Pharmaceuticals and Medical Devices Safety Information

No. 366 September 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.

Register here

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Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

Office of Informatics and Management for Safety,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan E-mail: safety.info@pmda.go.jp

Pharmaceuticals and Medical Devices Safety Information

No. 364 July 2019

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

ADRs	Adverse drug reactions
CK (CPK)	Creatine kinase (Creatine phosphokinase)
EPPV	Early Post-marketing Phase Vigilance
HPB/GAD	General Affairs Division, Health Policy Bureau
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
JIS	Japanese Industrial Standards
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PCR	Polymerase chain reaction
PEG	Percutaneous endoscopic gastrostomy
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB/MDED	Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
PSEHB/PED	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
PSEHB/PSD	Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau
TNF	Tumor Necrosis Factor

1
Introduction of the International Standards (ISO [IEC] 80369 series) Related to Connectors for Prevention of Interconnection
-Switching of small-bore connectors for enteral application

1. Introduction

To prevent the risk of injecting internal medication solutions for administration via an enteral nutrition line into a blood vessel by mistake, measures have been taken in Japan to ensure that the connectors of enteral nutrition lines and infusion lines have different shapes so that they are physically not interconnectable[*1].

In recent years, international standards related to connectors for the prevention of interconnection across product areas as shown in Table 1 (ISO [IEC] 80369 series) are being established in the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). To further promote measures to prevent medical accidents and to ensure a stable supply of products in line with international harmonization, the introduction of these international standards has also proceeded in Japan.

*1 Establishment etc. of Standards for Medical Devices to Prevent Medical Accidents (Standards for syringe-type manual infusion instruments, etc.) (PMSB Notification No. 888, by the Director of Pharmaceutical and Medical Safety Bureau dated August 31, 2000)

Table 1 Six product areas for which the international standards (ISO [IEC] 80369 series) are being established

Standard No.	Product area
ISO 80369-2	Breathing system and driving gases applications
ISO 80369-3[*2]	Enteral applications
ISO 80369-4	Urethral and urinary applications
IEC 80369-5[*2]	Limb cuff inflation applications
ISO 80369-6[*2]	Neuraxial applications (spinal anesthesia, epidural anesthesia and nerve block)[*3]
ISO 80369-7[*2]	Intravascular or hypodermic applications[*4]

*2 Standards have already been established.

*3 Small-bore connectors for neuraxial applications (ISO 80369-6) include sterilized anesthetic puncture needles, and are shown in the Appendix. Injection needles for subcutaneous administration, etc. are not subject to the scope of neuraxial applications regardless of the procedural site or procedure.

*4 Connectors for intravascular or hypodermic applications will be compatible with existing standard connectors under the new standards as well.

2. Switching of small-bore connectors for enteral application

In Japan, the introduction of the international standard for small-bore connectors is planned for enteral applications subsequently to neuraxial anesthesia among the product areas for which new standards have been established, and the Japanese Industrial Standards (JIS), which serve as the basis of the approval and certification standards of the new standard medical devices (see Table 2), have been revised as of May 1, 2018.

From December 2019 onwards, the new standard products complying with the new standard ISO 80369-3 will be distributed to the market as soon as required arrangements to ship such products are completed by their marketing authorization holders (MAHs). In view of prompt switching to the new standard products in medical practice within a certain period, the shipment of old standard products by MAHs will be terminated by the end of the month 42 months after the date of the JIS revision (i.e. the end of November 2021).

Some medical devices with small-bore connectors for enteral application are placed in the patient's body for a relatively long term, which may require a certain period for all medical institutions, sites, etc. to switch all standard products to the new standard products. In this regard, medical facilities will have to be prepared to take proper care of patients moving between facilities. For example, adapters to connect new and old standard products (conversion adapters) should be available.

Table 2 Examples of the new standard products*5 6

Transesophageal enteral feeding tube, set for nutrition infusion, enteral nutrition pump extension tube, enteral nutrition infusion stopcock, gastrostomy feeding tube (PEG tube/button), and injector (nutrition)

*5 The new standard products include products used in connection (combination) with the new standard products. Kits/sets containing such products are also subject to the new standards.

*6 Connecters for balloon inflation lumen, connectors of PEG buttons, and the connectors of a tube to connect with them are not included.

3. Requests to healthcare professionals

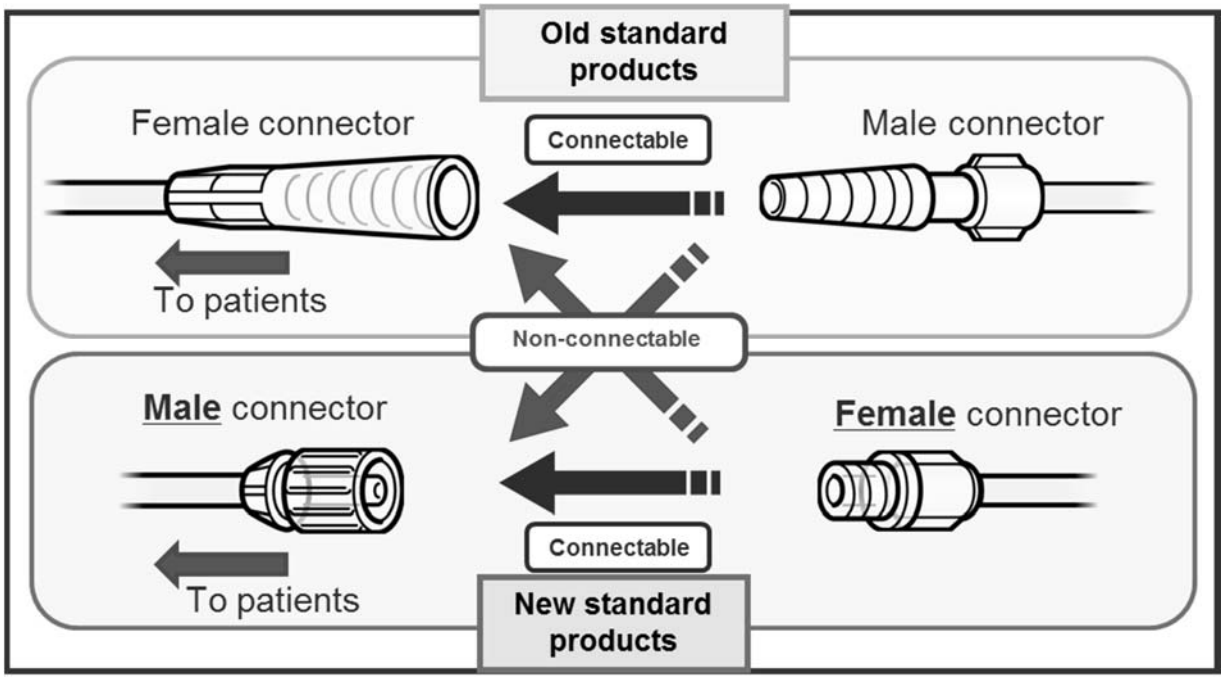
The new standard products (products complying with ISO 80369-3) are non-connectable with old standard products (Fig. 1)

Therefore, to switch to the new standard products, medical institutions should appoint a person responsible for standard switching (e.g. medical device safety management supervisor) and disseminate information on the switching of products subject to the new standard extensively to doctors, nurses, and other concerned persons. In addition, necessary information on the switch should be provided to patients and users who take enteral nutrition, and their helpers as well.

Medical institutions should also make such preparations: preparing a list of products subject to switching; appropriate inventory management in their own facilities; ensuring availability of conversion adapters (Fig. 2) based on sufficient information received from the MAH, etc. who supply the new standard products; coordinating the timing of the switch among affiliated sites and concerned parties; subsequently confirming patient-specific timing for switching and provision of conversion connectors in order to ensure complete switching of the products.

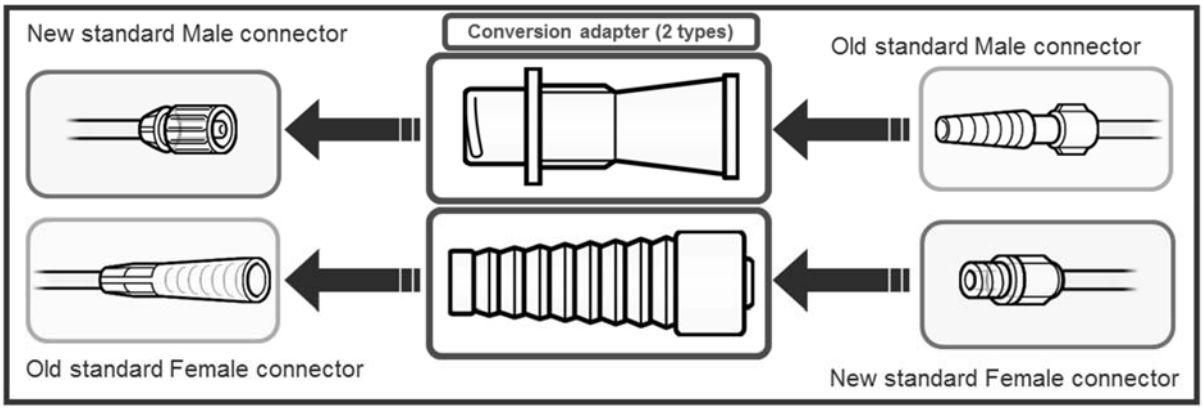
Points to note for switching, etc., are introduced in the PMDA Medical Safety Information. PMDA's website provides a briefing material for patients/users and their helpers (sample) as well as a checklist (sample) which is useful in preparing for switching from the old to new standard products prior to the introduction of the new products into sites. The relevant information is also provided on the websites of related organizations for reference by medical institutions.

Figure 1　Non-compatibility between new standard products and old standard products.



Source: PMDA Medical Safety Information No. 58

Figure 2　Details on small-bore connectors for enteral application and conversion adapters



Source: PMDA Medical Safety Information No. 58

○ Related notifications or precautions

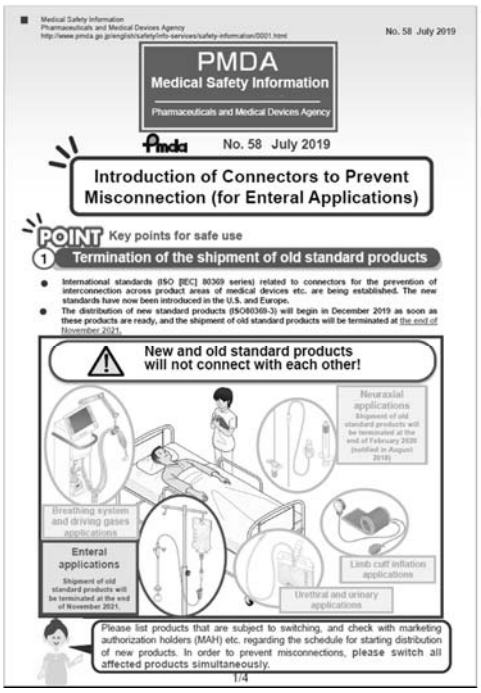
Introduction of the International Standards (ISO [IEC] 80369 series) Related to Connectors for Prevention of Interconnection
(HPB/GAD Notification No. 1004-1, PSEHB/PEB Notification No. 1004-1, PSEHB/MDED Notification No. 1004-1 and PSEHB/PSD Notification No. 1004-1 dated October 4, 2017, by the Director of General Affairs Division, Health Policy Bureau; Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau; Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau; Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau; Ministry of Health, Labour and Welfare)
http://www.pmda.go.jp/files/000220396.pdf

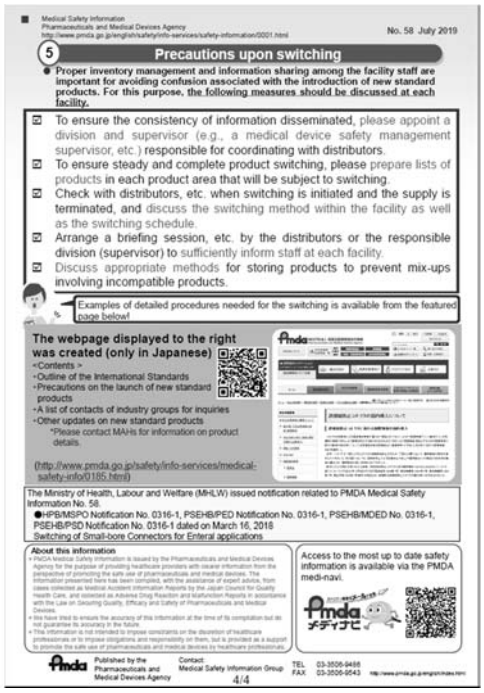
Switching of Small-bore Connectors for Neuraxial Anesthesia
(HPB/GAD Notification No. 1227-1, PSEHB/PED Notification No. 1227-1, PSEHB/MDED Notification No. 1227-1 and PSEHB/PSD Notification No. 1227-1 dated December 27, 2017, by the Director of General Affairs Division, Health Policy Bureau; Director of Pharmaceutical Evaluation Division,

Pharmaceutical Safety and Environmental Health Bureau; Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau; Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau; Ministry of Health, Labour and Welfare)
http://www.pmda.go.jp/files/000221984.pdf

Switching of Small-bore Connectors for Enteral Nutrition
(HPB/GAD/MSPO Notification No. 0316-1, PSEHB/PED Notification No. 0316-1, PSEHB/MDED Notification No. 0316-1 and PSEHB/PSD Notification No. 0316-1 dated March 16, 2018, by the Director of Medical Safety Promotion Office, General Affairs Division, Health Policy Bureau; Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau; Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau; Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau; Ministry of Health, Labour and Welfare)
http://www.pmda.go.jp/files/000223250.pdf (only in Japanese)

PMDA Medical Safety Information No. 58 issued in July 2019
Introduction of Connectors to Prevent Misconnection (for Enteral Applications)
http://www.pmda.go.jp/files/000230636.pdf

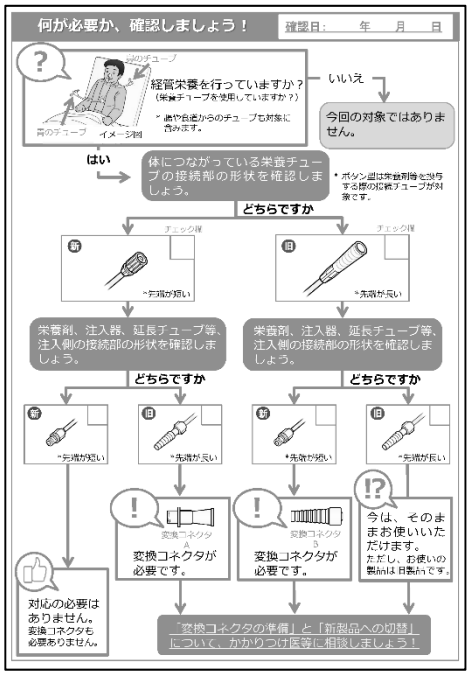




A checklist for medical institutions (sample)
http://www.pmda.go.jp/files/000230598.pdf (only in Japanese)

A checklist for long-term care facilities and homecare/long-term care (sample)
http://www.pmda.go.jp/files/000230600.pdf (only in Japanese)

A briefing material for patients/users and their helpers (sample).
http://www.pmda.go.jp/files/000230602.pdf (only in Japanese)



PMDA: Introduction in Japan of Connectors that Prevent Misconnections
http://www.pmda.go.jp/safety/info-services/medical-safety-info/0185.html (only in Japanese)

○ Information provided by related organizations
Website of the Medical Technology Association of Japan
: Information on connectors for prevention of interconnection
http://www.mtjapan.or.jp/jp/mtj/smallbore/index.php (only in Japanese)

Website of the Nihon Ryudoushoku Association
Provision of information on connectors (enteral application) for prevention of interconnection
http://www.ryudoshoku.org/info1 (only in Japanese)

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated August 22, 2019, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Freeze-dried BCG vaccine

Branded name (name of company)	Freeze-dried BCG Vaccine (for percutaneous use; for single dose) (Japan BCG Laboratory)
Therapeutic category	Vaccines
Indications	Prophylaxis of tuberculosis

PRECAUTIONS (revised language is underlined)

[Under Old instructions]

Adverse Reactions (Clinically Significant Adverse Reactions)

BCG infection:
Meningitis, osteitis, osteomyelitis, or periostitis may occur. When individuals with immunodeficiency syndrome are vaccinated, BCG may be disseminated in the bloodstream to the whole body and produce miliary tuberculosis-like lesions, resulting in systemically disseminated BCG infection. When BCG infection is suspected, appropriate measures should be taken immediately, such as administration of antituberculous drugs.

Reference information

Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 38-month period (April 2016 to May 2019)
Cases of tuberculous meningitis: 1 (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 940 000

Japanese market launch: February 1992

Case summary

No.	Patient		Daily dose Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male Younger than 10 years old	Immuno-prophylaxis, Tuberculosis Prophylaxis/ Immunization (none)	Percutaneous vaccination by stamp-type injection, unknown dose Once	Meningitis, ventriculitis Date of vaccination Approximately 10 months after vaccination Approximately 1 year after vaccination Approximately 1 year and 3 months after vaccination Approximately 1 year and 8 months after vaccination	The patient was vaccinated with this vaccine 7 months after birth. There was no redness or infiltration at the injection site, and there were no complications such as axillary lymphadenopathy in the clinical course. The patient was not able to walk straight or meet the gaze of other people and was increasingly eager to be held. He gradually had difficulty walking, standing and sitting. Head CT scan revealed marked hydrocephalus, and the patient was admitted to the hospital. At his first visit to the hospital, he was fully blind. Head MRI revealed an enhanced round lesion in the anterior horn of the right ventricle and disseminated lesions in the third and fourth ventricles. Cerebrospinal fluid examination showed increased protein level and decreased glucose level. Brain tissue biopsy also revealed non-caseating epithelioid granulomas, which led to an initial diagnosis of neurosarcoidosis. The patient was started on methyl prednisolone pulse therapy, methotrexate, and infliximab, which did not work well. A mycobacteria PCR result in the spinal fluid was positive, indicating tuberculous meningitis. Therefore, multi-drug therapy with rifampicin, isoniazid, pyrazinamide, and amikacin sulfate was initiated. *Mycobacterium bovis* was identified in brain tissue and spinal fluid biopsied in the same period, and PCR analysis revealed it as a BCG Tokyo strain. SCID or CGD was not suggested. The genes related to MSMD did not have any mutation. Spinal fluid findings gradually improved and the patient underwent VP shunt implantation surgery 5 months after the treatment was started.
	Concomitant medications: none.				

3

Revision of Precautions (No.306)

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 August 22, 2019.

1 Antiparkinsonian agents
Apomorphine hydrochloride hydrate

Branded name	Apokyn subcutaneous injection 30 mg (Kyowa Hakko Kirin Co., Inc.)
[Under Old instructions]	
Important Precautions (newly added)	When dose reduction or discontinuation of this drug is necessary, the dose should be gradually reduced. Rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).
Adverse Reactions Other Adverse Reactions (newly added)	Drug withdrawal syndrome* (apathy, anxiety, depression, fatigue, sweating, pain, etc.) *When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

2 Antiparkinsonian agents
Cabergoline

Branded name	Cabaser Tablets 0.25 mg, 1.0 mg (Pfizer Japan Inc.), and the others
[Under Old instructions]	
Precautions concerning Dosage and Administration	(deleted)
Careful Administration	Patients with hyperprolactinemic pituitary adenoma who have marked visual impairment, etc. caused by pituitary tumors that have grown beyond the sella turcica
Important Precautions (newly added)	Patients with hyperprolactinemic pituitary adenoma that has grown beyond the sella turcica may have cerebrospinal fluid rhinorrhea because of adenoma shrunk by treatment with this drug, leading to meningitis. When any abnormalities are observed, appropriate measures should be taken such as dose reduction or discontinuation of the drug. It has been reported that in patients with hyperprolactinemic pituitary adenoma who had visual field disorders, this drug shrunk the adenoma and improved the visual field disorders, which recurred later through invagination of the optic chiasm into the sella caused by the sella turcica's cavitation. When any abnormalities are observed, appropriate measures should be taken such as dose reduction or discontinuation of the drug. When dose reduction or discontinuation of this drug is necessary for treatment of Parkinson's disease, the dose should be gradually

	reduced. Rapid dose reduction or discontinuation may cause syndrome malin. In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).
Adverse Reactions	Drug withdrawal syndrome* (apathy, anxiety, depression, fatigue,
Other Adverse Reactions	sweating, pain, etc.)
<Parkinson's disease>	*When any abnormalities are observed, appropriate measures
(newly added)	should be taken such as resuming administration or returning the dose to the level prior to reduction.

3 **Antiparkinsonian agents**

Talipexole hydrochloride

Branded name	Domin Tablets 0.4 (Boehringer Ingelheim Japan, Inc.)
[Under Old instructions]	
Important Precautions	When dose reduction or discontinuation of this drug is necessary, the dose should be gradually reduced. Rapid dose reduction or discontinuation may cause syndrome malin with symptoms such as pyrexia, disturbed consciousness, akinetic mutism, severe muscle stiffness, involuntary movement, dysphagia, tachycardia, blood pressure fluctuation, sweating, increased serum CK (CPK). In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).
Adverse Reactions	Drug withdrawal syndrome* (apathy, anxiety, depression, fatigue,
Other Adverse Reactions	sweating, pain, etc.)
(newly added)	*When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

4 **Antiparkinsonian agents, Central nervous system agents-miscellaneous**

Pramipexole hydrochloride hydrate (conventional tablets, OD tablets)

Branded name	BI・Sifrol Tablets 0.125 mg, 0.5 mg (Boehringer Ingelheim Japan, Inc.), and the others
[Under Old instructions]	
Important Precautions	When dose reduction or discontinuation of this drug is necessary in patients with Parkinson's disease, the dose should be gradually reduced. Rapid dose reduction or discontinuation may cause syndrome malin. In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.). It should be noted that gradual dose reduction is not necessary in patients with idiopathic restless legs syndrome because their doses are lower than for patients with Parkinson's disease.
Adverse Reactions	Drug withdrawal syndrome* (apathy, anxiety, depression, fatigue,
Other Adverse Reactions	sweating, pain, etc.)
(newly added)	*When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

5 **Antiparkinsonian agents**

Pramipexole hydrochloride hydrate (sustained-release tablets)

Branded name	Mirapex-LA Tablets 0.375 mg, 1.5 mg (Boehringer Ingelheim Japan, Inc.), and the others
[Under Old instructions]	
Important Precautions	When dose reduction or discontinuation of this drug is necessary, the dose should be gradually reduced. Rapid dose reduction or discontinuation may cause syndrome malin. In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).
Adverse Reactions Other Adverse Reactions (newly added)	Drug withdrawal syndrome* (apathy, anxiety, depression, fatigue, sweating, pain, etc.) *When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

6 **Antiparkinsonian agents**

[1] Bromocriptine mesilate
[2] Pergolide mesilate

Branded name	[1] Parlodel Tablets 2.5 mg (Sun Pharma Japan Limited), and the others [2] Permax Tablets 50 μg, 250 μg (Kyowa Hakko Kirin Co., Inc.), and the others
[Under Old instructions]	
Important Precautions (newly added)	When dose reduction or discontinuation of this drug is necessary, the dose should be gradually reduced. Rapid dose reduction or discontinuation may cause syndrome malin. In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).
Adverse Reactions Other Adverse Reactions (newly added)	Drug withdrawal syndrome* (apathy, anxiety, depression, fatigue, sweating, pain, etc.) *When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

7 **Antiparkinsonian agents, Central nervous system agents-miscellaneous**

Rotigotine

Branded name	Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg, 18 mg (Otsuka Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Important Precautions	When dose reduction or discontinuation of this drug is necessary, the dose should be gradually reduced. Rapid dose reduction or discontinuation may cause syndrome malin. In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).
Adverse Reactions Other Adverse Reactions (newly added)	Drug withdrawal syndrome* (anxiety, depression, fatigue, sweating, pain, etc.) *When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

8 **Antiparkinsonian agents**

Ropinirole hydrochloride

Branded name	ReQuip Tablets 0.25 mg, 1 mg, 2 mg, CR Tablets 2 mg, 8 mg (Glaxo Smith Kline K.K.), and the others
[Under Old instructions]	
Important Precautions	When dose reduction or discontinuation of this drug is necessary, the dose should be gradually reduced. Rapid dose reduction or discontinuation may cause syndrome malin with symptoms such as pyrexia, disturbed consciousness, severe muscle stiffness, involuntary movement or shock symptom. In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).
Adverse Reactions	Drug withdrawal syndrome* (apathy, anxiety, depression, fatigue, sweating, pain, etc.)
Other Adverse Reactions (newly added)	*When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

9 Miscellaneous metabolism agents

Tofacitinib citrate

Branded name	Xeljanz Tablets 5 mg (Pfizer Japan Inc.)
[Under New instructions]	
5. PRECAUTIONS CONCERNING INDICATIONS (newly added)	<Common to all indications> Venous thromboembolism may occur. Alternative treatments should be considered when this drug is administered to patients with risk factors of cardiovascular events.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACGROUNDS	Patients with risk factors of cardiovascular events Alternative treatments should be considered. In particular, it should be carefully determined whether this drug should be administered at a dose of 10 mg twice daily.
9.1 Patients with Complication or History of Diseases, etc. (newly added)	When this drug is administered, the patients should be carefully monitored for signs and symptoms of venous thromboembolism. Venous thromboembolism may occur. In an ongoing overseas clinical study in patients aged 50 years or older with rheumatoid arthritis and at least 1 risk factor of cardiovascular events (smoking status, hypertension, diabetes mellitus, a history of coronary artery disease, etc.), the incidence of pulmonary embolism and deep vein thrombosis tended to be higher in a dose-dependent manner in patients who received 5 mg twice daily and those who received 10 mg twice daily of this drug compared to patients who received TNF inhibitors. It was reported that the incidence of death including sudden cardiac death tended to be similar in patients who received TNF inhibitors and those who received this drug at a dose of 5 mg twice daily while it was higher in patients who received this drug at a dose of 10 mg twice daily.
11. ADVERSE REACTIONS	Venous thromboembolism
11.1 Clinically Significant Adverse Reactions (newly added)	Pulmonary embolism and deep vein thrombosis may occur

10 Vaccines
Freeze-dried BCG vaccine (for percutaneous use)

Branded name	Freeze-dried BCG vaccine (for percutaneous use; for single dose) (Japan BCG Laboratory Ltd.)
[Under Old instructions]	
Adverse Reactions	BCG infection:
Other Adverse Reactions (newly added)	Meningitis, osteitis, osteomyelitis, or periostitis may occur. When individuals with immunodeficiency syndrome are vaccinated, BCG may be disseminated in the bloodstream to the whole body and produce miliary tuberculosis-like lesions, resulting in systemically disseminated BCG infection. When BCG infection is suspected, appropriate measures should be taken immediately, such as administration of anti-tuberculous drugs.

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 31 July, 2019)

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

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Freeze-dried inactivated tissue culture rabies vaccine Rabipur for intramuscular injection	Glaxo Smith Kline K.K.	July 26, 2019
◎	Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate Symtuza Combination Tablets	Janssen Pharmaceutical K.K.	July 26, 2019
◎	Peficitinib hydrobromide Smyraf Tablets 50 mg, 100 mg	Astellas Pharma Inc.	July 10, 2019
	Ceftolozane sulfate/tazobactam sodium Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	June 25, 2019
	Guanfacine hydrochloride*1 Intuitive Tablets 1 mg, 3 mg	Shionogi & Co., Ltd.	June 18, 2019
	Romiplostim (genetical recombination) *2 Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Inc	June 18, 2019
	Tocilizumab (genetical recombination) *3 Actemra Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	June 12, 2019
	Sodium selenite Aselend Injection 100 μg	Fujimoto Pharmaceutical Corporation	June 6, 2019
	Apalutamide Erleada Tablets 60 mg	Janssen Pharmaceutical K.K.	May 30, 2019
	Thiotepa Rethio Intravenous Infusion 100 mg	Sumitomo Dainippon Pharma Co., Ltd.	May 28, 2019
	Risankizumab (genetical recombination) Skyrizi Subcutaneous Injection 75 mg Syringe 0.83 mL	AbbVie GK	May 24, 2019
	Fluticasone furoate/vilanterol trifenatate/umeclidinium bromide Trelegy 100 Ellipta 14 doses, 30 doses	Glaxo Smith Kline K.K.	May 22, 2019
	Esaxerenone Minnebro Tablets 1.25 mg, 2.5 mg, 5 mg	Daiichi Sankyo Co., Ltd.	May 13, 2019

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Mirogabalin besilate Tarlige Tablets 2.5 mg, 5 mg, 10 mg, 15 mg	Daiichi Sankyo Co., Ltd	April 15, 2019
Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate Biktarvy Combination Tablets	Gilead Sciences Inc.	April 8, 2019
pH4- treated acidic normal human immunoglobulin (subcutaneous injection) *4 Hizentra 20% S.C. Injection 1g/5mL, 2g/10mL, 4g/20mL	CSL Behring K.K.	March 26, 2019
Tafamidis meglumine*5 Vyndaqel capsules 20 mg	Pfizer Japan Inc.	March 26, 2019
Landiolol hydrochloride*6 Onoact for Intravenous Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	March 26, 2019
Dupilumab (genetical recombination) *7 Dupixent Subcutaneous Injection 300 mg Syringe	Sanofi K.K.	March 26, 2019
Dapagliflozin propylene glycolate hydrate*8 Forxiga Tablets 5 mg, 10 mg	AstraZeneca K.K.	March 26, 2019
Nalmefene hydrochloride hydrate Selincro tablets 10 mg	Otsuka Pharmaceutical Co., Ltd	Match 5, 2019
Romosozumab (genetical recombination) Evenity subcutaneous injection 105 mg syringe	Amgen Astellas BioPharma K.K.	March 4, 2019
Dacomitinib Hydrate Vizimpro Tablets 15 mg, 45 mg	Pfizer Japan Inc.	March 1, 2019
Relugolix Relumina Tablets 40 mg	Takeda Pharmaceutical Company Limited.	March 1, 2019
Lorazepam Lora-pita Intravenous Injection 2mg	Pfizer Japan Inc.	March 1, 2019
Binimetinib Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
Encorafenib Braftovi Capsules 50 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
Sofosbuvir/velpatasvir Epclusa Combination Tablets	Gilead Sciences Inc.	February 26, 2019
Metirosine Demser Capsules 250 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
Taurine *9 Taurine powder 98% “Taisho”	Taisho Pharmaceutical Co., Ltd.	February 21, 2019
Damoctocog alfa pegol (genetical recombination) Jivi for i.v. injection 250, 500, 1000, 2000, 3000 Refixia I.V. Injection 500, 1000, 2000	Bayer Yakuhin Ltd	February 12, 2019

*1 Attention deficit/hyperactivity disorder in adult patients

*2 Aplastic anemia inadequately controlled with existing therapies

*3 Cytokine release syndrome induced by tumor-specific T cell infusion treatment

*4 Inhibiting progression of motor disability due to chronic inflammatory demyelinating polyneuropathy (in the cases where patients show an improvement in muscle weakness)

*5 Transthyretin cardiac amyloidosis (wild type and mutant type)

*6 The following life-threatening arrhythmias when they are refractory and time-critical

Ventricular fibrillation, ventricular tachycardia accompanied by haemodynamic instability

*7 Bronchial asthma (only for sever or refractory cases whose symptoms are not adequately controlled with existing treatments)
*8 Type 1 diabetes mellitus
*9 Inhibition of stroke-like episodes in patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS).

＜List of corrections in the PMDSI No.365＞

English version PDF p.4 Table 2. Major differences in the package inserts in Japan at the time of the Subcommittee on Drug Safety

（The corrections are underlined）

		Low-dose preparation	High-dose preparation
Original	Major product names	Glycoran Tablets 250 mg and the others	Metgluco Tablets 250 mg and the others
	Marketing authorization	Approved in January 1961	Approved in January 2010
	Maximum daily dose	750 mg	2,250 mg
	Use in patients with renal impairment	Contraindicated to patients with moderate or more severe renal impairment	Contraindicated to patients with mild to severe renal impairment
	Use in patients with hepatic impairment	Contraindicated to patients with mild to severe hepatic impairment	Contraindicated to patients with severe hepatic impairment
	Use in geriatric patients	Contraindication	Careful administration

		Low-dose preparation	High-dose preparation
Revised	Major product names	Glycoran Tablets 250 mg and the others	Metgluco Tablets 250 mg and the others
	Marketing authorization	Approved in January 1961	Approved in January 2010
	Maximum daily dose	750 mg	2,250 mg
	Use in patients with renal impairment	Contraindicated to patients with mild to severe renal impairment	Contraindicated to patients with moderate or more renal impairment
	Use in patients with hepatic impairment	Contraindicated to patients with mild to severe hepatic impairment	Contraindicated to patients with severe renal hepatic impairment
	Use in geriatric patients	Contraindication	Careful administration