Pharmaceuticals and Medical Devices Safety Information

No. 352 April 2018

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 352 April 2018

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 Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers 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 medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CRP	C-reactive protein
CT	Computed tomography
DPP4	Dipeptidyl peptidase-4
EPPV	Early Post-marketing Phase Vigilance
GAD	General Affairs Division
HPB	Health Policy Bureau
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
JIS	Japanese Industrial Standards
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MDED	Medical Device Evaluation Division
MHLW	Ministry of Health, Labour and Welfare
MSPO	Medical Safety Promotion Office
PED	Pharmaceutical Evaluation Division
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PMSB	Pharmaceutical and Medical Safety Bureau
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PT	Prothrombin time
RAI	Rejection activity index
SpO_2	Oxygen saturation
γ-GTP	Gamma-glutamyl transpeptidase

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

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, the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC) have proactively established international standards (ISO [IEC] 80369 series) related to connectors to prevent interconnection between different product areas as shown in Table 1. To further promote measures to prevent medical accidents and to ensure a stable supply of internationally harmonized products, 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) have been 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 are compatible with existing standard connectors, even under the new standards.

2. Switching of Small-bore Connectors for Neuraxial Anesthesia

In Japan, the first-in-Japan introduction of the international standard for small-bore connectors is planned for 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 February 1, 2018.

It is expected that the new standard products complying with the new standard ISO 80369-6 will be distributed on the market as soon as required arrangements to ship such products are completed by their marketing authorization holders. In view of prompt switching to the new standard products in medical practice, the shipment of existing standard products by marketing authorization

holders will be terminated by the end of the month 2 years after the date of revision of the JIS (i.e. the end of February 2020).

Precautions for the prevention of misconnections specify that connectors that can connect existing and new standard products (hereinafter referred to as “conversion connectors”) should not be used in principle. However, a minimum necessary number of conversion connectors may be supplied, only when requested by a medical institution to avoid the risk of obstructing treatment, etc. in medical practice.

Table 2 Examples of the new standard products*5

Spinal needles, epidural needles, epidural anesthesia catheters, epidural/spinal anesthetic needles, nerve block needles (mainly for epidural and spinal/subarachnoid administration), epidural anesthetic filters, loss of resistance syringes, syringes (for neuraxial applications), Elastomeric infusion system (for neuraxial applications), extension tubes (for neuraxial applications), three-way stopcocks (for neuraxial applications), liquid sampling needle (for neuraxial applications)

*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.

3. Requests to Healthcare Professionals

The new standard products (products complying with ISO 80369-6) are non-interconnectable with existing standard products (Fig. 1 and Fig. 2).

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 widely to doctors, nurses, and other concerned persons.

Medical institutions should also make such preparations as preparing a list of products subject to switching and appropriate inventory management in their own facilities based on sufficient information received from the marketing authorization holder, etc. supplying the new standard products.

Points to note for switching, etc., are introduced in the PMDA Medical Safety Information, and the relevant information is also provided on the websites of related organizations. Medical institutions should refer to such information to proceed with the switching at their own facilities.

Figure 1 Non-compatibility between the new standard products and existing standard products

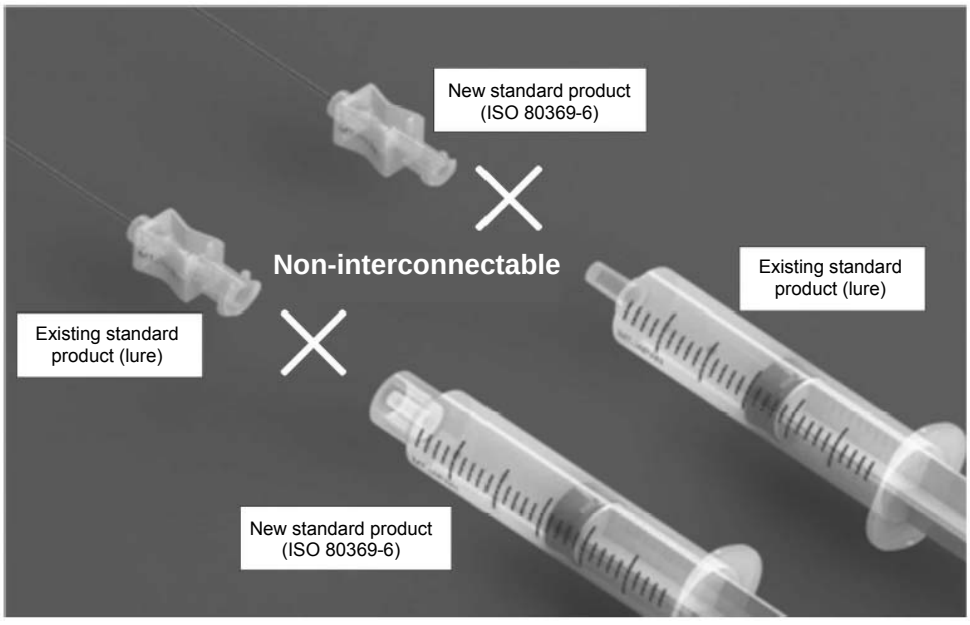
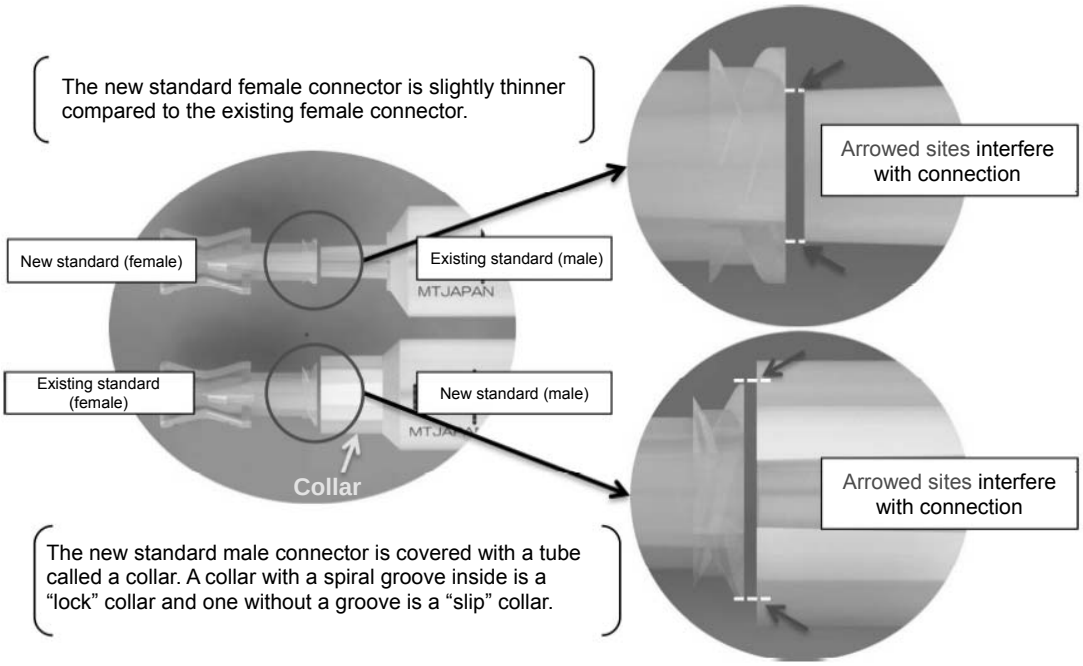


Figure 2 Details of small-bore connectors for neuraxial anesthesia



○ Related notifications or precautions

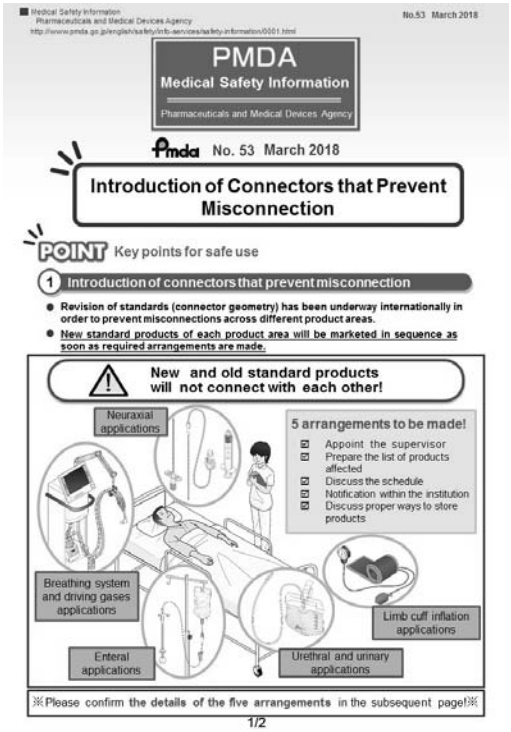
Introduction of the International Standards (ISO [IEC] 80369 series) Related to Connectors for Prevention of Interconnection
(HPB/GAD Notification No. 1004-1, PSEHB/PED Notification No. 1004-1, PSEHB/MDED Notification No. 1004-1 and PSEHB/PSD Notification No. 1004-1 dated October 4, 2017, by the Director 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/000223671.pdf

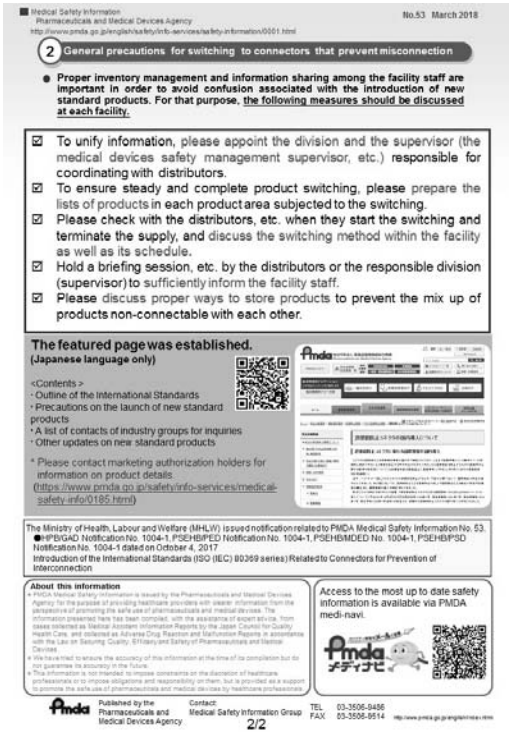
Switching of Small-bore Connectors for Neuraxial Anesthesia
(HPB/GAD Notification No. 1227-1, PSEHB/PED Notification No. 1227-1, PSEHB/MDED Notification No. 1227-1 and PSEHB/PSD Notification No. 1227-1 dated December 27, 2017, by the Director of General Affairs Division, Health Policy Bureau; Director 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/000223674.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 (currently Japanese language only)

PMDA Medical Safety Information No. 53, March 2018

Introduction of Connectors that Prevent Misconnections
http://www.pmda.go.jp/files/000223579.pdf





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

○ 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 (Japanese language only)

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated March 20, 2018, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Tolvaptan

Brand name (name of company)	Samsca tablets 7.5 mg, 15 mg, 30 mg, Samsca granules 1% (Otsuka Pharmaceutical Co., Ltd.)
Therapeutic category	Diuretics, hormones-miscellaneous
Indications	Samsca tablets 7.5 mg, Samsca granules 1% • Treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective. • Treatment of fluid retention in hepatic cirrhosis when treatment with other diuretics including loop diuretics is not sufficiently effective. • Slowing the progression of autosomal dominant polycystic kidney disease in patients with an increased kidney volume and a rapid rate of kidney volume increase. Samsca tablets 15 mg • Treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective. • Slowing the progression of autosomal dominant polycystic kidney disease in patients with an increased kidney volume and a rapid rate of kidney volume increase. Samsca tablets 30 mg • Slowing the progression of autosomal dominant polycystic kidney disease in patients with an increased kidney volume and a rapid rate of kidney volume increase.

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Acute hepatic failure, hepatic impairment:** Hepatic impairment associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, ALP, and bilirubin, etc. may occur and may lead to onset of acute hepatic failure. Patients should be observed carefully. If any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. Hepatic function should be closely monitored (through frequent blood tests, etc.) until the impairments are resolved.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 9 months (April 2014 to January 2018). Cases related to acute hepatic failure: 4 cases (including 3 patient mortalities) The number of patients using the drug estimated by the marketing authorization holder (MAH) in the past 1 year: Approximately 216 000 Launched in Japan: Samsca tablets 7.5 mg: June 2013 Samsca tablets 15 mg: December 2010

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Autosomal dominant polycystic kidney disease (ADPKD) (none)	15 mg 7 days ↓ 22.5 mg 25 days ↓ 30 mg 35 days ↓ 45 mg 35 days ↓ 60 mg 63 days ↓ 45 mg 14 days	**Acute hepatic failure** Day 1 of administration: Administration of tolvaptan 15 mg/day was started. Day 8 of administration: Dosage increased to 22.5 mg/day. Day 33 of administration: Dosage increased to 30 mg/day. Day 68 of administration: Dosage increased to 45 mg/day. Day 103 of administration: Dosage increased to 60 mg/day. Day 165 of administration: Elevated liver function test values (AST: 45, ALT 69) were observed without any symptoms. Day 166 of administration: Dosage reduced to 45 mg/day. Day 179 of administration (day of discontinuation) A blood test indicated further deterioration (AST: 82, ALT: 142). CT: No hepatic atrophy was observed. (Only hepatic cysts were observed and there were no findings of parenchymal disorder.) Administration of tolvaptan was discontinued. Day 19 of discontinuation: Liver function tests indicated further deterioration (AST: 860, ALT: 1293). As the patient had nausea and malaise, administration of glycyrrhizinate/glycine/cysteine injection was started. Day 23 of discontinuation: As a blood test showed an improving tendency, administration of glycyrrhizinate/glycine/cysteine injection was discontinued. Day 25 of discontinuation: Since nausea persisted, fluid replacement and a domperidone tablet were prescribed. Hypoproteinemia, thrombocytopenia, hyperbilirubinemia, and decreased prothrombin time (PT) developed. PT-international normalized ratio (PT-INR) was 1.64, which met the diagnostic criteria of acute hepatic failure (>1.5). CT: Findings of hepatic parenchymal disorder were observed. Day 29 of discontinuation: Nausea and malaise persisted. The patient was fully conscious. Jaundice became apparent. PT further decreased. Administration of glycyrrhizinate/glycine/cysteine injection was resumed and continued until the patient moved to another hospital. Day 32 of discontinuation (day of onset) Although the above-described symptoms persisted, there was no encephalopathy. Bilirubin increased and PT decreased further. Acute hepatic failure (without coma) developed. The patient was hospitalized. Day 33 of discontinuation: CT: Development of hepatic atrophy was observed. Day 37 of discontinuation: The patient was moved to another hospital. The patient was placed on bed rest and was treated with a diet for liver disease (1800 kcal, protein 40 g) and a light meal at bedtime (which the patient could hardly take). The patient took levocarnitine, rifaximin, clostridium butyricum preparation, and proton pump inhibitor (drug name unspecified). Drip infusion of glycyrrhizinate/glycine/cysteine injection/ menatetrenone was administered every day. Bowel movements were controlled with lactulose 90 mL/day+sodium picosulfate/ glycerin enema/sodium bicarbonate/anhydrous monobasic sodium phosphate. Day 38 of discontinuation: CT: Increased pleural effusion and ascites (+)

					were observed. Edema (+) was observed around the hepatic portal vein. Edema due to hepatic inflammation (acute inflammation) was suspected. The enhancement in the hepatic parenchyma was non-uniform. Bilateral renal cysts and hepatic cysts (+) were observed.
				Day 39 of discontinuation	Transfusion of 4 units fresh frozen plasma was performed. Albumin replacement was performed and furosemide 20 mg was intravenously administered (for 3 days).
				Day 40 of discontinuation	Administration of potassium chloride extended-release tablet was started.
				Day 44 days of discontinuation	Transfusion of 6 units fresh frozen plasma was performed. A total of 1600 mL ascites was aspirated. Transfusion of 2 units fresh frozen plasma was performed. A total of 3000 mL ascites was aspirated. CT: Pleural effusion and ascites increased. There were no marked changes in edema and atrophy in the liver in comparison with the previous result.
				Day 45 of discontinuation	Administration of potassium chloride extended-release tablet was completed.
				Day 53 of discontinuation	Administration of spironolactone 25 mg was started.
				Day 54 of discontinuation	Transfusion of 2 units fresh frozen plasma was performed. A total of 3000 mL ascites was aspirated.
				Day 57 of discontinuation	A total of 2000 mL ascites was aspirated.
				Day 58 of discontinuation	A total of 2800 mL ascites was aspirated, and cell-free, concentrated ascites reinfusion therapy was performed.
				Day 59 of discontinuation	Albumin replacement was performed and furosemide 20 mg was intravenously administered (for 3 days).
				Day 60 of discontinuation	CT: Acute hepatic failure and atrophy progressed. Multiple hepatic cysts were observed.
				Day 61 of discontinuation	A total of 3000 mL ascites was aspirated.
				Day 62 of discontinuation	The dose of spironolactone was increased to 50 mg.
				Day 64 of discontinuation	A liver transplant was performed.
				Day 73 of discontinuation	Due to increased hepatobiliary enzymes, liver biopsy was performed. Rejection activity index (RAI) was 5 (P2 + B1 + V2).
				Day 74 of discontinuation	The patient had acute rejection, for which steroid pulse therapy was performed.
				Day 78 of discontinuation	As donor-specific human leukocyte antigen (HLA) antibody was reported to be strongly positive, liver biopsy was performed. Administration of rabbit anti-human thymocyte immunoglobulin was started. Liver biopsy revealed that RAI was 5 (P2 + B1 + V2).
				Day 85 of discontinuation	As hepatobiliary enzymes increased during administration of rabbit anti-human thymocyte immunoglobulin, a liver biopsy was performed. Liver biopsy revealed that rejection improved, but there was an area of hepatocellular necrosis in the hepatic lobule.
				Day 89 of discontinuation	C4d staining showed a positive result. As there was a possibility of antibody-mediated rejection, plasma exchange was started.
				Day 90 of discontinuation	Plasma exchange was performed for the 2nd time. High-dose intravenous human immunoglobulin therapy (IVIG) was started at 50 g/day.
				Day 95 of discontinuation	Liver biopsy showed that inflammation had improved.
				Day 122 of discontinuation	The patient was discharged from the hospital.
				Day 130 of discontinuation	Laboratory tests were performed. The patient was recovering.

Laboratory Examination

	178 days before admin-istration	Day 3 of admin-istration	Day 1 of admin-istration	Day 7 of admin-istration	Day 32 of admin-istration	Day 67 of admin-istration	Day 102 of admin-istration	Day 130 of admin-istration	Day 165 of admin-istration	Day 179 of administration (day of discontinu-ation)
Hematological test										
Hemoglobin (g/dL)	11.7	11.7	—	12.6	12.6	12.3	11.0	11.5	12.1	12.3
Platelet (10^3/mm^3)	182	248	—	211	204	209	151	151	213	192
PT (%)	—	—	—	—	—	—	—	—	—	—
PT ratio (N/A)	—	—	—	—	—	—	—	—	—	—
Blood biochemical test										
AST (GOT) (IU/L)	14	18	—	20	24	17	15	15	45	82
ALT (GPT) (IU/L)	8	13	—	22	21	16	10	10	69	142
Blood bilirubin (mg/dL)	0.3	0.3	—	—	0.3	0.3	0.3	0.2	0.2	0.3
Conjugated bilirubin (mg/dL)	—	—	—	—	—	—	—	—	—	0.2
ALP (IU/L)	125	138	—	155	148	129	139	136	140	147
γ-GTP (IU/L)	8	9	—	11	10	8	10	12	15	23
Blood cholinesterase (IU/L)	—	—	—	—	—	—	—	—	—	313
Total protein (g/dL)	6.6	6.9	—	6.9	6.8	7.0	6.4	6.8	6.9	7.3
Blood albumin (g/dL)	4.4	4.4	—	—	4.4	4.5	4.2	4.5	4.6	4.8
Blood creatinine (mg/dL)	—	—	—	—	—	—	—	—	—	—
Ammonia (mcg/dL)	—	—	—	—	—	—	—	—	—	—
Blood sodium (mEq/L)	141	141	—	141	143	143	142	143	143	143

	Day 19 of discon-tinuation	Day 23 of discon-tinuation	Day 25 of discon-tinuation	Day 26 of discon-tinuation	Day 29 of r discon-tinuation	Day 30 of r discon-tinuation	Day 31 of discon-tinuation	Day 32 of discon-tinuation (day of onset)	Day 33 of discon-tinuation	Day 34 of discon-tinuation	Day 35 of discon-tinuation	Day 36 of discon-tinuation
Hematological test												
Hemoglobin (g/dL)	11.7	10.9	11.6	12.1	12.3	11.0	11.0	10.2	10.8	10.7	11.4	11.2
Platelet (103/mm3)	148	140	129	128	121	121	114	114	105	94	113	106
PT (%)	59	53	44	43	33	27	27	22	21	22	20	22
PT ratio (N/A)	1.36	1.45	1.64	1.65	1.97	2.37	2.42	2.82	2.90	2.87	3.09	2.87
Blood biochemical test												
AST (GOT) (IU/L)	860	236	303	415	417	434	302	232	210	153	143	145
ALT (GPT) (IU/L)	1293	609	573	635	636	609	517	426	379	313	293	275
Blood bilirubin (mg/dL)	0.9	1.2	2.1	2.5	3.8	3.9	4.3	5.2	5.4	6.5	8.4	8.7
Conjugated bilirubin (mg/dL)	0.4	—	1.4	1.6	—	—	—	3.5	—	—	—	—
ALP (IU/L)	302	290	307	332	312	270	344	305	325	316	—	295
γ-GTP (IU/L)	156	182	206	215	212	177	175	160	152	146	—	140
Blood cholinesterase (IU/L)	223	191	195	194	183	—	—	140	—	—	—	—
Total protein (g/dL)	6.2	5.9	6.1	6.2	6.2	5.3	5.4	5.1	4.9	4.7	—	5.0
Blood albumin (g/dL)	4.1	3.7	3.9	4.0	4.1	3.4	3.4	3.4	3.2	3.1	—	3.2
Blood creatinine (mg/dL)	—	—	—	—	—	—	—	—	—	—	—	—
Ammonia (mcg/dL)	19	—	12	—	13	54	69	83	102	84	72	—
Blood sodium (mEq/L)	140	140	139	141	141	138	140	140	139	140	142	140

	Day 37 of discon-tinuation	Day 38 of discon-tinuation	Day 39 of discon-tinuation	Day 40 of discon-tinuation	Day 41 of discon-tinuation	Day 42 of discon-tinuation	Day 43 of discon-tinuation	Day 44 of discon-tinuation	Day 45 of discon-tinuation	Day 46 of discon-tinuation	Day 47 of discon-tinuation	Day 48 of discon-tinuation
Hematological test												
Hemoglobin (g/dL)	10.3	10	9.6	9.6	9.3	9.2	9.4	9.2	9	9.7	10	9.8
Platelet (103/mm3)	102	102	97	84	74	71	76	72	69	69	84	72
PT (%)	—	—	—	—	—	—	—	—	—	—	—	—
PT ratio (N/A)	—	—	—	—	—	—	—	—	—	—	—	—
Blood biochemical test												
AST (GOT) (IU/L)	131	115	94	70	64	55	57	55	47	54	51	51
ALT (GPT) (IU/L)	228	203	175	127	105	91	88	81	66	71	64	61
Blood bilirubin (mg/dL)	8.4	—	—	—	—	—	—	—	—	—	—	—
Conjugated bilirubin (mg/dL)	—	—	—	—	—	—	—	—	—	—	—	—
ALP (IU/L)	238	266	279	252	221	246	229	229	234	260	222	246
γ-GTP (IU/L)	119	117	105	91	74	69	67	66	69	69	65	65
Blood cholinesterase (IU/L)	108	—	—	117	—	—	—	87	—	—	115	—
Total protein (g/dL)	4.6	—	—	4.7	4.6	4.8	4.7	4.5	4.5		4.7	4.7
Blood albumin (g/dL)	3.1	2.9	2.9	3.1	3.1	3.3	3.2	3.1;0.8	3.1	3.2	3.1	3
Blood creatinine (mg/dL)	0.57	0.65	0.81	0.93	0.87	0.9	0.89	0.88	0.84	0.81	0.85	0.85
Ammonia (mcg/dL)	—	—	—	—	—	—	—	—	—	—	—	—
Blood sodium (mEq/L)	139	141	140	140	141	142	142	142	142	143	142	141

	Day 50 of discon-tinuation	Day 51 of discon-tinuation	Day 52 of discon-tinuation	Day 54 of discon-tinuation	Day 55 of discon-tinuation	Day 56 of discon-tinuation	Day 57 of discon-tinuation	Day 59 of discon-tinuation	Day 60 of discon-tinuation	Day 62 of discon-tinuation	Day 64 of discon-tinuation (after liver transplant)	Day 130 of discon-tinuation
Hematological test												
Hemoglobin (g/dL)	10.5	10.1	10.8	10.4	9.8	10	10.3	11.5	11	9.4	10.7	—
Platelet (103/mm3)	82	80	87	85	77	81	80	94	84	70	59	—
PT (%)	—	—	—	—	—	—	—	—	—	—	—	—
PT ratio (N/A)	—	—	—	—	—	—	—	—	—	—	—	—
Blood biochemical test												
AST (GOT) (IU/L)	69	70	78	74	66	67	64	70	60	53	667	29
ALT (GPT) (IU/L)	68	67	73	70	61	61	60	63	54	44	239	32
Blood bilirubin (mg/dL)	—	—	—	—	—	—	—	—	—	—	—	0.6
Conjugated bilirubin (mg/dL)	—	—	—	—	—	—	—	—	—	—	—	—
ALP (IU/L)	284	266	309	275	277	299	295	346	296	256	249	315
γ-GTP (IU/L)	69	66	66	63	—	56	55	62	55	44	—	100
Blood cholinesterase (IU/L)	—	—	—	—	—	—	93	95	—	—	—	—
Total protein (g/dL)	4.8	—	5	4.9	—	4.7	4.5	—	—	—	4.9	6.6
Blood albumin (g/dL)	3.1	3.1	3.1	3.1	2.9	2.8	2.8	3	3.1	3.1	3.4	4.0
Blood creatinine (mg/dL)	0.92	1.05	1.05	1.09	1.13	1.12	1.08	1.14	1.14	1.12	1.11	0.60
Ammonia (mcg/dL)	—	—	—	—	—	—	—	—	—	—	—	—
Blood sodium (mEq/L)	143	141	140	139	142	142	140	139	141	140	145	141

Concomitant medications: none

2 [1] Anagliptin
[2] Linagliptin
[3] Teneligliptin hydrobromide hydrate
[4] Teneligliptin hydrobromide hydrate/canagliflozin hydrate

Brand name (name of company)	[1] Suiny Tab.100 mg (Sanwa Kagaku Kenkyusho Co., Ltd.) [2] Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.) [3] Tenelia Tablets 20 mg (Mitsubishi Tanabe Pharma Corporation.) [4] Canalia Combination Tablets (Mitsubishi Tanabe Pharma Corporation.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (underlined parts are revised)

Important precautions

Acute pancreatitis may occur. Patients should be instructed to consult with a physician immediately if initial symptoms including persistent and intense abdominal pain and/or vomiting occur.

Adverse reactions (clinically significant adverse reactions)

Acute pancreatitis: Acute pancreatitis may occur. Patients should be carefully monitored. If any abnormalities, including persistent and intense abdominal pain and/or vomiting are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 8 months (April 2014 to December 2017).
Cases related to acute pancreatitis:

[1] Anagliptin
2 cases (including no patient mortalities)
[2] Linagliptin
5 cases (including no patient mortaliteis)
[3] Teneligliptin hydrobromide hydrate
4cases (including no patient mortalities)
[4] Teneligliptin hydrobromide hydrate/canagliflozin hydrate
0 cases

The number of patients using the drug estimated by the MAH in the past 1 year: [1] Approximately 140 000
[2] Approximately 910 000
[3] Approximately 470 000
[4] Approximately 57 000

Launched in Japan: [1] November 2012
[2] September 2011
[3] September 2012
[4] September 2017

Case summary: Anagliptin

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Type 2 diabetes mellitus (none)	100 mg 36 days	**Acute pancreatitis** The patient did not drink alcohol and had no past history of gallstones or pancreatitis. Day 1 of administration: Dietary therapy (1800 kcal/day) and administration of anagliptin 100 mg once daily (in the morning) were started. Amylase was 142 IU/L. Day 36 of administration (day of discontinuation)

					The patient had sudden pain in the right hypochondrium and the back and visited the emergency outpatient unit of the hospital. As a blood test showed increased amylase (up to 2739 IU/L), the patient was diagnosed with acute pancreatitis and was urgently hospitalized. Administration of anagliptine was discontinued, and treatment for pancreatitis was performed. 1 day after discontinuation: Administration of mitiglinide calcium hydrate/voglibose 3 tablets/day was started. 2 days after discontinuation: During hospitalization, the patient had clear consciousness and was recovering. Amylase was 940 IU/L. 7 days after discontinuation: Amylase was 168 IU/L. 9 days after discontinuation: The patient recovered from pancreatitis and was discharged from the hospital. The dose of mitiglinide calcium hydrate/voglibose was reduced to 2 tablets/day (before breakfast and supper). 28 days after discontinuation: Pancreatitis did not recur. The patient's general condition was favorable.

Laboratory Examination

Test item	4 years and 1 month before administration	1 year and 9 months before administration	Day 1 of administration	Day 12 of administration	Day 29 of administration	Day 36 of administration (day of discontin-uation)	1 day after discontin-uation	2 days after discontin-uation	7 days after discontin-uation
Red blood cell (cells/mm^3)	—	4 230 000	—	—	—	4 630 000	—	—	4 580 000
White blood cell count (cells/mm^3)	12 500	4 700	4 200	4 000	3 500	5 000	13 000	9 600	4 000
Lymphocytes (%)	—	—	24.8	28.9	24.8	18.1	4.4	8.5	—
Platelet (cells/mm^3)	—	199 000	—	—	—	200 000	—	—	24 000
AST (GOT) (IU/L)	40	36	32	43	29	106	67	37	25
ALT (GPT) (IU/L)	53	28	32	33	28	65	103	65	34
γ-GTP (IU/L)	23	—	20	18	18	123	190	137	139
LDH (IU/L)	264	232	209	237	186	266	187	175	159
Total bilirubin (mg/dL)	—	0.5	—	—	—	—	—	—	—
Amylase (IU/L)	157	95	142	111	118	2 739	2 118	940	168
CRP (mg/dL)	0.46	0.05	—	0.48	—	0.07	8.27	19.27	—
BUN (mg/dL)	—	22.5	—	—	—	16.2	—	—	22.5

Concomitant medications: none

Case summary: Anagliptin

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 80s	Type 2 diabetes mellitus (Alzheimer's type dementia, left pontine infarction, hypertension, and depressed state)	100 mg 25 days ↓ 200 mg 9 days	**Acute pancreatitis** The patient had a drinking history (sake 150 mL approximately 3 times per week), but no past history of gallstones and pancreatitis. 70 days before administration: Amylase was 71 IU/L. Day 1 of administration: Administration of anagliptine100 mg once daily (after breakfast) was started. Day 26 of administration: Dosage increased to 100 mg twice daily (after breakfast and supper) because blood sugar was poorly controlled. Day 34 of administration (day of discontinuation): The patient took only several bites of lunch. The patient complained of giddiness and right upper quadrant pain and vomited slightly. The patient also had abdominal pain and board-like abdominal rigidity. After 2 hours, a glycerin enema was performed, and the patient had a bowel movement as a result. Provision of meals and medication were discontinued. After 30 minutes, the patient vomited again. An NG tube was inserted and opened. Body temperature was 37.8°C. 1 day after discontinuation: The patient did not have abdominal pain (-), nausea, or vomiting (-). Body temperature was 37.5°C. Based on the laboratory data (amylase 1407 IU/L, lipase 1409 U/L) and abdominal CT, which showed atrophy of the entire pancreas and unclear density of the surrounding fat tissue, the patient was diagnosed with pancreatitis. Administration of a drip infusion of gabexate mesilate 300 mg/day and fluid replacement of 1600 mL/day were started. 11 days after discontinuation: The patient restarted oral intake from a small amount of jelly. 12 days after discontinuation: Administration of gabexate mesilate was completed. 15 days after discontinuation: The patient was recovering from acute pancreatitis.

Laboratory Examination

Test item	70 days before administration	1 day after discontinuation	2 days after discontinuation	5 days after discontinuation	9 days after discontinuation	15 days after discontinuation	17 days after discontinuation
White blood cell count (cells/mm^3)	4 700	17 800	—	5 600	4 800	—	4 600
Platelet (cells/mm^3)	125 000	137 000	—	138 000	134 000	—	125 000
AST (GOT) (IU/L)	42	—	68	29	21	—	27
ALT (GPT) (IU/L)	39	80	—	35	22	—	—
LDH (IU/L)	220	—	258	—	—	—	—
Total bilirubin (mg/dL)	0.8	—	2.0	1.2	1.2	—	—
Amylase (IU/L)	71	1 407	—	39	43	48	49
CRP (mg/dL)	0.03	8.33	—	4.35	1.15	—	0.17
BUN (mg/dL)	20.0	16.5	—	—	4.1	—	9.1
Lipase (U/L)	—	1 409	—	—	—	—	—

Concomitant medications: irbesartan, trazodone hydrochloride, insulin human (genetical recombination), insulin degludec (genetical recombination)

3 Anagliptin

Brand name (name of company)	Suiny Tab. 100 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Pemphigoid: Pemphigoid may occur. If blister, erosion or other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate measures, such as discontinuation of administration, should be taken.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 8 months (April 2014 to December 2017).
Cases related to pemphigoid: 1 cases (including no patient mortalities)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 140 000

Launched in Japan: November 2012

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Type 2 diabetes mellitus (Hyperlipidemia, hypertension, prostatic hyperplasia, chronic gastritis, osteoporosis, insomnia)	200 mg 238 days	**Bullous pemphigoid** Day 1 of administration: The patient was diagnosed with type 2 diabetes mellitus. Administration of anagliptin was started. (Anagliptin was the only DPP4 inhibitor administered.) Month 7 of administration: Erythema and itching of the whole body developed. Day 209 of administration: The patient visited the department of dermatology of a nearby hospital. Day 211 of administration: Tense blisters of the whole body developed. Day 217 of administration: The patient had an initial consultation at the department. Although anti-BP180 antibody was negative, skin biopsy showed subepidermal blisters, and immunofluorescence (IF) showed deposition of IgG and C3 in the basement membrane. The patient was thus diagnosed with bullous pemphigoid. Day 224 of administration: Oral combination therapy with nicotinamide and minocycline hydrochloride was started. Day 229 of administration: Epithelialization of the erosion tended to occur. Day 238 of administration (day of discontinuation) The blister deteriorated. External administration of clobetasol propionate ointment was started. Administration of anagliptin was discontinued. 12 days after discontinuation The blister recovered and symptoms subsequently improved. — After that, no new blisters developed. 287 days after discontinuation The patient was recovering from bullous pemphigoid.
	Concomitant medications: silodosin, lafutidine, atenolol, alfacalcidol, zolpidem tartrate, losartan potassium, pitavastatin calcium hydrate			

4 Sterile talc

Brand name (name of company)	Unitalc Intrapleural Suspensions 4 g (Nobelpharma Co., Ltd.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Prevention of recurrent malignant pleural effusion

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

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

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 9 months (April 2014 to January 2018).
Cases related to shock or anaphylaxis: 3* cases (including no patient mortalities)
*The product was used for an unapproved indication in 1 case.

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 10 000

Launched in Japan: December 2013

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Malignant pleural effusion (Chronic obstructive pulmonary disease, liver metastases, and ulcerative colitis)	4 g Once	**Anaphylactic shock** Day 1 of administration: Sterile talc 4 g was infused in the pleural cavity for carcinomatous pleurisy. Immediately after that, respiratory discomfort developed, and blood pressure and SpO2 decreased to 103/76 mmHg and 84%, respectively (from 127/74 mmHg and 94% before the infusion). The patient was diagnosed with anaphylactic shock. An intravenous drip infusion of methylprednisolone sodium succinate 500 mg and subcutaneous injection of adrenaline 0.3 mL were then administered. Oxygen inhalation was started at 6 L/min. Accompanying symptoms when anaphylactic shock developed included respiratory discomfort and poor oxygenation as respiratory symptoms and tachycardia as cardiovascular symptoms. There were no cutaneous or mucosal symptom and no persistent gastrointestinal symptoms. 10 minutes after administration: The symptoms of anaphylactic shock improved. 17 minutes after administration: The drain clamp was opened, and sterile talc was discharged. 50 minutes after administration: As the heart rate increased to the 170s and respiratory discomfort developed again, intravenous drip infusion of verapamil hydrochloride 5 mg was administered. After that, the symptoms improved. 160 minutes after administration: Oxygen inhalation (that had been tapered) was completed. 1 day after administration: The patient recovered from anaphylactic shock. Chest X-ray revealed no changes.

Laboratory Examination

Test item	Before administration	After administration
Blood pressure (mmHg)	127/74	103/76

Chest X-ray: No changes (1 day after administration of sterile talc)

Concomitant medications: magnesium oxide, eprazinone hydrochloride, ambroxol hydrochloride, indacaterol maleate, celecoxib, sennoside, aminophylline hydrate, hydrocortisone sodium succinate, amino-acid preparation for hepatic failure, glycyrrhizin/glycine/L-cysteine

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/
Age</th><th>Reason for use
(complications)</th><th>Clinical course and therapeutic measures</th></tr>
<tr><td>2</td><td>Male
50s</td><td>Malignant neoplasm of the lung
(Malignant pleural effusion)</td><td>4 g
Once</td><td>Anaphylactic reaction
Start of administration
Administration of sterile talc 4 g and normal saline 50 mL was started from a drain in the left thoracic cavity.
2 minutes after administration
As soon as the infusion of sterile talc was completed, the patient experienced intense dyspnea and a hot feeling (of the whole body). Immediately after that, wheezing, generalized redness in the whole body, and sweating developed.
5 minutes after administration
O_2 was administered at 15 L/min by reservoir.
15 minutes after administration
An electrocardiogram monitor and SpO_2 monitor were attached to the patient.
Acetated Ringer's solution 500 mL was administered.
45 minutes after administration
Chlorpheniramine maleate (10 mg) 1 ampule and normal saline 100 mL were administered.
50 minutes after administration
The respiratory and circulatory dynamics were stabilized with SpO_2 98% (while O_2 was administered at 2 L/min) and blood pressure 94/69 mmHg.
110 minutes after administration
Methylprednisolone sodium succinate 80 mg and normal saline 100 mL were administered.</td></tr>
<tr><td colspan="5">Laboratory Examination
<table>
<tr><th>Test item</th><th>1 day before administration</th><th>5 minutes after administration</th><th>35 minutes after administration</th><th>50 minutes after administration</th><th>80 minutes after administration</th><th>1 day after administration</th></tr>
<tr><td>Blood pressure (mmHg)</td><td>98/58</td><td>138 (systolic)</td><td>96/70</td><td>94/69</td><td>94/69</td><td>100/60</td></tr>
</table></td></tr>
<tr><td colspan="5">Concomitant medications: loxoprofen sodium hydrate, rebamipide, cherry bark extract/codeine phosphate hydrate, magnesium oxide, senna leaf/senna pod</td></tr>
</table>

3

Revision of Precautions (No. 293)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs in accordance with the Notifications dated March 20, 2018.

1 Diuretics, Hormones-Miscellaneous

Tolvaptan

Brand name	Samsca tablets 7.5 mg, 15 mg, 30 mg, Samsca granules 1% (Otsuka Pharmaceutical Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Acute hepatic failure, hepatic impairment:** Hepatic impairment associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, ALP, and bilirubin, etc. may occur and may lead to onset of acute hepatic failure. Patients should be observed carefully. If any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. Hepatic function should be closely monitored (through frequent blood tests, etc.) until the impairments are resolved.

2 Cardiovascular agents-Miscellaneous

Selexipag

Brand name	Uptravi Tablets 0.2 mg, 0.4 mg (Nippon Shinyaku Co., Ltd.)
Contraindications	Patients receiving preparations containing clopidogrel
Contraindications for co-administration	Preparations containing clopidogrel

3 Blood and body fluid agents-Miscellaneous

[1] Clopidogrel sulfate
[2] Clopidogrel sulfate/aspirin

Brand name	[1] Plavix Tablets 25 mg, 75 mg (Sanofi K.K.) and the others [2] ComPlavin Combination Tablets (Sanofi K.K.)
Contraindications	Patients receiving selexipag
Contraindications for co-administration	Selexipag

4 **Antidiabetic agents**

Anagliptin

Brand name	Suiny Tab.100 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
Important precautions	Acute pancreatitis may occur. Patients should be instructed to consult with a physician immediately if initial symptoms including persistent and intense abdominal pain and/or vomiting occur.
Adverse reactions (clinically significant adverse reactions)	**Acute pancreatitis:** Acute pancreatitis may occur. Patients should be carefully monitored. If any abnormalities, including persistent and intense abdominal pain and/or vomiting are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Pemphigoid:** Pemphigoid may occur. If blister, erosion or other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate measures, such as discontinuation of administration, should be taken.

5 **Antidiabetic agents**

[1] Teneligliptin hydrobromide hydrate
[2] Teneligliptin hydrobromide hydrate/canagliflozin hydrate
[3] Linagliptin

Brand name	[1] Tenelia Tablets 20 mg (Mitsubishi Tanabe Pharma Corporation.) [2] Canalia Combination Tablets (Mitsubishi Tanabe Pharma Corporation.) [3] Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Important precautions	Acute pancreatitis may occur. Patients should be instructed to consult with a physician immediately if initial symptoms including persistent and intense abdominal pain and/or vomiting occur.
Adverse reactions (clinically significant adverse reactions)	**Acute pancreatitis:** Acute pancreatitis may occur. Patients should be carefully monitored. If any abnormalities, including persistent and intense abdominal pain and/or vomiting are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6 **Antineoplastics-Miscellaneous**

Sterile talc

Brand name	Unitalc Intrapleural Suspensions 4 g (Nobelpharma Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Shock, anaphylaxis:** Shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

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 new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting adverse drug reaction (ADR) from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of February 28, 2018)
◎: Products for which EPPV was initiated after February 1, 2018

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Abatacept (genetical recombination)[*1] Orencia for I.V. Infusion 250 mg	Bristol-Myers Squibb K.K.	February 23, 2018
◎	Sarilumab (genetical recombination) Kevzara 150 mg, 200 mg Syringe for SC Injection Kevzara 150 mg, 200 mg Auto-injector for SC Injection	Sanofi K.K.	February 5, 2018
	Sildenafil citrate Revatio Dry Syrup for Suspension 900 mg, Revatio OD Film 20 mg	Pfizer Japan Inc.	January 29, 2018
	Esomeprazole magnesium hydrate Nexium Capsules 10 mg, 20 mg, Nexium Granules for Suspension 10 mg, 20 mg	AstraZeneca K.K.	January 19, 2018
	Eculizumab (genetical recombination)[*2] Soliris for Intravenous Infusion 300 mg	Alexion Pharma G.K.	December 25, 2017
	Aminolevulinic acid hydrochloride[*3] Alaglio Divided Granules 1.5 g	SBI Pharmaceuticals Co., Ltd.	December 19, 2017
	Palbociclib Ibrance Capsules 25 mg, 125 mg	Pfizer Japan Inc.	December 15, 2017
	Belimumab (genetical recombination) Benlysta for I.V. Infusion 120 mg, 400 mg Benlysta for S.C. Injection 200 mg Autoinjector, 200 mg Syringe	GlaxoSmithKline K.K.	December 13, 2017
	Bezlotoxumab (genetical recombination) Zinplava for Intravenous Drip Infusion 625 mg	MSD K.K.	December 8, 2017
	Budesonide Rectabul 2 mg Rectal Foam 14 Doses	EA Pharma Co., Ltd.	December 7, 2017
	Lonoctocog alfa (genetical recombination) Afstyla I.V. Injection 250, 500, 1000, 1500, 2000, 2500, 3000	CSL Behring K.K.	December 1, 2017
	Glecaprevir hydrate/pibrentasvir Maviret Combination Tablets	AbbVie GK	November 27, 2017

Nonproprietary name Brand name		Name of the MAH	Date of EPPV initiate
	Rupatadine fumarate Rupafin Tablets 10 mg	Teikoku Seiyaku Co., Ltd.	November 27, 2017
	Avelumab (genetical recombination) Bavencio Intravenous Injection 200 mg	Merck Serono Co., Ltd.	November 22, 2017
	Daratumumab (genetical recombination) Darzalex Intravenous Infusion 100 mg, 400 mg	Janssen Pharmaceutical K.K.	November 22, 2017
	Flutemetamol (^{18}F) Vizamyl Intravenous Injectable	Nihon Medi-Physics Co., Ltd.	November 10, 2017
	Quetiapine fumarate*4 Bipresso Extended Release Tablets 50 mg, 150 mg	Astellas Pharma Inc.	October 27, 2017
	Sildenafil citrate Revatio Tablets 20 mg	Pfizer Japan Inc.	September 27, 2017
	Nusinersen sodium*5 Spinraza Intrathecal Injection 12 mg	Biogen Japan Ltd.	September 22, 2017
	Lyophilized human prothrombin complex concentrate Kcentra for I.V. Injection 500, 1000	CSL Behring K.K.	September 19, 2017
	Teneligliptin hydrobromide hydrate/ Canagliflozin hydrate Canalia Combination Tablets	Mitsubishi Tanabe Pharma Corporation	September 7, 2017
	Amenamevir Amenalief Tab. 200 mg	Maruho Co., Ltd.	September 7, 2017
	Baricitinib Olumiant Tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	September 1, 2017
	Nusinersen sodium Spinraza Intrathecal injection 12 mg	Biogen Japan Ltd.	August 30, 2017

*1 Polyarticular juvenile idiopathic arthritis that does not adequately respond to existing treatments

*2 Generalized myasthenia gravis (for use only in patients whose symptoms are difficult to control with high-dose intravenous immunoglobulin therapy or hemocatharsis)

*3 Visualization of tumor tissues of the non-muscle invasive bladder cancer in transurethral resection of bladder tumor

*4 Depressive symptoms in bipolar disorder

*5 Spinal muscular atrophy