

Pharmaceuticals and Medical Devices Safety Information

No. 322 April 2015

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on 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 available in Japanese language).

Available information is listed here



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Pharmaceuticals and Medical Devices Safety Information

No. 322 April 2015

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	Adherence to the Cleaning and Disinfection Method to Prevent Transmission of Multidrug-resistant Bacteria by Duodenoscopes		Cases of infection by multidrug-resistant bacteria suspected to be associated with duodenoscopes have been reported in the US. The relevant Food and Drug Administration safety information, the situation in Japan, and information on the points to consider when using a duodenoscope are presented in section 1.	4
2	Cyclophosphamide hydrate and 4 others	<i>P</i> <i>C</i>	Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated March 24, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are presented in section 2.	7
3	Rebamipide (ophthalmic suspension) and 2 others		Revision of Precautions (No. 264)	20
4	List of Products Subject to Early Post-marketing Phase Vigilance		A list of products subject to Early Post-marketing Phase Vigilance as of April 1, 2015 is presented in section 4.	21
References	Precautions concerning recurrent medical accidents and similar incidents		Precautions for recurring medical accidents and similar incidents in the notifications or the PMDA Medical Safety Information are presented in the reference section.	23

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications *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
AI-P	Alkaline Phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CK (CPK)	Creatine kinase (Creatine phosphokinase)
EPPV	Early Post-marketing Phase Vigilance
ERCP	Endoscopic retrograde cholangiopancreatography
FDA	Food and Drug Administration
HPB	Health Policy Bureau
JCQHC	Japan Council for Quality Health Care
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MCPB	Medical Care Planning Division
MHLW	Ministry of Health, Labour and Welfare
MP	Metacarpal phalangeal
MRI	Magnetic resonance imaging
PFSB	Pharmaceutical and Food Safety Bureau
PLT	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSL	Prednisolone
RBC	Red blood cell count
SD	Safety Division
SJS	Stevens–Johnson syndrome
US	United States
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

Adherence to the Cleaning and Disinfection Method to Prevent Transmission of Multidrug-resistant Bacteria by Duodenoscopes

1. Introduction

Duodenoscopes are medical devices used for endoscopic retrograde cholangiopancreatography (ERCP), and unlike many other endoscopes. They can be inserted into the pancreaticobiliary duct by fine adjustment of the contrast tube that extends in and out of the tip opening because it has a moving part of the elevator mechanism containing a microscopic crevice on the distal end. In Japan, various duodenoscopes are currently marketed by the following three companies: Olympus Medical Systems Corporation, Fujifilm Corporation, and HOYA Corporation.

Duodenoscope Product sample

<Duodenoscope>



<Scope tip Enlarged image>



(Supplied by Olympus Medical Systems Corporation)

Endoscopes that are repeatedly used must be reprocessed by appropriate methods such as cleaning, disinfection, or sterilization after use to prevent infection. However, potential transmission of multidrug-resistant bacteria has been reported in the US, where because of the complicated structure of the duodenoscope tip, the device was not sufficiently cleaned or disinfected. This report aims to inform and caution healthcare professionals of the details of this infection, the difference in the duodenoscopes marketed in Japan, and the points to consider when using duodenoscopes.

2. US Food and Drug Administration Safety Information

The US Food and Drug Administration (FDA) released safety information¹⁾ concerning duodenoscopes in February 2015. In this, the FDA states that a total of 75 cases (approximately 135 patients) of Medical Device Reports have been received between January 2013 and December 2014 in the US concerning potential infection caused by carbapenem-resistant Enterobacteriaceae such as *Klebsiella* and *E. coli* from reprocessed duodenoscopes and that the complex design of duodenoscopes may impede effective cleaning and high-level disinfection.

The FDA requires that those working in reprocessing units must follow all the reprocessing steps provided by the manufacturer and that they should meticulously hand clean the forceps elevator and surrounding crevices using tools such as brushes, even when using automatic endoscope reprocessors.

The health care professionals are asked to provide information and explain to the patients the benefits and risks of ERCP and additional follow-up in case certain symptoms appear after ERCP. Additionally, they are requested to meticulously clean and disinfect duodenoscopes after use, introduce a quality control program for reprocessing, and report to the manufacturer and FDA if there are any suspected cases where problems in reprocessing may have contributed to infection.

3. Situation in Japan

To date, concerning the cleaning and disinfection or sterilization procedures of medical devices, the Ministry of Health, Labour and Welfare (MHLW) stated that at least the guides established by the relevant societies should be followed to the extent possible in “Measures for hospital-acquired infection control” (Health Policy Bureau (HPB)/Medical Care Planning Division (MCPB) Notification No. 1219-1, by the Director of Medical Care Planning Division, Health Policy Bureau, MHLW, dated December 19, 2014), and for handling of medical devices, healthcare professionals have been requested to adhere to the usage method specified by the marketing authorization holder of the medical device in “Points to consider on the operation for securing a system for safety control of medical devices” (Joint Notification of HPB/Guidance of Medical Service Division Notification No. 0330001, and HPB/Research and Development Division No. 0330018, by the Director of Guidance of Medical Service Division, Health Policy Bureau and by the Director of Research and Development Division, Health Policy Bureau, MHLW, dated March 30, 2007).

For duodenoscopes, the necessity for careful cleaning to prevent infection and the method and precautions for cleaning the tip area are described in the package inserts and instruction for use of product, respectively. The usage methods of automatic endoscope reprocessors and disinfectants and duodenoscope models for which they can be used for cleaning and disinfection are also described in the package inserts and instruction for use. “Multisociety Guide on Infection Control of Gastrointestinal Endoscope”²⁾ for all gastrointestinal endoscopes was published by relevant societies.

As stated above, cases of infection by drug-resistant bacteria associated with duodenoscope have been reported in the US, and safety information has been released. Duodenoscopes distributed in Japan have a design in which the cap on the tip where the forceps elevators are located can be mainly taken out, which is advantageous for cleaning compared with duodenoscopes marketed in the US, in which the tip cannot be taken out.

Moreover, while the percentage of Enterobacteriaceae resistant to carbapenem is approximately 11% in the US, it is below 1% in Japan. Thus, the infection risk of these multidrug-resistant bacteria greatly differs.

However, these differences do not confirm that the infection risk is sufficiently low in Japan, and care must still be taken.

4. Points to Consider during Use

Considering the situation, the MHLW issued the Joint Notification of HPB/MCPB No. 0320-3 and Pharmaceutical and Food Safety Bureau (PFSB) / Safety Division (SD) Notification No. 0320-4, by the Director of Medical Care Planning Division, Health Policy Bureau and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 20, 2015, “Transmission of Multidrug-resistant Bacteria from Duodenoscopes”³⁾ and cautioned each medical facility to consider the following points when using duodenoscopes.

- (1) As the FDA Safety Information published in the US states that they “do not recommend that healthcare providers cancel ERCP procedures for their patients who need them,” it is not necessary to discontinue this treatment immediately in Japanese patients who require treatment such as ERCP using duodenoscopes.
- (2) Prior to performing a test or treatment using duodenoscopes, inform patients of the benefits and possible potential risks associated with ERCP procedures.
- (3) To minimize the infection risk, adhere to the guide³⁾ on cleaning and sterilizing or disinfecting duodenoscopes established by the relevant societies and the methods provided by the market authorization holders in the package inserts or instructions for use.
- (4) The tip where the forceps elevator is located has a complex structure; thus, the cap on the tip should be removed and carefully cleaned using a dedicated brush.
- (5) If transmission of multidrug-resistant bacteria such as carbapenem-resistant Enterobacteriaceae through an examination using duodenoscopes is confirmed or suspected, immediately report this to the health center, which has jurisdiction over the area. In addition, a report (Adverse Reaction Reporting by Medical and Pharmaceutical Professionals)⁴⁾ based on Article 68 Paragraph 10-2 of the Pharmaceutical Affairs Act (Act No. 145 of 1960) should be submitted to the Pharmaceuticals and Medical Devices Agency (PMDA).

Moreover, each market authorization holder is being instructed to confirm their system for collecting information in cases when transmission of multidrug-resistant bacteria is confirmed or suspected, so that such information can be reliably grasped.

At the MHLW, we strive to promptly grasp information on confirmed or suspected cases of multi-drug resistant bacteria transmission. We ask each medical facility to reduce the risk of infection by considering the above points and following the package inserts and instruction for using each device and also to promptly provide information in case of confirmed or suspected transmission of multidrug-resistant bacteria.

<References>

- 1) Design of ERCP Duodenoscopes May Impede Effective Cleaning: FDA Safety Communication
<http://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm434871.htm>
- 2) Multisociety Guide on Infection Control of Gastrointestinal Endoscopes (Japanese Society of Infection Prevention and Control, Japan Gastroenterological Endoscopy Society, Japan Gastroenterological Endoscopy Technicians Society [July 2013])
http://www.kankyokansen.org/other/syoukaki_guide.pdf
or
http://www.jgets.jp/CD_MSguide20130710.pdf
- 3) “Transmission of Multidrug-resistant Bacteria by Duodenoscopes” (Joint Notification of HPB/MCPB No. 0320-3 and PFSB/SD Notification No. 0320-4, by the Director of Medical Care Planning Division, Health Policy Bureau and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 20, 2015)
- 4) Adverse Reaction Reporting by Medical and Pharmaceutical Professionals
<http://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html>

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated March 24, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are presented in this section.

1 Cyclophosphamide hydrate

Brand name (name of company)	(1) Endoxan Injections 100 mg and 500 mg (Shionogi & Co., Ltd.) (2) Endoxan Tablets 50 mg and Endoxan Powder for oral use 100 mg (Shionogi & Co., Ltd.)
Therapeutic category	Antineoplastics-Alkylating agents
Indications	<p>(1) 1. Remission of signs and symptoms of the following diseases: Multiple myeloma, malignant lymphoma (Hodgkin's disease, lymphosarcoma, and reticulosarcoma), lung cancer, breast cancer, acute leukaemia, polycythaemia vera, uterine cervical cancer, endometrial cancer, ovarian cancer, nervous system tumour (neuroblastoma and retinoblastoma), and bone tumour It should be noted that this drug should be concomitantly used with other antineoplastics for the following diseases: Chronic lymphocytic leukaemia, chronic myeloid leukaemia, pharyngeal cancer, gastric cancer, pancreatic carcinoma, hepatic cancer, colon cancer, testicular tumour, trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole), rhabdomyosarcoma, and malignant melanoma</p> <p>2. Concomitant therapy with other antineoplastics for the following cancers: Breast cancer (neoadjuvant or adjuvant chemotherapy in operable patients)</p> <p>3. Pheochromocytoma</p> <p>4. Pretreatment for hematopoietic stem cell transplantation for the following diseases: Acute leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome, severe aplastic anaemia, malignant lymphoma, genetic diseases (immunodeficiency, congenital metabolic disorders, and congenital blood diseases [Fanconi's anaemia, Wiskott–Aldrich syndrome, Hunter's syndrome, etc.]</p> <p>5. The following treatment-resistant rheumatic diseases: Systemic lupus erythematosus, systemic vasculitis (microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, aortitis syndrome, etc.), polymyositis/dermatomyositis, scleroderma, mixed connective tissue disease, and refractory rheumatic diseases with vasculitis</p> <p>(2) 1. Remission of signs and symptoms of the following diseases: Multiple myeloma, malignant lymphoma (Hodgkin's disease, lymphosarcoma, and reticulosarcoma), breast cancer Acute leukaemia, polycythaemia vera, lung cancer, nervous system tumour (neuroblastoma and retinoblastoma), and bone tumour It should be noted that this drug should be concomitantly used with other antineoplastics for the following diseases: Chronic lymphocytic leukaemia, chronic myeloid leukaemia,</p>

	<p>pharyngeal cancer, gastric cancer, pancreatic carcinoma, hepatic cancer, colon cancer, uterine cervical cancer, endometrial cancer, ovarian cancer, testicular tumour, trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole), rhabdomyosarcoma, and malignant melanoma</p> <p>2. The following treatment-resistant rheumatic diseases: Systemic lupus erythematosus, systemic vasculitis (microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa, Churg–Strauss syndrome, aortitis syndrome, etc.), polymyositis/dermatomyositis, scleroderma, mixed connective tissue disease, and refractory rheumatic diseases with vasculitis</p> <p>3. Nephrotic syndrome (in patients who are not sufficiently responsive to appropriate treatment with corticosteroids)</p>
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PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased creatine kinase (creatin phosphokinase), increased blood myoglobin, and increased urine myoglobin may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 11 months (April 2011 to February 2015)

- Rhabdomyolysis
 (1) 1 case (no fatal cases)
 (2) No cases

The number of patients using this drug estimated by the marketing authorization holder (MAH): (1) approximately 77 000 (2013), (2) approximately 10 000 (2013)

Launched in Japan: (1) August 1962
 (2) October 1992

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Pretreatment for bone marrow transplant (none)	2600 mg for 2 days	<p>Rhabdomyolysis</p> <p>History of allergy (Platelet transfusion allergy, mackerel)</p> <p>Day 1 of administration</p> <p>Infusion of cyclophosphamide hydrate 2600 mg/day (60 mg/kg) was started as a pretreatment for allogeneic peripheral blood stem cell transplantation for acute myeloid leukaemia (for 2 days).</p> <p>Administration of mesna 800 mg × 3 times/day (for 2 days), multiple electrolyte transfusion 500 mL × 5 times/day (for 7 days), and sodium bicarbonate 1.4 g × 5 times/day (for 7 days) was started for the prevention of haemorrhagic cystitis.</p> <p>Granisetron hydrochloride 3 mg/day (for 2 days) was started for the prevention of nausea.</p> <p>Day 2 of administration (day of completion)</p> <p>The same treatment as that on the previous day was performed.</p> <p>From the night, the patient developed severe nausea and</p>

				<p>malaise.</p> <p>1 day after completion The patient developed pyrexia (38°C). After blood, urine, and throat swab cultures, administration of meropenem was started. From the evening, tea-colored urine was noted. The patient had pain in the buttocks and lower limbs. Results of blood, urine, and throat swab cultures: negative</p> <p>2 days after completion Red wine-colored urine was noted (myoglobinuria was suspected). The patient could not get up because of severe systemic malaise, and the lower body felt heavy like lead and could not be moved. Creatine kinase (creatin phosphokinase) (CK [CPK]) increased to 16 846 IU/L, aspartate aminotransferase (glutamate oxaloacetate transaminase) (AST [GOT]) to 120 IU/L, and lactate dehydrogenase (LDH) to 607 IU/L. Total body irradiation (2 Gy × 2 doses/day for 3 days; a total radiation dose of 12 Gy) was performed.</p> <p>5 days after completion Allogeneic peripheral blood stem cell transplantation was performed.</p> <p>8 days after completion Muscular and urinary symptoms disappeared. Rhabdomyolysis resolved. [Physician's assessment] This time, 6 h after the second day of high-dose cyclophosphamide hydrate treatment, the patient developed systemic malaise and red wine-colored urine (myoglobinuria was suspected). After 48 h, the symptoms reached a peak, and the patient had symptoms such as red wine-colored urine (myoglobinuria was suspected), increased creatine kinase (creatin phosphokinase) (CK (CPK)), and the lower limbs were so fatigued that the patient could not move. The appearance of systemic malaise and muscle pain after the administration of cyclophosphamide hydrate and the subsequent appearance of red wine-colored urine and increased blood CK (CPK) were considered to be related to cyclophosphamide hydrate because the symptoms and changes in test values were temporally consistent with the administration of cyclophosphamide hydrate.</p>
Concomitant drugs: granisetron hydrochloride, mesna, multiple electrolyte transfusion (maintenance solution), and sodium bicarbonate				

Laboratory examination

	(before administration) Day 1 of administration	2 days after completion	11 days after completion	25 days after completion
CK (CPK) (IU/L)	42	16 846	84	40
AST (GOT) (IU/L)	13	120	24	11
ALT (GPT) (IU/L)	6	22	51	6
AI-P (IU/L)	175	156	175	256
LDH (IU/L)	157	607	162	174
γ-GTP (IU/L)	15	13	26	17
Total bilirubin (mg/dL)	0.3	0.8	0.3	0.3
BUN (mg/dL)	9.7	5.1	4.7	7.4
Serum creatinine (mg/dL)	0.52	0.46	0.34	0.48

	(before administration) Day 1 of administration	2 days after completion	11 days after completion	25 days after completion
Urinary occult blood	(-)	(2+)	-	-
Urinary sediment (reticulocyte)	(-)	(-)	-	-

2 Sitagliptin phosphate hydrate

Brand name (name of company)	(1) Glactiv Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg (Ono Pharmaceutical Co., Ltd.) (2) Januvia Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg (MSD K.K.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Thrombocytopenia: Thrombocytopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 10 months (April 2011 to January 2015)

Thrombocytopenia 2 cases (no fatal cases)

The number of patients using this drug estimated by MAH: 2 000 000 (2014)

Launched in Japan: December 2009

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Type 2 diabetes mellitus (none)	50 mg for 1106 days	<p>Thrombocytopenia</p> <p>Previously, the patient visited the hospital once a year for periodic examination. The patient started showing an increased blood glucose level in these examinations.</p> <p>5 days before administration Hemoglobin A1c level increased to 7% on physical examination. Platelet (PLT) count 152 000/mm³</p> <p>Day 1 of administration Administration of sitagliptin phosphate hydrate (50 mg × 1 dose/day) was started for type 2 diabetes mellitus. Subsequently, decrease in the blood glucose level was confirmed.</p> <p>Day 304 of administration PLT count 146 000/mm³</p> <p>Day 694 of administration PLT count 127 000/mm³</p> <p>Day 1079 of administration PLT count had decreased on physical examination. PLT count 22 000/ mm³</p> <p>Day 1080 of administration The test center reported a low PLT count from the examination the day before, but the cause was unknown.</p> <p>Day 1086 of administration</p>

				<p>The patient was prescribed sitagliptin phosphate hydrate for 30 days. PLT count 32 000/mm³ Day 1106 of administration (date of discontinuation) Because the patient was only taking sitagliptin phosphate hydrate, it was discontinued. 29 days after discontinuation PLT count increased. PLT count 116 000/mm³ 64 days after discontinuation PLT count became normal, and the patient recovered. PLT count 141 000/mm³</p>
Concomitant drugs: none				

Laboratory examination

Laboratory parameter	5 days before administration	Day 304 of administration	Day 694 of administration	Day 1079 of administration	Day 1086 of administration	29 days after discontinuation	64 days after discontinuation
PLT count (10 000/mm ³)	15.2	14.6	12.7	2.2	3.2	11.6	14.1
RBC count (10 000/mm ³)	447	434	412	441	430	412	438
Hemoglobin level (g/dL)	12.3	12.2	11.9	12.5	12.4	12.1	12.4
Hematocrit (%)	38.7	38.8	37.5	37.4	37.9	36.7	38.4
WBC count (10 000/mm ³)	0.56	0.54	0.72	0.49	0.42	0.49	0.56

3 Triamcinolone acetonide (for intramuscular, intra-articular, and intradermal injections)

Brand name (name of company)	<p>(1) Kenacort-A Intramuscular Intraarticular Suspension Liquid Injection 40 mg/1 mL (Bristol-Myers K.K.) (2) Kenacort-A Intradermal Intraarticular Suspension Liquid Injection 50 mg/5 mL (Bristol-Myers K.K.)</p>
Therapeutic category	Adrenal hormone preparations
Indications	<p>(1) Kenacort-A Intramuscular Intraarticular Suspension Liquid Injection 40 mg/1 mL Intramuscular injection</p> <ul style="list-style-type: none"> Chronic adrenocortical insufficiency (primary, secondary, pituitary, and iatrogenic), adrenogenital syndrome*, subacute thyroiditis*, and thyrotoxicosis* (thyroid crisis) Rheumatoid arthritis, juvenile rheumatoid arthritis (including Still's disease), rheumatic fever (including rheumatic carditis), and polymyalgia rheumatica Lupus erythematosus (systemic and chronic discoid), systemic vasculitides (including aortitis syndrome, periarteritis nodosa, polyarteritis, and Wegener's granulomatosis), polymyositis (dermatomyositis), and scleroderma* Nephrosis and nephrotic syndrome* Congestive cardiac failure* Bronchial asthma (to be used only when other routes of administration, except intramuscular injection, are inappropriate), allergies to drugs and other chemicals/drug toxicity (including drug eruption and toxicoderma)*, and serum sickness* Severe infections (to be concomitantly used with chemotherapy)* Haemolytic anaemia (immune haemolytic anaemia or haemolytic anaemia with an immune mechanism) *, leukaemia (acute leukaemia, transformation of chronic myeloid leukaemia, and chronic lymphocytic leukaemia) (including

leukaemia cutis)*, granulocytopenia (essential and secondary)*, purpura (thrombocytopenic and non-thrombocytopenic)*, aplastic anaemia*, and haemorrhagic diathesis due to coagulation factor disorders*

- Regional enteritis* and ulcerative colitis*
- Improvement of general symptoms in severely debilitating disease (including terminal stage of cancer and sprue)*
- Cirrhosis (active, with refractory ascites and/or with cholestasis)*
- Encephalomyelitis (including encephalitis and myelitis) (regarding primary encephalitis, this drug should be used for short term only when the patient has intracranial hypertension and does not sufficiently respond to other drugs)*, peripheral neuritis (including Guillain–Barre syndrome)*, myasthenia gravis*, multiple sclerosis (including neuromyelitis optica)*, chorea minor*, facial palsy*, and spinal arachnoiditis*
- Malignant lymphoma (lymphosarcoma, reticulum cell sarcoma, Hodgkin's disease, cutaneous reticulosis, and mycosis fungoides), variants (related diseases)*, and eosinophilic granuloma*
- Idiopathic hypoglycemia*
- Adrenalectomy*, organ transplant/tissue transplant*, surgery in the setting of adrenal cortex insufficiency*
- Snake venom/insect venom (including serious insect sting)*
- Ankylosing spondylitis (rheumatoid spondylitis)
- Prevention of adhesions after tuboplasty
- Prostate cancer (when the patient does not respond to other therapies) and recurrence and/or metastasis of breast cancer*
- Eczema and dermatitis*† (acute eczema, subacute eczema, chronic eczema, contact dermatitis, nummular eczema, autosensitization dermatitis, atopic dermatitis, pediatric eczema, lichen simplex chronicus Vidal, other neurodermatitis, seborrhoeic dermatitis, keratoderma tylodes palmaris progressiva, other dermatitis of the fingers, genital or anal eczema, dermatitis/eczema of the auricle or ear canal, dermatitis/eczema of the nasal vestibule or around nasal ala, etc.) (if possible, this drug should not be administered to patients with non-serious symptoms), urticaria (excluding chronic urticaria) (to be administered only to patients with serious symptoms), psoriasis and variants (psoriasis [with serious symptoms], arthropathic psoriasis, erythrodermic psoriasis, pustular psoriasis, acrodermatitis continua, impetigo herpetiformis, Reiter's syndrome) *†, palmoplantar pustulosis (to be administered only to patients with serious symptoms) *†, lichen planus *† (to be administered only to patients with serious symptoms), scleredema adutorum*, erythema* (erythema exsudativum multiforme†, and erythema nodosum) (regarding erythema exsudativum multiforme†, this drug should be administered only to patients with serious symptoms), oculomucocutaneous syndrome* (ectodermosis erosiva pluriorificialis, Stevens–Johnson syndrome, dermatostomatitis, Fuchs' syndrome, Behcet's syndrome [without ophthalmic symptoms], Lipschutz ulcer vulvae acutum), pemphigus (pemphigus vulgaris, pemphigus foliaceus, Senear–Usher syndrome, and pemphigus vegetans), dermatitis herpetiformis (including pemphigoid and herpes gestationis)*, herpes zoster* (to be administered only to patients with serious symptoms), erythroderma (including Hebra pityriasis rubra) *†
- Prurigo*† (including pediatric strophulus, urticarial lichen, and urticaria perstans) (to be administered only to patients with serious symptoms. Localized injection is appropriate for urticaria perstans)
- Symptomatic therapy for inflammatory diseases of the eye, optic nerve, orbit, eye muscle* (uveitis, chorioretinitis, retinal vasculitis, optic neuritis, orbital inflammatory pseudotumor, orbital apex syndrome, and ophthalmoplegia), symptomatic therapy for inflammatory diseases of the outer ocular area and anterior eye segment when the ophthalmic topical treatment is not appropriate or sufficient (blepharitis, conjunctivitis, keratitis, scleritis, and iridocyclitis) *

- Acute/chronic otitis media*, serous otitis media/eustachian tube stenosis*, allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, pharyngitis/laryngeal oedema, laryngeal polyp/nodules*, oesophagitis (corrosive oesophagitis after endoscopy) *, and post-treatment for oesophageal dilation and otorhinolaryngological surgery
- Post-treatment for oral surgery

Intra-articular injection

- Rheumatoid arthritis, juvenile rheumatoid arthritis (including Still's disease)
- Acroarthritis associated with ankylosing spondylitis (rheumatoid spondylitis), osteoarthritis (when inflammatory symptom is obvious), traumatic arthritis, and non-infectious chronic arthritis

Injection into soft tissue

- Periarthritis (only non-infectious periarthritis), tendonitis (only non-infectious tendonitis), peritendinitis (only non-infectious peritendinitis)
- Post-treatment for otorhinolaryngological surgery
- Refractory stomatitis and glossitis (when the patient does not recover with local treatment)

Intratendovaginal injection

- Periarthritis (only non-infectious periarthritis), tendonitis (only non-infectious tendonitis), tenosynovitis (only non-infectious tenosynovitis), and peritendinitis (only non-infectious peritendinitis)

Intrasynovial bursa injection

- Periarthritis (only non-infectious periarthritis), peritendinitis (only non-infectious peritendinitis), and bursitis (only non-infectious bursitis)

Nebulizer

- Bronchial asthma
- Diffuse interstitial pneumonia (pulmonary fibrosis) (including radiation pneumonitis)
- Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, laryngitis/laryngeal oedema, laryngeal polyp/nodules, oesophagitis (corrosive oesophagitis after endoscopy), and post-treatment for oesophageal dilation and otorhinolaryngological surgery

Injection in the nasal cavity

- Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, and post-treatment for otorhinolaryngological surgery

Injection into the paranasal sinus

- Sinusitis/nasal polyps, and post-treatment for otorhinolaryngological surgery

Injection into the nasal turbinate

- Allergic rhinitis, pollinosis (hay fever), and post-treatment for otorhinolaryngological surgery

Injection into the nasal polyp

- Sinusitis/nasal polyps

Injection in the larynx/trachea

- Laryngitis/laryngeal oedema, laryngeal polyp/nodules, and post-treatment for otorhinolaryngological surgery

Injection in the middle ear cavity

- Acute/chronic otitis media*, serous otitis media/eustachian tube stenosis, and post-treatment for otorhinolaryngological surgery

Injection into the eustachian tube

- Serous otitis media/eustachian tube stenosis

Injection into the oesophagus

- Oesophagitis (corrosive oesophagitis after endoscopy), and post-treatment for oesophageal dilation and otorhinolaryngological surgery

Notes

* This drug should be used in patients who are not able to use the oral treatment.

†This drug should be used only when the patient does not or is not expected to sufficiently respond to topical treatment.

(2) Kenacort-A Intradermal Intraarticular Suspension Liquid Injection 50 mg/5 mL
Intra-articular injection

- Rheumatoid arthritis and juvenile rheumatoid arthritis (including Still's disease)
- Acroarthritis associated with ankylosing spondylitis (rheumatoid spondylitis), osteoarthritis (when inflammatory symptom is obvious), traumatic arthritis, and non-infectious chronic arthritis

Injection into soft tissue

- Periarthritis (only non-infectious periarthritis), tendonitis (only non-infectious tendonitis), peritendinitis (only non-infectious peritendinitis)
- Post-treatment for otorhinolaryngological surgery
- Refractory stomatitis and glossitis (when the patient does not recover with local treatment)

Intratendovaginal injection

- Periarthritis (only non-infectious periarthritis), tendonitis (only non-infectious tendonitis), tenosynovitis (only non-infectious tenosynovitis), and peritendinitis (only non-infectious peritendinitis)

Intrasynovial injection

- Periarthritis (only non-infectious periarthritis), peritendinitis (only non-infectious peritendinitis), and bursitis (only non-infectious bursitis)

Topical intradermal injection

- Eczema and dermatitis†(acute eczema, subacute eczema, chronic eczema, contact dermatitis, nummular eczema, autosensitization dermatitis, atopic dermatitis, pediatric eczema, lichen simplex chronicus Vidal, other neurodermatitis, seborrheic dermatitis, keratoderma tylodes palmaris progressiva, other dermatitis of the fingers, genital or anal eczema, eczema/dermatitis of the auricle or ear canal, eczema/dermatitis of the nasal vestibule or around nasal ala, etc.) (if possible, this drug should not be administered to patients with non-serious symptoms. Topical injection should be used in only patients with serious infiltration or lichen), prurigo (including pediatric strophulus, urticarial lichen, and urticaria perstans)†(to be administered only to patients with serious symptoms), psoriasis and variants (psoriasis [with serious symptoms], arthropathic psoriasis, erythrodermic psoriasis, pustular psoriasis, acrodermatitis continua, impetigo herpetiformis, Reiter's syndrome)†, lichen planus (to be administered only to patients with serious symptoms)†, circumscribed scleroderma, areata alopecia (to be administered only to patients with serious symptoms)†, and early stage of keloid and prevention of keloid†
- Post-treatment for otorhinolaryngological surgery

Nebulizer

- Bronchial asthma
- Diffuse interstitial pneumonia (pulmonary fibrosis) (including radiation pneumonitis)

	<ul style="list-style-type: none"> Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, laryngitis/laryngeal oedema, laryngeal polyp/nodule, oesophagitis (corrosive oesophagitis after endoscopy), and post-treatment for oesophageal dilation and otorhinolaryngological surgery
	<p>Injection in the nasal cavity</p> <ul style="list-style-type: none"> Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, and post-treatment for otorhinolaryngological surgery
	<p>Injection into the paranasal sinus</p> <ul style="list-style-type: none"> Sinusitis/nasal polyps, and post-treatment for otorhinolaryngological surgery
	<p>Injection into the nasal turbinate</p> <ul style="list-style-type: none"> Allergic rhinitis, pollinosis (hay fever), and post-treatment for otorhinolaryngological surgery
	<p>Injection into the nasal polyp</p> <ul style="list-style-type: none"> Sinusitis/nasal polyps
	<p>Injection in the larynx/trachea</p> <ul style="list-style-type: none"> Laryngitis/laryngeal oedema, laryngeal polyp/nodules, and post-treatment for otorhinolaryngological surgery
	<p>Injection in the middle ear cavity</p> <ul style="list-style-type: none"> Acute/chronic otitis media, serous otitis media/eustachian tube stenosis, and post-treatment for otorhinolaryngological surgery
	<p>Injection into the eustachian tube</p> <ul style="list-style-type: none"> Serous otitis media/eustachian tube stenosis
	<p>Injection into the oesophagus</p> <ul style="list-style-type: none"> Oesophagitis (corrosive oesophagitis after endoscopy) and post-treatment for oesophageal dilation and otorhinolaryngological surgery
	<p>Note</p> <p>†This drug should be used only when the patient is not expected to sufficiently respond to topical treatment.</p>

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Tendon rupture: Tendon rupture may occur when this drug is repeatedly injected into the peritendon. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 11 months (April 2011 to February 2015)
 Events related to tendon rupture 9 cases (no fatal cases)
 The number of patients using this drug estimated by MAH: approximately 780 000 (2014)
 Launched in Japan: December 1965

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Right thumb trigger finger	4 mg 17 times in total	Tendon rupture Medical history: tendon rupture of left extensor hallucis longus muscle and bronchial asthma

	(Damage to the flexor tendon of the right thumb) (Fracture nonunion of the left tarsal)		<p>Day 1 of administration Intratendovaginal injection of triamsinolone acetonide was started for the right thumb trigger finger (4 mg/dose). A total of 17 doses were given for approximately 4 years from the start of administration.</p> <p>221 days after the end of administration The patient experienced a sudden pain in the right thumb metacarpal phalangeal (MP) joint on the palm side, and extension of the thumb became difficult. The patient visited the reporting facility. Curving of the long flexor sheath of the right thumb was noted. It was determined to be flexor sheath damage (rupture).</p> <p>232 days after the end of administration The MP joint of the right thumb was fixed during surgery, and an apparatus was created and fitted so that the patient could move the interpharangeal joint.</p> <p>269 days after the end of administration Detachment of the right thumb flexor tendon and reconstruction of the desmogenous peritendon were performed under general anesthesia.</p> <p>273 days after the end of administration Rehabilitation of the right thumb was started. (Apparatus was taken off 1 month after the surgery.)</p> <p>312 days after the end of administration The patient was discharged. After discharge, the patient continued rehabilitation as an outpatient.</p> <p>384 days after the end of administration Damage to the reconstructed peritendon of the right thumb was suspected. The MP joint of the right thumb was fixed with an apparatus again. Rehabilitation was continued.</p> <p>Unknown date The patient rarely needed to wear the apparatus.</p>
Concomitant drugs: none			

4 Pazopanib hydrochloride

Brand name (name of company)	Vorient Tablets 200 mg (GlaxoSmithKline K.K.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Soft tissue sarcoma Radically unresectable or metastatic renal cell carcinoma

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Retinal detachment: Retinal detachment may occur. Patients should be carefully monitored. If any abnormalities such as muscae volitantes, photopsia, visual field defect, or reduced visual acuity are observed, ophthalmologic examinations should be performed, and appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years (from initial marketing to November 2014)

Retinal detachment 2 cases (no fatal cases)
 The number of patients using this drug estimated by MAH:
 approximately 2500 (2014)
 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 50s	Soft tissue cancer (lung metastasis, soft tissue metastasis, chemotherapy)	600 mg for 56 days 800 mg for 14 days 600 mg for 12 days	<p>Retinal detachment, diarrhea, and hypertension</p> <p>Day 1 of administration Administration of pazopanib hydrochloride was started.</p> <p>8 days after the start of administration The patient developed hypertension. Nifedipine and doxazosin were administered for hypertension.</p> <p>15 days after the start of administration The patient developed diarrhea.</p> <p>43 days after the start of administration The hypertension resolved.</p> <p>57 days after the start of administration Dose of pazopanib hydrochloride was changed to 800 mg.</p> <p>Date unknown The patient developed myodesopsia.</p> <p>71 days after the start of administration Dose of pazopanib hydrochloride was changed to 600 mg. The diarrhea resolved.</p> <p>79 days after the start of administration The patient developed (noticed) visual field defect.</p> <p>82 days after the start of administration Administration of pazopanib hydrochloride was discontinued.</p> <p>2 days after the discontinuation The patient's retinal detachment was diagnosed by funduscopy.</p> <p>5 days after the discontinuation The patient underwent surgery.</p> <p>101 days after the discontinuation Retinal detachment: sequelae</p>
Concomitant drug: allopurinol				

5 Panitumumab (genetical recombination)

Brand name (name of company)	Vectibix Intravenous Infusions 100 mg and 400 mg (Takeda Pharmaceutical Company Limited)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	KRAS wild-type, curatively unresectable advanced or recurrent colorectal cancer

PRECAUTIONS (underlined parts are revised)

**Adverse reactions
(clinically significant
adverse reactions)**

Oculomucocutaneous syndrome (Stevens–Johnson syndrome): Oculomucocutaneous syndrome may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference information The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 9 months (April 2011 to December 2014)

Oculomucocutaneous syndrome 2 cases (no fatal cases)
 The number of patients using this drug per year estimated by MAH: approximately 9400 (October 2013 to September 2014)
 Launched in Japan: June 2010

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Rectal cancer, lung metastasis	Dose unknown 1 dose/2 weeks Approximately 1 month	<p>Oculomucocutaneous syndrome (Stevens–Johnson syndrome)</p> <p>History of adverse reactions: None Drinking, smoking, or allergy: No</p> <p>Day 1 of administration Start of intravenous administration of panitumumab and fluorouracil (1 dose/2 weeks). Subsequently, the patient developed systemic dryness and purpura on the lower limbs. The patient was prescribed betamethasone valerate lotion, heparinoid lotion, hydrocortisone butyrate ointment, and betamethasone butyrate propionate ointment, but the symptoms did not improve.</p> <p>Approximately 1 month after the start of administration (date of the last administration) The patient received an intravenous infusion of panitumumab and fluorouracil.</p> <p>1 day after the end of administration The patient developed eyelid oedema, and subsequently, ocular hyperaemia, lip erosion, and scab were noted. Scattered skin eruption was systemically noted, over less than approximately 10% of the body. The patient had severe mucosal symptoms. No fever was noted. The patient was admitted to the dermatological department for medical treatment for the diagnosis of oculomucocutaneous syndrome (Stevens–Johnson syndrome [SJS]).</p> <p>Date unknown Partial cellular necrosis was observed on the epidermis as a result of skin biopsy.</p> <p>22 days after the end of administration The patient received intravenous administration of methylprednisolone 1000 mg for 3 days.</p> <p>25 days after the end of administration Oral administration of prednisolone (PSL) 30 mg/day was started. Skin eruption and dryness gradually receded, and epithelization of erosion was noted.</p> <p>32 days after the end of administration The dose of PSL was reduced to 20 mg/day.</p> <p>37 days after the end of administration The dose of PSL was reduced to 10 mg/day.</p> <p>41 days after the end of administration End of PSL. Outcome of SJS: recovered No recurrence after the end of PSL treatment.</p>
Concomitant drug: fluorouracil				

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 20s	Sigmoid colon cancer (liver metastasis) (lung metastasis)	380 mg for 1 day	<p>Oculomucocutaneous syndrome (Stevens–Johnson syndrome)</p> <p>Day 1 of administration (date of discontinuation) Concomitant administration of irinotecan hydrochloride hydrate and panitumumab (first dose) was started (last administration).</p> <p>6 days after discontinuation The patient phoned to say that skin eruption and nausea (grade unknown) appeared. The patient was advised to treat it with petrolatum and metoclopramide.</p> <p>9 days after discontinuation The skin eruption aggravated (grade unknown).</p> <p>11 days after discontinuation (date of occurrence) The patient developed bleeding of the skin eruption and pyrexia and was admitted to the hospital (as an emergency outpatient). Body temperature was 38.1°C, pulse rate was 101 bpm, and blood pressure was 120/73 mmHg. Skin eruption grade 3 (acneform rash); multiple follicular pustules on the face, neck, front chest, and upper back; partial erythema; delamination of oral mucosa (oral mucositis: grade 3); and erosion of the oral cavity and tongue were observed. The patient was prescribed clindamycin (gel and lotion), minocycline (200 mg/day bid), and bepotastine besilate (20 mg/day bid) by the dermatological department.</p> <p>14 days after discontinuation Although oral symptoms (oral mucositis: grade 2) tended to improve, the skin eruption (grade 3) expanded. Episodes that occurred 11 days after discontinuation of the drug were diagnosed as Stevens–Johnson syndrome. Therefore, the patient was started with treatment by prednisolone (40 mg/day).</p> <p>18 days after discontinuation The skin eruption showed tendency of scabbing (Grade 2) and recovering. Oral erosion was epithelized and improved (oral mucositis: grade 0). The dose of prednisolone was reduced to 35 mg/day.</p> <p>21 days after discontinuation The dose of prednisolone was reduced to 30 mg/day.</p> <p>25 days after discontinuation The dose of prednisolone was reduced to 20 mg/day.</p> <p>28 days after discontinuation The dose of prednisolone was reduced to 10 mg/day.</p> <p>32 days after discontinuation Administration of prednisolone was discontinued.</p> <p>35 days after discontinuation The patient recovered from Stevens–Johnson syndrome. Skin biopsy: not performed</p>
				Concomitant drugs: irinotecan hydrochloride hydrate, white petrolatum, diphenhydramine hydrochloride, palonosetron hydrochloride, dexamethasone sodium phosphate, famotidine, and fosaprepitant meglumine

3

Revision of Precautions (No. 264)

This section presents the details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised as instructed with the Notifications dated March 24 (1) and April 1 (2 and 3), 2015.

1

Sensory organ agents-Ophthalmic agents

Rebamipide (ophthalmic solution)

Brand name	Mucosta ophthalmic suspension UD 2% (Otsuka Pharmaceutical Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	<u>Lacrimal duct obstruction and dacryocystitis: Lacrimal duct obstruction and/or dacryocystitis may occur. Patients should be carefully monitored through ophthalmologic examinations. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted. White matter may be observed in the lacrimal passage of patients with lacrimal duct obstruction and/or dacryocystitis.</u>

2

Antineoplastics-Miscellaneous

Cetuximab (genetical recombination)

Brand name	Erbix Injection 100 mg (Merck Serono Co., Ltd.)
Precautions	Prior to the initiation of treatment for patients with EGFR-positive, incurable, unresectable, advanced, or recurrent colorectal cancer, assess <u>RAS (KRAS and NRAS)</u> mutation status and select suitable patients.

3

Antineoplastics-Miscellaneous

Panitumumab (genetical recombination)

Brand name	Vectibix Intravenous Infusions 100 mg and 400 mg (Takeda Pharmaceutical Co., Ltd.)
Precautions	<u>Prior to the initiation of treatment, assess RAS (KRAS and NRAS) mutation status and select suitable patients.</u>

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 the 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 April 1, 2015)

⊙: Products for which EPPV was initiated after March 2, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
⊙	efraloctocog alfa (genetical recombination) Eloctate Intravenous for Intravenous Injection 250, 500, 750, 1000, 1500, 2000, 3000	Biogen Idec Japan Ltd.	March 9, 2015
	secukinumab (genetical recombination) Cosentyx for S.C. Injection 150 mg Syringe, Cosentyx for S.C. Injection 150 mg	Novartis Pharma K.K.	February 27, 2015
	vonoprazan fumarate Takecab Tablets 10 mg, 20 mg	Takeda Pharmaceutical Company Limited	February 26, 2015
	vemurafenib Zelboraf Tablets 240 mg	Chugai Pharmaceutical Co., Ltd.	February 26, 2015
	rabeprazole sodium Pariet Tablets 5 mg, 10 mg*1	Eisai Co., Ltd.	February 26, 2015
	empagliflozin Jardiance Tablets 10 mg, 25 mg	Nippon Boehringer Ingelheim Co., Ltd.	February 24, 2015
	streptozocin Zanosar IV Infusion 1 g	Nobelpharma Co., Ltd.	February 23, 2015
	fexofenadine hydrochloride Allegra 5% Dry Syrup	Sanofi K.K.	January 19, 2015
	alemtuzumab (genetical recombination) MabCampath 30 mg I.V. Infusion	Sanofi K.K.	January 15, 2015
	sirolimus Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	December 22, 2014
	caspofungin acetate Cancidas for Intravenous Drip Infusion 50 mg, 70 mg*2	MSD K.K.	December 18, 2014
	darbepoetin alfa (genetical recombination) Nesp Injection 5 µg Plastic Syringe, 10 µg Plastic Syringe, 15 µg Plastic Syringe, 20 µg Plastic Syringe, 30 µg Plastic Syringe, 40 µg Plastic Syringe, 60 µg Plastic Syringe, 120 µg Plastic Syringe, and 180 µg Plastic Syringe*3	Kyowa Hakko Kirin Co., Ltd.	December 18, 2014

Nonproprietary name Brand name on		Name of the MAH	Date of EPPV initiate
Midazolam Midafresa Injection 0.1%		Alfresa Pharma Corporation	December 17, 2014
rilpivirine hydrochloride/tenofovir disoproxil fumarate/emtricitabine Complera Combination Tablets		Janssen Pharmaceutical K.K.	December 12, 2014
bosutinib hydrate Bosulif Tablets 100 mg		Pfizer Japan Inc.	December 5, 2014
progesterone Lutinus Vaginal Tablets 100 mg		Ferring Pharmaceuticals Co., Ltd.	December 5, 2014
ripasudil hydrochloride hydrate Glanatec Ophthalmic Solution 0.4%		Kowa Company, Ltd.	December 2, 2014
anhydrous caffeine Respia Injection or oral solution 60 mg		Nobelpharma Co., Ltd.	December 1, 2014
pegfilgrastim (genetical recombination) G-lasta Subcutaneous Injection 3.6 mg		Kyowa Hakko Kirin Co., Ltd.	November 28, 2014
suvorexant Belsomra Tablets 15 mg, 20 mg		MSD K.K.	November 26, 2014
vaniprevir Vanihep Capsules 150 mg		MSD K.K.	November 25, 2014
anagrelide hydrochloride hydrate Agrylin Capsules 0.5 mg		Shire Japan KK	November 25, 2014
tiotropium bromide hydrate Spiriva 2.5 µg Respimat 60 puffs*4		Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2014
aflibercept (genetical recombination) Eylea Solution Intravitreal Injections 40 mg/mL, Eylea Solution Intravitreal Injections Kit 40 mg/mL*5		Bayer Yakuhin, Ltd.	November 18, 2014
Freeze-dried activated human blood coagulation factor VII concentrate containing factor X Byclot for Intravenous Injection		The Chemo-Sero-Therapeutic Research Institute	November 11, 2014
standardized Japanese cedar pollen extract original solution Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL bottle, 2 000 JAU/mL bottle, 2 000 JAU/mL pack		Torii Pharmaceutical Co., Ltd.	October 8, 2014
edoxaban tosilate hydrate Lixiana Tablets 15 mg, 30 mg, 60 mg*6		Daiichi Sankyo Company, Limited	September 26, 2014

*1 An additional indication for “the treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low doses of aspirin”

*2 An additional administration for “pediatrics”

*3 An additional indication for “the treatment of patients with anaemia associated with myelodysplastic syndrome”

*4 An additional indication for “the remission of various symptoms associated with airway obstructive disorder in patients with the following diseases: bronchial asthma (to be used only in patients with severe and persistent disease)”

*5 An additional indication for “the treatment of patients with diabetic macular oedema”

*6 An additional indication for “the reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and the treatment and suppression of relapse for venous thromboembolisms (deep vein thrombosis and pulmonary thromboembolism).” EPPV was initiated in December 8, 2014, for Lixiana 60 mg tablets.

(Reference)

Precautions Concerning Recurrence and Similar Incidents of Medical Accidents

The MHLW and PMDA are currently analyzing information on medical accidents and near-miss events collected as a part of the Project to Collect Medical Near-Miss/Adverse Event Information and the Project to Collect and Analyze Pharmaceutical Near-Miss Events run by the Japan Council for Quality Health Care (JCQHC). The MHLW and PMDA also strive to caution healthcare professionals by issuing notifications on the prevention of medical accidents related to pharmaceuticals and medical devices and by preparing the “PMDA Medical Safety Information.”

However, as a result of recent analysis of cases reported to the JCQHC between January 1 and June 30, 2014, the occurrence of following events that had been cautioned in the notification or “PMDA Medical Safety Information” was confirmed; thus, we urge further caution on the following matters.

Recurrence or similar incidents of events already cautioned in the notification or “PMDA Medical Safety Information” [Pharmaceuticals] (Analysis results of cases reported to the JCQHC between January 1 and June 30, 2014)

No.	Content	No. of cases	Notification or PMDA Medical Safety Information
1	Prescription error of the total weight of the formula and weight of the active ingredient of powders	2	Joint Notification of HPB No. 0129-3 and PFSB No. 0129-5 dated January 29, 2010, “Publication of the Expert Panel Report on Description Method of Oral Prescription Drugs (request for dissemination)” http://www.pmda.go.jp/files/000145210.pdf • The method of the describing details of powders on the prescription is basically described as the weight of the formula contents, and drug name is described as the brand name, and if the weight of the drug substance was exceptionally described, clearly show that it is the [amount of drug substance].
2	Error in the method of administering potassium formula (accidental one-shot intravenous injection)	1	Joint Notification of HPB No. 1204001 and PFSB/SD Notification No. 1204001 dated December 4, 2010 “Strengthening and enforcing preventative measures for medical accidents due to pharmaceuticals with similar brand names (precautions)” http://www.pmda.go.jp/files/000146020.pdf • Potassium formulae are pharmaceuticals that require particular safety control (pharmaceuticals that require caution for cardiac arrest). PMDA Medical Safety Information No. 19 “Administration error of concentrated potassium (K) solutions for injections” http://www.pmda.go.jp/files/000153903.pdf • Recheck the label and administration method of the drug before administration.

3	Accidental ingestion of PTP sheet	1	<p>Joint Notification of HPB/GAD No. 0915-2, PFBSB/GAD Notification No. 0915-5, and PFBSB/SD Notification No. 0915-1 dated September 15, 2010 “Preventative measures for accidental ingestion of PTP sheet (request for precaution and dissemination to medical facilities and pharmacies)” http://www.pmda.go.jp/files/000145758.pdf</p> <ul style="list-style-type: none"> • As precautions for preventing accidental ingestion, (1) do not cut into individual pieces while dispensing, administering, etc., (2) instruct the patients and family (to oversee oral administration for patients who may find administration difficult) on the method of storage and administration, (3) if necessary, confirm the prescribing physician to dispense a one dose package.
4	Mistakenly dispensing methylergometrine maleate and ritodrine hydrochloride	1	<p>PFBSB/SD Notification No. 1008-1, 1008-2, and 1008-3 dated October 8, 2010 “Medical safety measures on error in administration of pharmaceuticals in the area of obstetrics and gynecology (methylergometrine maleate and ritodrine hydrochloride)” http://www.pmda.go.jp/files/000145298.pdf</p> <ul style="list-style-type: none"> • Because there have been repeated reports of incidents where these drugs were mistakenly prepared, the design was changed to a PTP sheet, which considers the visibility.

**Recurrence or similar incidents of events already cautioned in the notification or “PMDA Medical Safety Information” [Medical Devices]
(Analysis results of cases reported to the JCQHC between January 1 and June 30, 2014)**

No.	Content	No. of cases	Notification or PMDA Medical Safety Information
1	Burn from contact with the endoscope tip (heat from the light source)	1	PMDA Medical Safety Information No.33 “Accidental Burns during Surgery” http://www.pmda.go.jp/files/000153041.pdf <ul style="list-style-type: none"> When using a light source with an endoscope or a retractor., do not place the tip of the light source directly on a drape.
2	Burn from loop formation during an MRI examination	1	PMDA Medical Safety Information No. 25 “Precautions for Magnetic Resonance Imaging (MRI) Scans (Part 1)” http://www.pmda.go.jp/files/000153597.pdf <ul style="list-style-type: none"> As precautions to prevent loop formation during MRI, (1) make sure that there is no skin contact in the patients’ arms and legs on positioning, (2) place a cushion or non-conductive pads to prevent contact with the gantry.
3	Burn caused by the ignition of alcoholic antiseptics during electric scalpel use	4	PMDA Medical Safety Information No. 15 (revised) “Precautions in Handling of Electric Scalpels (Part 2)” http://www.pmda.go.jp/files/000204452.pdf <ul style="list-style-type: none"> As a precaution for using alcoholic antiseptics, carefully check that the antiseptic has completely dried. Check whether the product to be used around the electric scalpel is flammable.

[References] (Pharmaceuticals and Medical Devices website)

- 1 MHLW: Survey on the Safe Use of Pharmaceuticals and Medical Devices
<http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000057965.html>
- 2 PMDA: Results of FY 2014 Survey on the Safe Use of Pharmaceuticals, Medical Devices and Regenerative Medical Products
<http://www.pmda.go.jp/safety/info-services/medical-safety-info/0004.html>
- 3 PMDA Medical Safety Information
<http://www.pmda.go.jp/safety/info-services/medical-safety-info/0001.html>