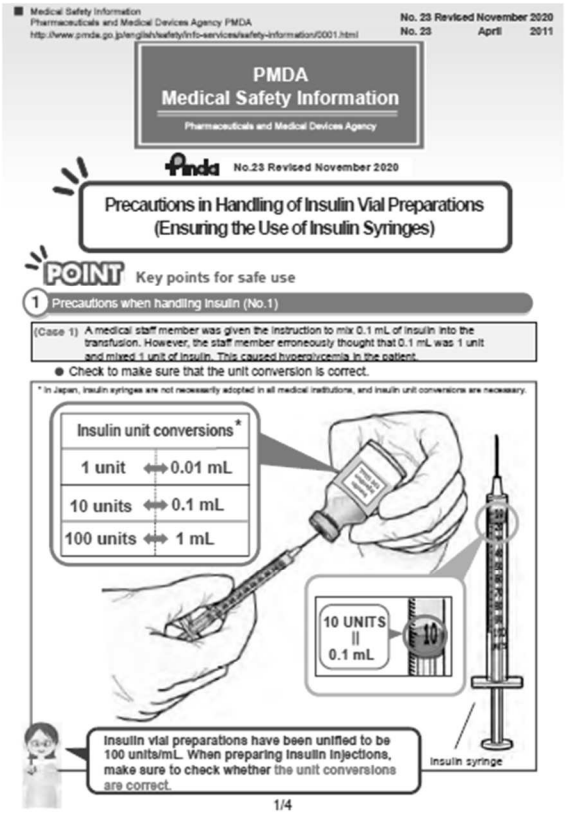
1
Revision of PMDA Medical Safety Information for Ensuring Use of Insulin Syringes

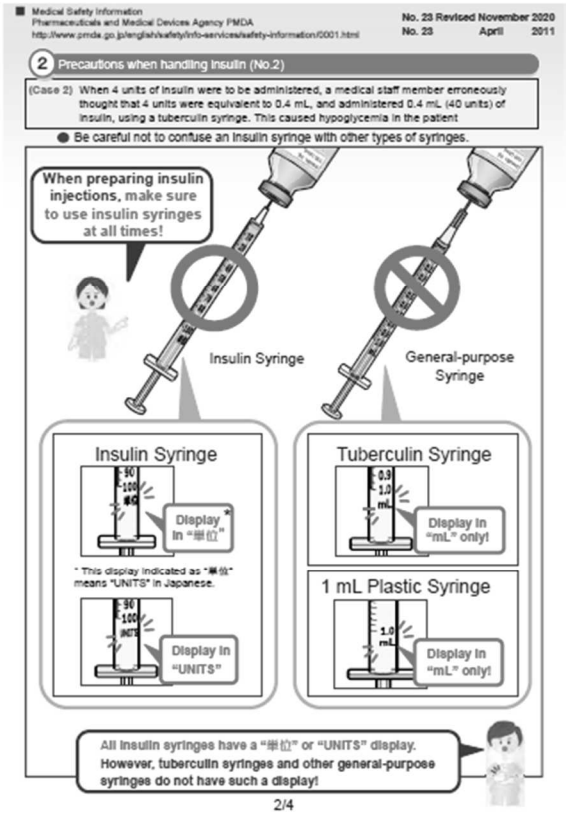
1. Introduction

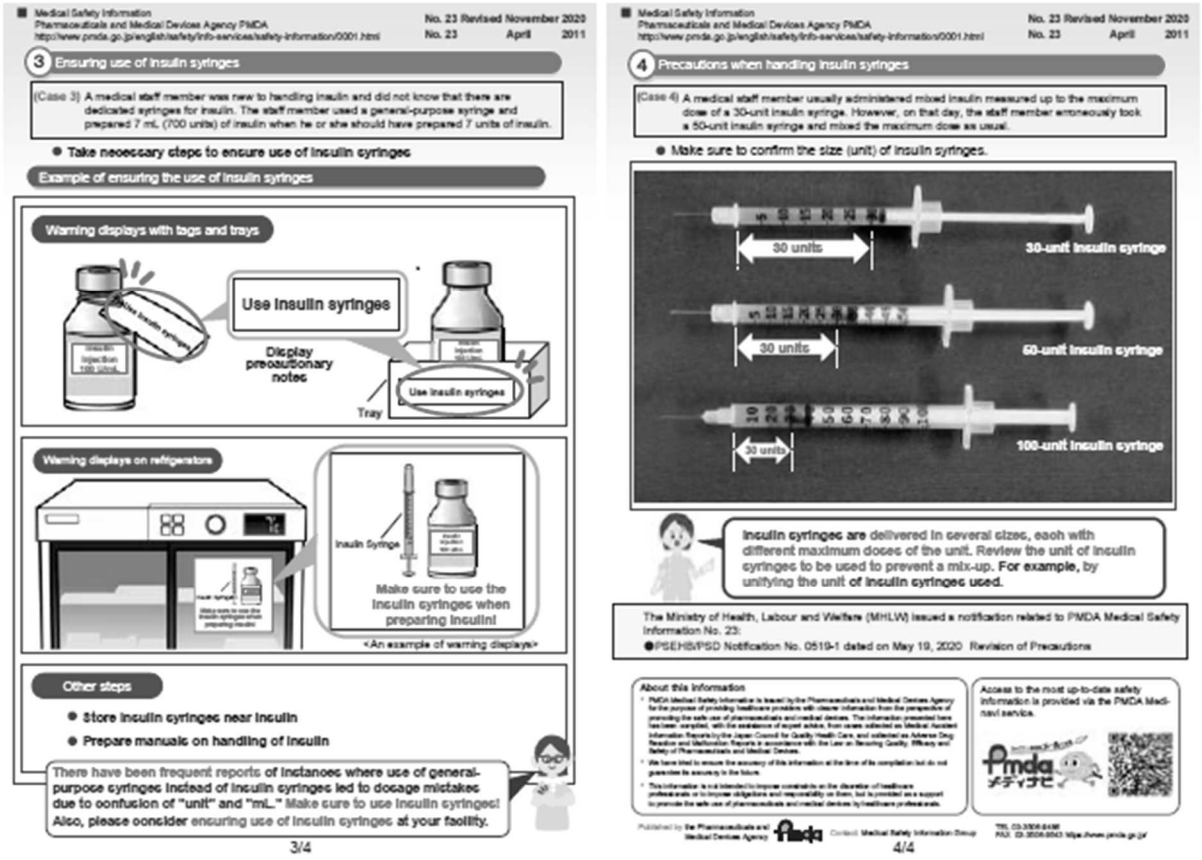
In response to persistently reported cases of medical accidents as a result of the failure to use a dedicated insulin syringe in handling insulin vial preparations, the package inserts of insulin vial preparations were revised in May 2020.

To ensure the use of insulin syringes, PMDA Medical Safety Information No. 23 was revised in November 2020. This section will introduce the details of the revision of No. 23. For the reporting status of cases of the medical accidents and outline of the revision of the package inserts, please refer to Revision of Package Inserts regarding Insulin Vial Preparations, Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 374 (July 2020).

Revised PMDA Medical Safety Information No. 23
Precautions in Handling of Insulin Vial Preparation (Ensuring the Use of Insulin Syringes)
https://www.pmda.go.jp/files/000237478.pdf







2. Precautions for ensuring use of insulin syringes

Cases of wrong dose administration of insulin have been reported persistently. Use of a general purpose syringe instead of an insulin syringe in handling insulin vial preparations resulted in such wrong dose administration by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL).

<Case 1>
A medical staff member was new to handling insulin and did not know that there are dedicated syringes for insulin. The staff member used a general-purpose syringe and prepared 7 mL (700 units) of insulin when he or she should have prepared 7 units of insulin.

<Case 2>
When 4 units of insulin were to be administered, a medical staff member erroneously thought that 4 units of insulin were equivalent to 4 mL (400 units) in a general purpose syringe and administered 100 fold the necessary insulin.

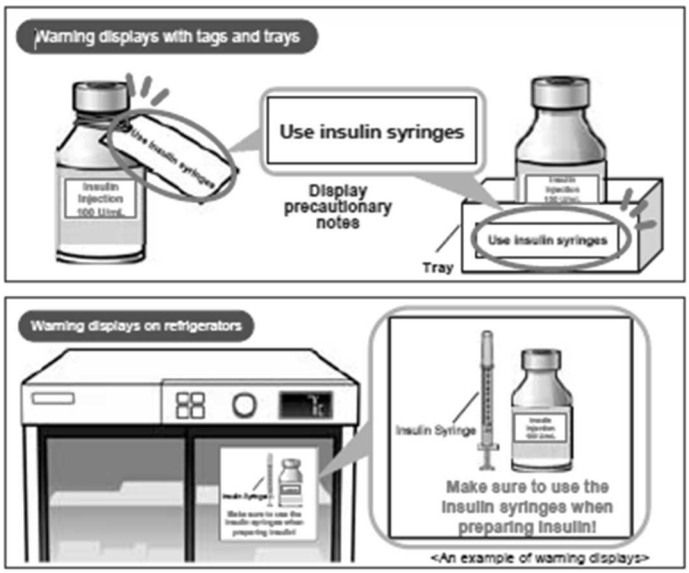
To address these situations, the updated No. 23 revised the title to Precautions in Handling of Insulin Vial Preparations from the previous Precautions in Handling of Insulin Syringes to highlight the importance of using insulin syringes among medical professionals.

Specific examples of precautions to ensure the use of insulin syringes are provided as follows:

Medical institutions are requested to consider ensuring the use of insulin syringes at their own facilities to support the prevention of medical accidents resulting from the failure to use insulin syringes.

(Example 1) Precaution displays

Precautionary notes easy to recognize for medical personnel who are new to handling insulin vial preparations should be placed on tags, trays, and refrigerators for the “Use Insulin Syringes.”



(Example 2) Preparing manuals ready for use

The Manual for Preparation of Standard Operating Procedure for Safe Use of Drugs (revised edition 2018) appended to the Administrative Notice, Revision of Manual for Standard Operating Procedure for Safe Use of Drugs dated December 28, 2018 states in Chapter 7, Use of Drugs to Inpatients that “For insulin particularly, awareness of proper management and use of dedicated syringes should also be ensured because of the high risk of grave adverse events as a result of confusing insulin units and mL.” In line with the statement, a. Keeping insulin syringes in the proximity of insulin, or b. Preparing manuals for handling insulin ready for use, is suggested.

3. Closing remark

Medical professionals are requested to review the specific examples presented here and circulate precaution within their own institutions to ensure the use of insulin syringes. Insulin syringes are available in several sizes, each with different maximum doses of the unit. Medical institutions might want to review the sizes of insulin syringes they currently use and consider measures to prevent confusion, unifying the sizes of insulin syringes to adopt across their own institution for example.

[Reference]

·Ministry of Health, Welfare and Labour Pharmaceuticals and Medical Devices Safety Information No. 374 (July 2020)
https://www.pmda.go.jp/files/000235772.pdf
(Accessed December 3, 2020)
·Medical Accident Information, Medical Accident Information Reports by the Japan Council for Quality Health Care
http://www.med-safe.jp/mpreport/view/AB7CD7B5C7EA7835B (source of adaptation for a case example, only in Japanese)
http://www.med-safe.jp/mpreport/view/A55DF4BF2CB8E38BA (source of adaptation for a case example, only in Japanese)
(accessed December 3, 2020)
・Revision of Manual for Preparation of Standard Operating Procedure for Safe Use of Drugs (Administrative Notice dated December 28, 2018)
Https://www.mhlw.go.jp/topics/bukyoku/isei/i-anzen/hourei/dl/181228-1.pdf (only in Japanese)
(only in Japanese, accessed December 3, 2020)
・Appendix: Manual for Preparation of Standard Operating Procedure for Safe Use of Drugs (revised edition 2018)
Https://www.mhlw.go.jp/topics/bukyoku/isei/i-anzen/hourei/dl/181228-2.pdf (only in Japanese)
(only in Japanese, accessed December 3, 2020)

2
Revision of Precautions (No.319)

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 December 8, 2020.

1 Other agents relating to blood and body fluides
Clopidogrel sulfate

Branded name Plavix Tablets 25 mg, 75 mg (Sanofi K.K.), and the others

[Under Old instructions]

Precautions concerning Dosage and Administration

For ischaemic heart disease for which percutaneous coronary intervention (PCI) is indicated,
This drug should be co-administered with aspirin (81-10 mg/day) during dual anti-platelet therapy (DAPT). The latest Japanese and overseas guidelines or other similar sources should be referred to for the post-DAPT administration.

[Under New instructions]

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

<For ischaemic heart disease for which percutaneous coronary intervention (PCI) is indicated>
This drug should be co-administered with aspirin (81-100 mg/day) during dual anti-platelet therapy (DAPT). The latest Japanese and overseas guidelines or other relevant sources should be referred to for the post-DAPT administration.

2 Other agents relating to blood and body fluides
Prasugrel hydrochloride

Branded name Efient Tablets 2.5 mg, 3.75 mg, 5 mg, 20 mg; Efient OD Tablets 20 mg (Daiichi Sankyo Co., Ltd.)

[Under New instructions]

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

This drug should be co-administered with aspirin (81-100 mg/day, up to 324 mg for the initial loading dose) during dual anti-platelet therapy (DAPT). The latest Japanese and overseas guidelines or other relevant sources should be referred to for the post-DAPT administration.

3 Other antitumor agents
Venetoclax

Branded name Venclexta Tablets 10 mg, 50 mg, 100 mg (AbbVie GK)

[Under New instructions]

2. CONTRAINDICATIONS

Patients receiving a potent CYP3A inhibitor (ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole, or preparations containing cobicistat) during the dose escalation phase of this drug.

10. INTERACTIONS
10.1 Contraindications for Co-administration

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Potent CYP3A inhibitors during the dose escalation phase of this drug (ritonavir, clarithromycin, itraconazole,	The risk of tumor lysis syndrome may be increased.	Blood concentration of this drug may increase due to inhibition of CYP3A by these drugs.

voriconazole, posaconazole, or preparations containing cobicistat)		

10.2 Precautions for Co-administration

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Potent CYP3A inhibitors during the maintenance phase of this drug (such as clarithromycin, itraconazole, voriconazole, or posaconazole)	Adverse reactions to this drug may be increased. Doses of this drug should be reduced and patients should be closely monitored for any signs of adverse reactions.	Blood concentration of this drug may increase due to inhibition of CYP3A by these drugs, etc.

4 Antibiotic preparations acting mainly on mold

Posaconazole

Branded name

Noxafil Tablets 100 mg, Noxafil for Intravenous Infusion 300 mg (MSD K.K.)

[Under New instructions]

2. CONTRAINDICATIONS

Patients receiving ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, methylergometrine, ergometrine, simvastatin, atorvastatin, pimozide, quinidine, or venetoclax (during its dose escalation phase)

10. INTERACTIONS

10.1 Contraindications for Co-administration (newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Venetoclax (during its dose escalation phase)	Co-administration of this drug with venetoclax during its dose escalation phase may increase the risk of tumor lysis syndrome.	Plasma concentration of venetoclax is expected to rise due to inhibition of CYP3A by co-administration of posaconazole.

10.2 Precautions for Co-administration (newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Venetoclax (during its maintenance phase)	When co-administered with venetoclax during its maintenance phase, doses of venetoclax should be reduced and patients should be closely monitored for any signs of adverse reactions related to venetoclax.	Plasma concentration of venetoclax is expected to rise due to inhibition of CYP3A by co-administration with posaconazole.

5 Other biological preparations

Eculizumab (genetical recombination)

Branded name	Soliris for Intravenous Infusion 300 mg (Alexion Pharma Godo Kaisha)
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Serious infection Serious infection such as disseminated gonococcal infection, pneumococcal infection, and haemophilus influenzae infection may occur.

3

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 30 November 2020)

◎: Products for which EPPV was initiated after November 1, 2020

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Roxadustat*1 Evrenzo Tablets 20 mg, 50 mg, 100 mg	Astellas Pharma Inc.	November 27, 2020
◎	Dapagliflozin propylene glycolate hydrate*2 Forxiga 5 mg Tablets, Forxiga 10 mg Tablets	AstraZeneca K.K.	November 27, 2020
◎	Cabozantinib malate*3 Cabometyx tablets 20 mg, 60 mg	Takeda Pharmaceutical Company Limited.	November 27, 2020
◎	Binimetinib*4 Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	November 27, 2020
◎	Encorafenib*4 Braftovi Capsules 50 mg, 75 mg	Ono Pharmaceutical Co., Ltd.	November 27, 2020
◎	Brodalumab (genetical recombination) *5 Lumicef Subcutaneous Injection 210 mg Syringe	Kyowa Kirin Co., Ltd.	November 27, 2020
◎	Baloxavir marboxil*6 Xofluza Tablets 20 mg, Xofluza Granules 2%	Shionogi & Co., Ltd.	November 27, 2020
◎	Sofpironium bromide Ecclock gel 5%	Kaken Pharmaceutical Co., Ltd.	November 26, 2020
◎	Niraparib tosilate hydrate Zejula capsules 100 mg	Takeda Pharmaceutical Company Limited.	November 20, 2020
◎	Filgotinib maleate Jyseleca Tablets 100 mg, 200 mg	Gilead Sciences K.K.	November 18, 2020
◎	Paliperidone palmitate*7 Xeplion TRI Aqueous Suspension for IM Injection 175 mg, 263 mg, 350 mg, 525 mg	Janssen Pharmaceutical K.K.	November 18, 2020
	Oxycodone hydrochloride hydrate*8 OxyContin TR Tablets 5 mg, 10 mg, 20 mg, 40 mg	Shionogi Pharma Co., Ltd.	October 29, 2020
	Glucagon Baqsimi Nasal Powder 3 mg	Eli Lilly Japan K.K.	October 2, 2020
	Trastuzumab deruxtecan (genetical recombination) *9	Daiichi Sankyo Co., Ltd.	September 25, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Enhertu For Intravenous Drip Infusion 100 mg		
Ravulizumab (genetical recombination) *10 Ultomiris for Intravenous Infusion 300 mg	Alexion Pharma Godo Kaisha	September 25, 2020
Tildrakizumab (genetical recombination) Ilumya Subcutaneous Injection 100 mg Syringe	Sun Pharma Japan Limited	September 23, 2020
Siponimod fumaric acid Mayzent tablets 0.25 mg, 2 mg	Novartis Pharma K.K.	September 14, 2020
Ferric carboxymaltose Ferinject solution for injection/infusion 500 mg	Zeria Pharmaceutical Co., Ltd.	September 1, 2020
Isatuximab (genetical recombination) Sarclisa 100 mg I.V. Infusion, Sarclisa 500 mg I.V. Infusion	Sanofi K.K.	August 31, 2020
Indacaterol acetate/glycopyrronium bromide/ mometasone furoate Enerzair medium dose inhalation powder with hard capsules, Enerzair high dose inhalation powder with hard capsules	Novartis Pharma K.K.	August 26, 2020
Indacaterol acetate/mometasone furoate Atectura low dose inhalation powder with hard capsules, Atectura medium dose inhalation powder with hard capsules, Atectura high dose inhalation powder with hard capsules	Novartis Pharma K.K.	August 26, 2020
Sacubitril valsartan sodium hydrate Entresto Tablets 50 mg, 100 mg, 200 mg	Novartis Pharma K.K.	August 26, 2020
Capmatinib hydrochloride hydrate Tabrecta tablets 150 mg, 200 mg	Novartis Pharma K.K.	August 26, 2020
Satralizumab (genetical recombination) Enspryng Syringes for Subcutaneous Injection 120 mg	Chugai Pharmaceutical Co., Ltd.	August 26, 2020
Daprodustat Duvroq Tablets 1 mg, 2 mg, 4 mg, 6 mg	GlaxoSmithKline K.K.	August 26, 2020
Vadadustat Vafseo Tablets 150 mg, 300 mg	Mitsubishi Tanabe Pharma Corporation	August 26, 2020
Opicapone Ongentys Tablets 25 mg	Ono Pharmaceutical Co., Ltd.	August 26, 2020
Tirabrutinib hydrochloride*11 Velexbru Tablets 80 mg	Ono Pharmaceutical Co., Ltd.	August 21, 2020
Vonicog alfa (genetical recombination) Vonvendi Intravenous 1300	Shire Japan KK	August 17, 2020
Remimazolam besilate Anerem 50 mg for I.V. Injection	Mundipharma K.K.	August 7, 2020
Posaconazole Noxafil for Intravenous Infusion 300 mg	MSD K.K.	July 21, 2020
Lemborexant	Eisai Co., Ltd.	July 6,

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Dayvigo Tablets 2.5 mg, 5mg, 10 mg		2020
Fluticasone propionate/formoterol fumarate hydrate Flutiform 50 Aerosol 56 puffs, 120 puffs	Kyorin Pharmaceutical Co., Ltd.	June 29, 2020
Semaglutide (genetical recombination) Ozempic Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD	Novo Nordisk Pharma Ltd.	June 29, 2020
Tolvaptan*12 Samsca tablets 7.5 mg, 15 mg, 30 mg, Samsca OD tablets 7.5 mg, 15 mg, 30 mg, Samsca granules 1%	Otsuka Pharmaceutical Co., Ltd.	June 29, 2020
Landiolol hydrochloride*13 Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	June 29, 2020
Levothyroxine sodium hydrate Thyradin-S I.V. Injection 200 µg	Aska Pharmaceutical. Co., Ltd.	June 29, 2020
Delgocitinib Corectim Ointment 0.5%	Japan Tabacco Inc.	June 24, 2020
Melatonin Melatobel granules 0.2% for pediatric	Nobelpharma Co., Ltd.	June 23, 2020
Insulin lispro (genetical recombination) Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD Lyumjev Injection 100 U/mL	Eli Lilly Japan K.K.	June 17, 2020
Lurasidone hydrochloride Latuda tablets 20 mg, 40 mg, 60 mg, 80 mg	Sumitomo Dainippon Pharma Co., Ltd.	June 11, 2020
Insulin glargine (genetical recombination)/lixisenatide Soliqua Injection SoloStar	Sanofi K.K.	June 8, 2020
Tepotinib hydrochloride hydrate Tepmetko Tablets 250 mg	Merck Biopharma Co., Ltd	June 1, 2020

*1 Nephrogenic anaemia

*2 Chronic heart failure (only in patients who are receiving standard of care)

*3 Unresectable hepatocellular carcinoma that has progressed after chemotherapy

*4 Unresectable advanced or recurrent BRAF-mutant colorectal cancer that has progressed after chemotherapy

*5 Ankylosing spondylitis and non-radiographic axial spondyloarthritis that respond inadequately to existing therapies

*6 Treatment and prevention of influenza virus infection types A and B

*7 Schizophrenia (only in patients who have been adequately treated with 4-week intramuscular paliperidone palmitate)

*8 Relief of moderate to severe chronic pain difficult to manage with non-opioid analgesics or other opioid analgesics

*9 HER2 positive unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy

*10 Atypical haemolytic uraemic syndrome

*11 Primary macroglobulinaemia and lymphoplasmacytic type lymphoma

*12 Improvement of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

*13 Tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) associated with sepsis