Pharmaceuticals and Medical Devices Safety Information

No. 373 June 2020

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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
DLST	Drug-induced lymphocyte stimulation test
EPPV	Early Post-marketing Phase Vigilance
IMDRF	International Medical Device Regulators Forum
IoT	Internet of Things
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
TEN	Toxic epidermal necrolysis

1
Recent Trends in Cybersecurity Assurance of Medical Devices

1. Introduction

Safety and effectiveness of the medical devices that are currently marketed in Japan are ensured by the guaranteed quality of the products themselves and proper use on the part of users to be used for the purpose of diagnosis and treatment of disease.

In recent years, these medical devices have increasingly involved communications technologies such as the Internet of Things (IoT), and through these technologies they are connected to medical institutions' networks, communicate with external devices or engage in intermittent data exchange via recording media, etc. during their use. With advances in communications technology as the basis of IoT devices etc., opportunities for medical devices to be connected to medical institutions' networks or to other medical devices or electric machinery are expected to increase.

The ability for medical devices to exchange data with external devices during their use also means increased opportunities for them to be exposed to the risk of unauthorized access from outside via data communications. For example, there is a risk for a medical device to be attacked as well if a computer connected to the same medical institutions' network is subjected to a cyberattack through the network. Likewise, if the medical device is attacked, other medical devices and computers could be attacked through the network of the medical institution to which the medical device is connected, and further damage may result.

To ensure the cybersecurity of medical devices at medical institutions, it should be ensured by medical devices manufacturers that devices be designed and developed as products that are resistant to cyberattacks before they are provided to the clinical setting. In addition, intended use environments, information sharing, rectification of their vulnerabilities, and incident responses be properly implemented post-market. Proper management in clinical settings is also critical.

This article introduces the domestic and international efforts in dealing with cybersecurity of medical devices including the status of related risk analysis in Japan with some examples in other countries.

2. Status of risk analysis on medical device cyberattacks in other countries

When a medical device is subjected to a cyberattack, the consequences may be suspension of diagnosis or incorrect diagnosis if the device is a testing or diagnostic instrument, interruption of treatment if it is a therapeutic device, or excessive or inadequate irradiation if it is a dose calculation program for radiotherapy. In Japan, at the time of this writing, no health damage to patients has been reported to have been caused by cyberattacks against medical devices. However, several cases of patient injuries involving the cybersecurity of medical devices have been reported overseas.

One incident was concerning the vulnerability of drug infusion pumps. In July 2015, the U.S. FDA became aware that Symbiq Infusion System, drug infusion pumps made by Hospira of the USA, could be accessed from outside through an unused network port, making it possible for a third party without the usual administrative authority to access the product remotely through the medical institution's network and modify the dosage of medication injected by the pump. Although Hospira discontinued marketing of the product, the U.S. FDA announced that it strongly recommended that medical institutions using the product stop doing so and switch to another product. This is a case where the regulatory authority issued a warning over a breach of the cybersecurity of a medical device as an adverse event.

Another such incident involved the vulnerability of a remote monitoring device for implantable cardiac pacemakers. In January 2017, as a result of performing a review of a remote monitoring system for cardiac pacemakers, the U.S. FDA confirmed that the risk assessment of cybersecurity vulnerabilities had not been performed according to the procedure for medical device quality regulations based on Part 820 of the CFR (Code of Federal Regulations), and thus, the design verification for cybersecurity of the product had not been adequate. This vulnerability could allow a third-party attacker to illegally access a pacemaker and interfere with its functions by executing commands or changing the settings of the pacemaker, and the MAH of pacemakers addressed the problem by updating the firmware of the medical device. This was a case where a proactive action was taken based on the results of a risk assessment

that examined the risk of cyberattacks against the vulnerabilities of a medical device, and no actual health damage from an attack occurred.

3. Status of responses to cybersecurity in each country

Since the start of the 2000s, various countries, including Japan, have compiled guidance on how to handle cybersecurity for medical devices.

In July 2005, the U.S. FDA compiled Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software, followed by an additional Postmarket Management of Cybersecurity in Medical Devices in December 2016. At the same time, in Europe, regulations on the cybersecurity of medical devices were issued in May 2017. In addition, guidance according to their national conditions was issued in France, Germany, Australia, and China.

In Japan, marketing authorization holders (MAHs) for medical devices were instructed to properly evaluate the risk of cyberattacks against medical devices and handle cybersecurity in a manner commensurate with the characteristics of the medical device. Moreover, Guidance on Ensuring the Cybersecurity of Medical Devices was compiled to outline the regulator's thinking on concrete risk management for the cybersecurity of medical devices and the related countermeasures.

This guidance holds that, in order to predict the risk of cyberattacks, it is necessary to identify the environment under which the medical device will be used, examine the medical facility or home that will be the site of use, and identify the method of connection to a network when the medical device will be used, and devise measures separately for cases where it is connected to a network in a wired or wireless manner from those where there is data exchange with external equipment through an external recording medium such as a USB memory device. This guidance states that medical device MAHs should handle cybersecurity by providing information to the users of medical devices, and it presents examples of package inserts and technical data as methods of providing information on cybersecurity. The guidance also states the need for appropriate cooperation with medical institutions as an aspect of medical device cybersecurity that requires attention.

As described above, various kinds of guidance on cybersecurity have been compiled in a number of countries, including Japan. However, in recent years, medical devices have been distributed over multiple countries, opening the possibility for cyberattacks that transcend national borders being launched against medical devices connected to the Internet. For this reason, Principles and Practices for Medical Device Cybersecurity (hereinafter referred to as the “IMDRF guidance”) was compiled by the International Medical Device Regulators Forum (IMDRF) in April of 2020 for the purpose of promoting international alignment of the cybersecurity of medical devices and providing general principles and best practices.

4. IMDRF guidance

The IMDRF guidance was compiled on the basis of the aforementioned guidance issued by regulatory authorities in various countries. It mentions the importance of not delaying, proactive information sharing among the various stakeholders in medical device cybersecurity, including governments, medical device MAHs, and persons involved at medical institutions.

Among the General Principles mentioned in the IMDRF guidance, Operating Devices in the Intended Use Environment, Information Sharing among stakeholders, Coordinated Vulnerability Disclosure (CVD), Vulnerability Remediation, and Incident Responses are included as items to consider as part of the Post-market Management Strategy considerations that must be addressed in handling post-market medical device cybersecurity.

Particularly important to stakeholders at medical institutions of the general principles mentioned in the IMDRF guidance is CVD, which refers to information disclosure as a means of ensuring cybersecurity. In the IMDRF guidance, CVD is positioned as one method of preparing for cybersecurity incidents and enhancing transparency in responses to incidents. The IMDRF guidance describes, because it is difficult to secure what is not known, the importance of medical device MAHs obtaining and evaluating information on cybersecurity vulnerabilities, and disclosing it with transparency to stakeholders including healthcare professionals, after developing mitigation and complementary measures.

At the same time, the IMDRF guidance describes how it is necessary for stakeholders at medical institutions as healthcare providers to engage in role-sharing and cooperation with medical device MAHs in order to continuously monitor, evaluate, and mitigate latent cybersecurity risks and threats throughout the entire lifecycle from purchase of the medical device to disposal, as well as share information and handle incidents.

This article summarizes the content of the IMDRF guidance that involves post-market information

provision, which is thought to be especially important for stakeholders at medical institutions. The original document and the Japanese translation prepared by the National Institute of Health should be referred to for further details.

5. Future cybersecurity responses in Japan

In order to respond to medical device cybersecurity properly, it will be important for medical device MAHs to take sufficient measures to mitigate the risk of cyberattacks after performing risk analysis according to the characteristics of individual medical devices in cooperation with medical stakeholders, including healthcare professionals.

From the standpoint of improving safety related to medical device cybersecurity, introduction of the IMDRF guidance by MAHs and related business operators in Japan is being considered over a time frame of approximately 3 years. To this end, your understanding and continued cooperation are requested in the establishment of systems with medical device MAHs to further ensure medical device cybersecurity.

References

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7) PSEHB/MDED0724No.1 and PSEHB/PSD 0724 No.1 Joint Notification, Guidance on Ensuring Cyber Security of Medical Devices by the Director of Medical Device Evaluation Division and Director of the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated July 24, 2018 (only in Japanese)
8) Principles and Practices for Medical Device Cybersecurity http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-200318-pp-mdc-n60.pdf (confirmed May 7, 2020)
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Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated May 19, 2020, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Apalutamide

Branded name (name of company)	Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Castration-resistant prostate cancer without remote metastasis Prostate cancer with remote metastasis

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Important Precautions (newly added)	Severe skin disorders such as toxic epidermal necrolysis (TEN), erythema multiforme may occur. If a rash occurs, a dermatologist should be consulted at an early stage, and temporary discontinuation or discontinuation of this drug should be considered. Patients should be instructed to immediately seek medical attention if any skin abnormalities are observed
Clinically Significant Adverse Reactions	**Severe skin disorders**: Severe skin disorder such as toxic epidermal necrolysis (TEN), erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 11-month period (May 2019 to March 2020) Cases involving toxic epidermal necrolysis: 2 (1 patient mortality) Number of patients using the drug as 150 000 Japanese market launch: May 2019

Case summary 1

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		No.	
1	Male 70s	Prostate cancer (metastases to lymph nodes, hyperlipidaemia, diabetes mellitus)	240 mg Duration unknown ↓ Discontinued ↓	**Toxic epidermal necrolysis (TEN)**	
				History: dehydration, extrapyramidal disorder, disturbed consciousness, hyponatraemia, deep vein thrombosis, glaucoma, hyperuricaemia	
				Allergic history (drugs, food, etc.): none	
				Approx. 1 year and half before administration	The patient was diagnosed with prostate cancer. Metastases to left external iliac lymph nodes were observed. Prostate specific antigen (PSA) at diagnosis was 48.16 ng/mL. Gleason score was 5+5.
				Approx. 5 months before administration	CAB therapy with degarelix acetate was initiated.
				Approx. 3 months before administration	Administration of abiraterone acetate (until the day before the initiation of apalutamide), prednisolone, lansoprazole (until 2 days before the initiation of apalutamide) was initiated in the urology department.
				Approx. 1 month before administration	Left external iliac venous thrombosis due to metastases to the lymph nodes of the prostate cancer. Degarelix acetate was discontinued.
				Date unknown	Imaging procedures observed rectal infiltration.
				Day of start of administration	Apalutamide (240 mg/day) was initiated (administered at night)
				Date unknown	Prostate cancer advanced and induced hydronephrosis.
				Day 20 of administration	The patient visited the hospital and sought advice for his persistent rash emerging at night and disappearing the next morning since DAY 16 of apalutamide (upper limb and inner sides of thighs). Betamethasone valerate/gentamicin ointment was prescribed. The rash was mild and apalutamide was continued at 240 mg/day. Co-administration of prednisolone 5 mg/day continued.
				Date unknown	The outcome of the rash (upper limbs, inner sides of thighs) was "recovery".
				Day 27 of administration (day of onset)	Systemic erythema, pyrexia (39.5 °C), pyrexia-induced tremor occurred.
				Date unknown (day of discontinuation)	Administration of apalutamide and co-administered drugs was discontinued.

				2 days after discontinuation	The patient visited the emergency department, was diagnosed with TEN. Elevation of CK as well as Cr values were noted. [Clinical findings prior to the transfer to another hospital] Epidermal abrasion extending over 95% of body surface, systemic erythema except for the face, lift foot erosion, oral erosion were observed. Bulbar conjunctiva hyperaemia was noted. Pyrexia in 39 °C range occurred. Nikolsky's sign was positive. Infectious disease test (blood culture) was negative. With decreased hepatic and renal function, the patient was in a state of multi-organ failure and was immediately transferred to another hospital. Skin biopsy was performed after the transfer. Steroid pulse therapy (methylprednisolone 1 g/day) was performed for 3 days. [Clinical findings after the transfer] Epidermal erosion extended over 100% of body surface. Mucosal erosion was noted in the mouth, anus, and genitals. Oral, anal, genital mucosal erosion was also noted. Bulbar conjunctiva hyperaemia was noted. Dry eye was marked. Pyrexia at 40 °C developed. The patient complained of pharyngodynia.
				Date unknown	Based on an elevation in anti-SS-A antibody and marked dry eye, suspected Sjogren's syndrome was diagnosed.
				5 days after onset	High dose immunoglobulin therapy was performed for 5 days.
				6 days after onset	Infectious disease test (artery line) was positive for staphylococcus capitis. Virus test was negative. Anti-SS-A antibody was 1810.
				9 days after onset	Results of the skin biopsy for samples collected 2 days after the onset of TEN were obtained. Final diagnosis of TEN was made by the pathological department. Betamethasone 8 mg/day was initiated.
				10 days after onset	Infectious disease test (tracheal sputum) was negative.
				14 days after onset	Plasma exchange therapy was performed twice. Infectious disease test (urine) was negative.
				16 days after onset	Pyrexia at 38 °C or higher had persisted since the onset of TEN. ICU management was required. Plasma exchange therapy was performed.

				18 days after onset	Betamethasone was reduced to 6 mg/day.
				Approx. 20 days after onset	High dose immunoglobulin therapy was performed once.
				25 days after onset	Semi-pulse therapy (prednisolone 40 mg/day) was performed for 5 days.
				Date unknown	Ocular topical steroid was administered.
				27 days after onset	DLST (drug-induced lymphocyte stimulation test) was performed and the result was weakly positive for apalutamide.
				28 days after onset	Plasma exchange therapy was performed twice.
				Date unknown	The patient recovered from oral erosion and genital erosion. Sepsis, fungal infections were noted. CMV antigen was positive.
				30 days after onset	Prednisolone 40 mg/day was administered (until 45 days after onset). CT findings: prostate cancer metastasized to the lung and adrenal gland.
				33 days after onset	High dose immunoglobulin therapy was performed for 5 days.
				39 days after onset	Bacteraemia of corynebacterium was noted and administration of daptomycin was initiated.
				41 days after onset	The patient's skin was reddish. Corneal and conjunctival epidermal disorders developed.
				44 days after onset	An ophthalmologist confirmed new development of corneal erosion.
				45 days after onset	Epidermal erosion extending over 60% of body surface (reddishness enhanced), conjunctival hyperaemia, corneal and conjunctival epithelium disorders were observed. Pyrexia at 38 °C or higher (with vertical fluctuations) developed.
				47 days after onset	Infectious disease test (artery line) was positive for staphylococcus epidermidis (MRSE). Considering the circulatory instability, echocardiography was taken. There were no abnormal findings.
				54 days after onset	The patient was under sedation by sedatives administered, which led to decreased blood pressure and eventually circulatory failure. The patient died from circulatory failure, multi-organ failure, and sepsis induced by TEN. Outcome of TEN was “patient mortality”.
	Suspected concomitant drugs: Vonoprazan fumarate Concomitant drugs: Prednisolone, degarelix acetate, magnesium hydroxide, lubiprostone, apixaban, irbesartan, linagliptin, omega-3-acid ethyl				

Case summary 2

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		No.	
2	Male 80s	Prostate cancer (metastases to lymph nodes, peritoneal dissemination, myelodysplastic syndrome, metastases to pelvis, lung, bone, lung cancer, cardiac failure)	240 mg for 42 days ↓ 180 mg for 11 days ↓ Discontinued	**Toxic epidermal necrolysis (TEN)** History: chronic obstructive pulmonary disease, rectal cancer, thrombocytopenia Allergic history: none	
				Approx. 8 year and a half before administration	The patient was diagnosed with prostate cancer cT4N1M1b, stage D2.
				Approx. 7 months before administration	Lansoprazole 15 mg/day was initiated.
				Day of start of administration	Apalutamide (240 mg/day) started.
				Day 43 of administration (day of onset)	Furosemide 20 mg/day was initiated for lower limb swelling. Small red rash emerged from the lower limb to body trunk, extending to the abdomen. The patient was on bepotastine besilate prescribed by another hospital. Administration of apalutamide continued at a dose reduced to 180 mg/day.
				Date unknown	Pneumonia developed.
				6 days after onset	Respiratory failure worsened in association with pneumonia.
				8 days after onset	Rash worsened and the patient visited the emergency department. Consciousness was clear, body temperature was 37.2 °C. Numerous red rash covered the head, face, trunk, and limb. Oral olopatadine hydrochloride 5 mg was prescribed.
				10 days after onset (day of discontinuation)	Apalutamide was administered in the morning (final administration). The patient visited the urology department. Sporadic stomatitis was noted over the palate. Dark red, limb & trunk rash with signs for being fused, slightly swollen. Red face rash/oedema, bulbar conjunctiva hyperaemia were noted with pyrexia at 40.1 °C. Stevens-Johnson syndrome was suspected and the patient was immediately admitted to the hospital. All co-administered drugs were discontinued. A dermatologist was consulted. Oral prednisolone 30 mg/day (The patient was choked on the oral medication. Ampicillin/sulbactam was co-administered.) d-chlorpheniramine maleate infusion, famotidine infusion started. Sodium lactate Ringer's solution was administered (for 4 days) DLST was performed and the results were positive for apalutamide, negative for lansoprazole, negative for furosemide.
				1 day after discontinuation	The patient had fever at 38.1 °C, face oedema, and red rash on trunk. With oral erosion, choking on water, the patient had difficulty taking medicine orally. Administration was switched from oral to infusion of an equivalent dose of prednisolone.

				2 days after discontinuation	Buttok and back abrasion emerged. Ocular mucosa redness was noted. Pyrexia persisted. In consultation with the dermatologist, steroid pulse therapy (methylprednisolone 1 g/day) was performed for 3 days, high dose immunoglobulin (globulin preparation 25 g/day) was performed for 5 days. An oral surgery dentist was consulted. Formation of erosion was noted extensively on the oral mucosa. Oral care was continued to protect the erosion from infection: dimethyl isopropyl azulene ointment to the lips, and moisturizer was applied to the oral cavity.
				3 days after discontinuation	Erosion and erythema extended further. Abrasion was noted focused on the face, back, and buttok. Pyrexia at 38.6 °C developed. CV catheter was inserted. Prescription was changed to prednisolone 80 mg/day. An ophthalmologist was consulted. Enanthema was noted. Gatifloxacin hydrate eyedrops, betamethasone eyedrops were prescribed. Infectious disease test (sputum, catheter, skin) was positive for streptococcus and corynebacterium.
				4 days after discontinuation	The patient was transferred to the dermatology department of another hospital. Pneumonia was noted at admission (imaging procedures ruled out interstitial pneumonia). The patient had sputum. [Clinical findings] Skin lesion such as erythema, blisters, and erosion extended over 50-60% (erosion accounting for 15%), abrasion, oral or genital mucosal conditions over 10-30% of body surface. Skin ulcer reached the dermis in the buttok and back. Conjunctivitis (improved with steroid eyedrops), conjunctival hyperaemia, eye wax (ocular discharge), swollen red hot eyelid were noted. Pharyngalgia, breathing difficulty, and face oedema were noted. Niikolsky's sign was positive. Skin pathological findings (for samples collected from the epidermis to subcutaneous adipose tissue) were considered consistent with conditions for TEN. Infectious disease test (sputum culture, pharingeal culture) was positive for candida albicans (small quantity).
				6 days after discontinuation	The outcome of pneumonia was “recovery”.
				7 days after discontinuation	Betamethasone 8 mg/day was intravenously administered.
				8 days after discontinuation	Steroid pulse therapy (methylprednisolone 1 g/day) was performed.
				10 days after discontinuation	Plasma exchange therapy was performed.
				11 days after discontinuation	Betamethasone 12 mg/day started, plasma exchange therapy was performed. Signs for improvement were observed.

				13 days after discontinuation	Plasma exchange therapy was performed.
				14 days after discontinuation	Aspiration pneumonia occurred. The patient had sputum (small amount). Chest X-ray revealed decreased permeability to the left lung. Urine catheter infection was noted.
				15 days after discontinuation	Betamethasone was decreased to 10 mg/day. Plasma exchange therapy was performed. Pneumonia induced pyrexia at 38.3 °C.
				17 days after discontinuation	Betamethasone was reduced to 8 mg/day.
				20 days after discontinuation	Betamethasone was reduced to 6 mg/day.
				21 days after discontinuation	Inflammation was abated and the affected area was reduced from 50-60% to 10-20%. Ulcer persisted and infection was observed. Unable to ingest orally, the patient was fed by a tube.
				23 days after discontinuation	Pale and circular erythema remained on the thighs and shoulders. Betamethasone was reduced to 4 mg/day (until 40 days after discontinuation)
				25 days after discontinuation	Erythema on the thighs exacerbated. Condition of aspiration pneumonia worsened. ADL declined. Infectious disease test was positive for staphylococcus.
				26 days after discontinuation	Plasma exchange therapy was performed for 2 days for the exacerbation of erythema.
				28 days after discontinuation	High dose immunoglobulin therapy (25 g/day) was performed for 5 days for the exacerbation of erythema. Conditions of aspiration pneumonia worsened.
				Date unknown	The patient recovered to the extent that he could converse in response to the treatment then got worse. Haematuria and melaena occurred and transfusion and albumin preparations were administered. Cardiac failure (complication) worsened and carperitide was administered.
				35 days after discontinuation	Reactivation of cytomegalovirus occurred.
				40 days after discontinuation	Ulcer remained on the right buttok. Epithelialization was observed on other affected areas. The outcome of TEN was “improving”. Betamethasone was reduced to 3.5 mg/day.
				41 days after discontinuation	The patient died from respiratory failure induced by aspiration pneumonia. No autopsy was performed.
	Suspected concomitant drugs: lansoprazole, furosemide, galantamine hydrobromide, Concomitant drugs: shakuyakuannzoto, amlodipine besilate, torasemide, ambroxol hydrochloride, prednisolone, bepotastine besilate				

3
Revision of Precautions (No.313)

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 May 19, 2020.

1 Hormones-miscellaneous

[1] Insulin human (genetical recombination) (vial preparations)
[2] Insulin aspart (genetical recombination) (vial preparations without description for continuous subcutaneous insulin infusion (CSII) therapy in the Dosage and Administration section)
[3] Insulin glargine (genetical recombination) (vial preparations)

Branded name	[1] Novolin R 100 IU/mL (Novo Nordisk Pharma Ltd.), Humulin R Injection 100 units/mL, Humulin 3/7 Injection 100 units/mL, Humulin N Injection 100 units/mL (Eli Lilly Japan K.K.) [2] NovoRapid 100 U/mL (Novo Nordisk Pharma Ltd.) [3] Lantus Inj. 100 U/mL (Sanofi K.K.)
[Under Old instructions]	
Important Precautions (newly added)	By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows: ・This drug should be injected at least 2 to 3 cm apart from the previous injection site. ・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided. Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control. Incorrect doses of insulin may be injected by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL). Syringes dedicated to the insulin vials that are calibrated in insulin units or other measurement units should be used to formulate or administer an injection liquid.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows: ・This drug should be injected at least 2 to 3 cm apart from the previous injection site.

・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided.
Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control.
Incorrect doses of insulin may be injected by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL). Syringes dedicated to the insulin vials that are calibrated in insulin units or other measurement units should be used to formulate or administer an injection liquid.

2 Hormones-miscellaneous

[1] Insulin human (genetical recombination) (cartridge preparations, prefilled preparations)
[2] Insulin aspart (genetical recombination) (cartridge preparations, prefilled preparations)
[3] Insulin glargine (genetical recombination) (cartridge preparations, prefilled preparations)
[4] Insulin glargine (genetical recombination) [insulin glargine biosimilar 1]
[5] Insulin glargine (genetical recombination) [insulin glargine biosimilar 2]
[6] Insulin glulisine (genetical recombination) (cartridge preparations, prefilled preparations)
[7] Insulin degludec (genetical recombination)
[8] Insulin degludec (genetical recombination)/insulin aspart (genetical recombination)
[9] Insulin detemir (genetical recombination)

Branded name

[1] Novolin R FlexPen, Novolin 30R FlexPen/InnoLet 30R, Novolin N FlexPen (Novo Nordisk Pharma Ltd.), Humulin R Injection Cart, Humulin R Injection MirioPen, Humulin 3/7 Injection Cart, Humulin 3/7 Injection MirioPen, Humulin N Injection Cart, Humulin N Injection MirioPen (Eli Lilly Japan K.K.)
[2] NovoRapid 30 Mix FlexPen, NovoRapid 30 Mix Penfill, NovoRapid 50 Mix FlexPen, NovoRapid 70 Mix FlexPen, NovoRapid FlexTouch, NovoRapid FlexPen, NovoRapid InnoLet, NovoRapid Penfill, Fiasp Injection FlexTouch, Fiasp Injection Penfill (Novo Nordisk Pharma Ltd.)
[3] Lantus XR inj. SoloStar, Lantus Inj. Cart, Lantus Inj. SoloStar (Sanofi K.K.)
[4] Insulin Glargine BS Inj. Cart [Lilly], Insulin Glargine BS Inj. MirioPen [Lilly] (Eli Lilly Japan K.K.)
[5] Insulin Glargine BS Injection Kit [FFP] (FUJIFILM Toyama Chemical Co., Ltd.)
[6] Apidra Inj. Cart, Apidra Inj. SoloStar (Sanofi K.K.)

	[7] Tresiba FlexTouch, Tresiba Penfill (Novo Nordisk Pharma Ltd.) [8] Ryzodeg FlexTouch (Novo Nordisk Pharma Ltd.) [9] Levemir FlexPen, Levemir InnoLet, Levemir Penfill (Novo Nordisk Pharma Ltd.)
[Under Old instructions]	
Important Precautions (newly added)	By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows: ・This drug should be injected at least 2 to 3 cm apart from the previous injection site. ・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided. Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows: ・This drug should be injected at least 2 to 3 cm apart from the previous injection site. ・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided. Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control.

3 Hormones-miscellaneous

Insulin aspart (genetical recombination) (vial preparations with description for continuous subcutaneous insulin infusion (CSII) therapy in the DOSAGE and ADMINISTRATION section)

Branded name
[Under New instructions]
Fiasp Injection 100 U/mL (Novo Nordisk Pharma Ltd.)

8. IMPORTANT PRECAUTIONS (newly added)

By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows:

・This drug should be injected at least 2 to 3 cm apart from the previous injection site.

・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided.

Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control.

Incorrect doses of insulin may be injected by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL). Syringes dedicated to the insulin vials that are calibrated in insulin units or other measurement units should be used to formulate or administer an injection liquid, except when the drug is used for continuous subcutaneous insulin infusion (CSII) therapy. In that case, the device that is specified in the user manual of the portable insulin infusion pump should be used.

4 Hormones-miscellaneous

Insulin glulisine (genetical recombination) (vial preparations)

Branded name
[Under Old instructions]
Apidra Inj. 100 U/mL (Sanofi K.K.)

Important Precautions (newly added)

By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows:

・This drug should be injected at least 2 to 3 cm apart from the previous injection site.

・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided.

Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with

	the poor glycemic control. Incorrect doses of insulin may be injected by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL). Syringes dedicated to the insulin vials that are calibrated in insulin units or other measurement units should be used to formulate or administer an injection liquid, except when the drug is used for continuous subcutaneous insulin infusion (CSII) therapy. In that case, the device that is specified in the user manual of the portable insulin infusion pump should be used.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows: ・This drug should be injected at least 2 to 3 cm apart from the previous injection site. ・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided. Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control. Incorrect doses of insulin may be injected by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL). Syringes dedicated to the insulin vials that are calibrated in insulin units or other measurement units should be used to formulate or administer an injection liquid, except when the drug is used for continuous subcutaneous insulin infusion (CSII) therapy. In that case, the device that is specified in the user manual of the portable insulin infusion pump should be used.

5 Hormones-miscellaneous

[1] Insulin lispro (genetical recombination) (vial preparations)
[2] Insulin lispro (genetical recombination) [insulin lispro biosimilar 1] (vial preparations)

Branded name	[1] Humalog Injection 100 units/mL, Lyumjev Injection 100 U/mL (Eli Lilly Japan K.K.) [2] Insulin Lispro BS Injection HU 100 units/ml [Sanofi] (Sanofi K.K.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows: ・This drug should be injected at least 2 to 3 cm apart from the previous injection site. ・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided. Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is

recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control.
Incorrect doses of insulin may be injected by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL). Syringes dedicated to the insulin vials that are calibrated in insulin units or other measurement units should be used to formulate or administer an injection liquid, except when the drug is used for continuous subcutaneous insulin infusion (CSII) therapy. In that case, the device that is specified in the user manual of the continuous subcutaneous infusion pump should be used.

6 Hormones-miscellaneous, antidiabetic agents

[1] Insulin lispro (genetical recombination) (cartridge preparations, prefilled preparations)
[2] Insulin lispro (genetical recombination) [insulin lispro biosimilar 1] (cartridge preparations, prefilled preparations)
[3] Insulin glargine (genetical recombination)/lixisenatide
[4] Insulin degludec (genetical recombination)/liraglutide (genetical recombination)

Branded name

[1] Humalog Injection Cart, Humalog Injection MirioPen, Humalog Injection MirioPen HD, Humalog Mix Injection 25 Cart, Humalog Mix Injection 25 MirioPen, Humalog Mix Injection 50 Cart, Humalog Mix Injection 50 MirioPen, Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD (Eli Lilly Japan K.K.)
[2] Insulin Lispro BS Injection HU Cart [Sanofi], Insulin Lispro BS Injection HU SoloStar [Sanofi] (Sanofi K.K.)
[3] Soliqua Injection SoloStar (Sanofi K.K.)
[4] Xultophy combination Injection FlexTouch (Novo Nordisk Pharma Ltd.)

[Under New instructions]

8. IMPORTANT PRECAUTIONS (newly added)

By repeated injection into the same spot, cutaneous amyloidosis or lipodystrophy may occur in the injection site. Injection sites should be examined periodically and patients should be instructed as follows:
・This drug should be injected at least 2 to 3 cm apart from the previous injection site.
・If any masses and indurations that formed in the injection site are noted, injection into the affected area should be avoided.
Injection of this drug into areas where cutaneous amyloidosis or lipodystrophy developed may impede the absorption of this drug and result in poor glycemic control. If poor glycemic control is recognized, the injection site should be examined for mass or induration and appropriate measures should be taken such as changing the injection site as well as dose adjustment. Cases of hypoglycemia have been reported that occurred after the injection site was changed, and insulin preparation was injected into an unaffected area in doses excessively increased in association with the poor glycemic control.

7 Antineoplastics-miscellaneous

Apalutamide

Branded name [Under Old instructions]	Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.)
Important Precautions (newly added)	Severe skin disorders such as toxic epidermal necrolysis (TEN), erythema multiforme may occur. If a rash occurs, a dermatologist should be consulted at an early stage, and temporary discontinuation or discontinuation of this drug should be considered. Patients should be instructed to immediately seek medical attention if any skin abnormalities are observed
Adverse Reactions (Clinically Significant Adverse Reactions)	**Severe skin disorders**: Severe skin disorder such as toxic epidermal necrolysis (TEN), erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug.

8 Antineoplastics-miscellaneous

Fulvestrant

Branded name [Under Old instructions]	Faslodex Intramuscular Injection 250 mg (AstraZeneca K.K.)
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Injection site necrosis, ulcer**: Injection site necrosis, ulcer may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect 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 April, 2020)
◎: Products for which EPPV was initiated after April 1, 2020

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Upadacitinib hydrate Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	April 24, 2020
◎	Posaconazole Noxafil Tablets 100 mg	MSD K.K.	April 24, 2020
◎	Lurasidone hydrochloride Latuda tablets 20 mg, 40 mg, 60 mg, 80 mg	Sumitomo Dainippon Pharma Co., Ltd.	April 22, 2020
◎	Dinoprostone Propess vaginal inserts 10 mg	Ferring Pharmaceuticals Co., Ltd.	April 2, 2020
	Mepolizumab (genetical recombination) Nucala for s.c. injection 100 mg	Glaxo Smith Kline K.K.	March 25, 2020
	Dupilumab (genetical recombination) *1 Dupixent 300 mg Syringe for S.C. Injection	Sanofi K.K.	March 25, 2020
	pH4-Treated normal human immunoglobulin*2 Privigen 10% I.V. Drip Infusion 5g/50mL, 10g/100mL, 20g/200mL	CSL Behring K.K.	February 21, 2020
	Entrectinib*3 Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	February 21, 2020
	Modafinil*4 Modiodal Tablets 100 mg	Alfresa Pharma Corporation	February 21, 2020
	Doravirine Pifeltro Tablets 100 mg	MSD K.K.	February 17, 2020
	Insulin aspart (genetical recombination) Fiasp Injection FlexTouch, Fiasp Injection Penfill, Fiasp Injection 100 U/mL	Novo Nordisk Pharma Ltd.	February 7, 2020
	Dolutegravir sodium/lamivudine Dovato combination tablets	Viiv Healthcare K.K.	January 31, 2020
	Freeze-dried recombinant herpes zoster vaccine (prepared from Chinese hamster ovary cells) Shingrix for intramuscular injection	Glaxo Smith Kline K.K.	January 29, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Turoctocog alfa pegol (genetical recombination) Esperoct for i.v. injection 500, 1000, 1500, 2000, 3000	Novo Nordisk Pharma Ltd.	January 29, 2020
Perampanel hydrate*5 Fycompa tablets 2 mg, 4 mg	Eisai Co., Ltd.	January 23, 2020
Lascufloxacin hydrochloride Lasvic Tablets 75 mg	Kyorin Pharmaceutical Co.,Ltd.	January 8, 2020
Nintedanib ethanesulfonate*6 Ofev capsules 100 mg, 150 mg	Boehringer Ingelheim Japan, Inc.	December 20, 2019
Avelumab (genetical recombination)*7 Bavencio intravenous infusion 200 mg	Merck Biopharma Co., Ltd	December 20, 2019
Ceftolozane sulfate/tazobactam sodium*8 Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	December 20, 2019
Certolizumab pegol (genetical recombination) *9 Cimzia 200 mg Syringe for S.C. Injection, Cimzia 200 mg AutoClicks for S.C. Injection	UCB Japan Co. Ltd.	December 20, 2019
Evocalcet*10 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*11 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*12 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) *13 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
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	Takeda Pharmaceutical	November 27,

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
	Trintellix Tablets 10 mg, 20 mg	Company Limited.	2019
	Necitumumab (genetical recombination) Portrazza Injection 800 mg	Nippon Kayaku Co., Ltd.	November 22, 2019
	Ranibizumab (genetical recombination) *14 Lucentis solution for intravitreal injection 10mg/mL	Novartis Pharma K.K.	November 22, 2019
	Ixekizumab (genetical recombination) *15 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

*1 Chronic rhinosinusitis with nasal polyps (only in patients not adequately controlled with existing therapies)

*2 Agammaglobulinemia or hypogammaglobulinemia

*3 ROS1 fusion-positive, unresectable, advanced or metastatic non-small cell lung cancer

*4 Excessive daytime sleepiness associated with idiopathic hypersomnia

*5 Partial-onset seizures (including secondarily generalized seizures)

*6 Systemic sclerosis-associated interstitial lung disease

*7 Unresectable or metastatic renal cell carcinoma

*8 <Applicable microorganisms> *Serratia* Bizio and *Haemophilus influenzae* susceptible to ceftolozane sulfate/tazobactam sodium <applicable conditions> pneumonia and sepsis

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

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

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

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

*13 Seasonal allergic rhinitis (only in severe to the most severe cases inadequately controlled with existing treatment)

*14 Retinopathy of prematurity

*15 Ankylosing spondylitis with inadequate response to existing therapies