Pharmaceuticals and Medical Devices Safety Information

No. 361 March 2019

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only in Japanese).

Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 361 March 2019

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries

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

If providers of medical care and pharmaceutical products such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse Drug Reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CK	Creatine kinase
CRP	C-reactive protein
CT	Computed tomography
DIMD	Drug-induced muscle disorder
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
GI	Glucose/insulin
HER	Human epidermal growth factor receptor
HLA	Human leucocyte antigen
ILD	Interstitial lung disease
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
NIHS	National Institute of Health Sciences
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
SJS	Stevens-Johnson Syndrome
TEN	Toxic epidermal necrolysis
TLS	Tumour lysis syndrome
WBC	White blood cell

1

Genome Research relating to Drug-induced Muscle Disorders

1. Introduction

Some of adverse drug reactions (ADRs) are idiosyncratic, and not caused by intended pharmacological effects. It is generally difficult to predict the onset of such adverse reactions and they tend to be severe, requiring intensive treatments. The associated genomic information to potentially predict the onset of such ADRs has been reported since around 2004. The MHLW and the National Institute of Health Sciences (NIHS) in order to enable prediction and prevention style safety measures against ADRs based on such genomic information, have been collecting and analyzing genomic samples and clinical information from patients who developed adverse reactions namely rhabdomyolysis (drug-induced muscle disorder [DIMD]), skin disorder (Stevens-Johnson Syndrome [oculomucocutaneous syndrome; SJS] and toxic epidermal necrolysis [TEN]), and interstitial lung disease (ILD). As of December 31, 2018, MHLW and NIHS have accumulated samples on a total of 233 cases of rhabdomyolysis (muscle disorder), 327 cases of skin disorder, and 226 cases of ILD. Analyzed results on SJS and TEN were reported in No. 336 of PMDSI[1)]. This section will introduce the progress overseas and achievements in Japan in the research on DIMD.

2. Drug-induced muscle disorders including rhabdomyolysis

Rhabdomyolysis is a condition where cells in skeletal muscles dissolve or become necrotic, which causes pain or weakness in the muscle. In severe cases, a large amount of myoglobin may be released from the muscle into the bloodstream and injure the renal tubule, subsequently causing acute renal failure[2)]. During this process, levels of serum creatine kinase (CK) which is widely expressed in the skeletal muscles elevate and therefore, they are used as an aid for diagnosis. DIMD is sometimes called myopathy, collectively from milder conditions such as myositis/muscle pain or muscular weakness to rhabdomyolysis. The expert committees of the American College of Cardiology and American Heart Association define the conditions with a statin (HMG-CoA reductase inhibitor) as suspected drug as follows[3)]: Muscle pain; muscle pain or muscle weakness without CK elevation,
Myositis; muscle symptoms with CK elevation,
Rhabdomyolysis; muscle symptoms with creatinine elevation (usually with brown urine and urinal myoglobin elevation) that exhibit marked CK elevation (typically greater than 10 times the upper limit of normal). Corresponding clinical guidelines have been published recently in Japan as well[4)].

Hyperlipidemia agents fibrates, antipsychotic agents, drugs for treatment of Parkinson's disease, and synthetic antibacterials (predominantly new quinolones) are known as potential suspected drugs for these DIMDs besides the above mentioned statins. An investigation conducted in the US reported that muscle pain, myositis, and serious muscle disorders occurred in 2% to 7%, 0.1% to 1%, and 0.08% respectively of patients with statins[2)]. Although the mechanism of its onset is unknown, an involvement of intracellular mitochondrial metabolic abnormality has been suggested[4), 5)] for statins, and risk factors include elderly women, smaller physical frames, Asian ethnicity, renal impairment, and hypothyroidism[4), 6)]. Dehydration, viral infection, and hard exercise are also potential risk factors[2)] in general.

3. Genome research relating to drug-induced muscle disorders

Numerous works on genomic biomarkers have been done so far regarding DIMD. Reports on such works are predominantly with statins as the suspected drug and therefore, this section will focus on muscle disorders induced by statins.

3.1 Results of overseas studies

In a study conducted in Britain for patients administered simvastatin at 80 mg daily, significant association with the development of DIMD was reported for 521T>C (Val174Ala), a functionally defect polymorphism in the *SLCO1B1* gene which encodes OATP1B1, the statin-uptake transporter into hepatocytes[7] based on the analyses of cases with CK elevation greater than 10 times the upper limit of normal and tolerant controls. Compared to the wild-type 521TT group, the homozygous 521CC group showed significant association with an odds ratio of 16.9 (95% CI, 4.7 to 61.1, $P=2x10^{-9}$.) This result was replicated primarily using patients with 40 mg of simvastatin daily. Since the maximum daily dose in Japan is 20 mg, it is unclear whether these results can be directly applied to Japanese patients.

Numerous replication studies have been conducted thereafter with the polymorphism in the *SLCO1B1* gene. Significant association with or trend towards DIMD have been observed in multiple reports[8-10] regarding simvastatin. Whereas no significant association have been observed in other statins such as atorvastatin and pravastatin[8-10]. On the other hand, significant association of DIMD with the polymorphism has been reported in cerivastatin[11], a drug voluntarily withdrawn from the market because of a pronounced increase in the risk of rhabdomyolysis in the US (also voluntarily withdrawn in Japan), which led to numerous patient mortalities. The significant association with the polymorphism found in simvastatin and cerivastatin has been also shown in a recent meta-analysis[12].

Whereas several papers have been published regarding the association of a polymorphism of *GATM* gene which encodes glycine admidinotransferase, a transferase that participates in the synthesis of creatine by transferring a guanidino group to glycines in the mitochondria, reported results have been varying without certain trend.

3.2 Results of analysis in the National Institute of Health Science

Genomic analyses were conducted[13] for 52 cases of DIMD by statins (comprised of cases administered one of 6 types of statins including 20 cases with atorvastatin and 14 cases with pravastatin) as a collaborative study with Kanazawa Medical University hospital and other 7 university hospitals. Results of 2 878 Japanese healthy volunteers were used as the control. Polymorphisms of the *SLCO1B1*, *RYR2*, and *GATM* genes did not show significant associations with DIMD (a weak trend was observed in the *SLCO1B1* polymorphism with an odds ratio of 1.609 [95% CI, 0.999 to 2.591, P=0.067]), whereas *HLA-DRB1*04:06*, a type of human leucocyte antigen (HLA) was significantly associated with DIMD onset (odds ratio of 3.19 [95% CI, 1.53 to 6.66, P=0.045 corrected for multiple comparison].) Although the mechanism for DIMD onset is currently unclear, HLA molecules are involved in the immune responses and thus, the onset of DIMD could be related to an immunological mechanism.

4. Closing Remarks

Current status of genomic analysis associated with rhabdomyolysis (DIMD) and progress of the work currently underway at NIHS has thus far been overviewed as above. Whereas results of such analysis have been published as scientific papers, numbers of Japanese patients studied are still limited and the association with genomic information may depends on the type of statins. In addition, the actual usage and dosage practiced in Japan are different from overseas and thus, it could be difficult to directly apply overseas results to Japanese patients. Because of these issues currently unresolved, immediate use of these results in clinical practice to avoid DIMD is difficult. However, if the usefulness of these results is demonstrated in future validation analysis, this genomic information may become the basis for clinical application.

The NIHS conducts the genomic research in cooperation with Federation of Pharmaceutical Manufacturers' Associations of JAPAN, PMDA, MAHs, health care professionals and patients. The ADRs addressed in this research are rare but can be life-threatening. In addition, given that different factors associated with onset of these ADRs have been identified depending on geographical locations, it is critical to collect information on Japanese cases with these ADRs so as to obtain useful analytical results to predict onset. Healthcare professionals are encouraged to continue cooperation with this research in addition to providing information to the PMDA or MAH of suspected drugs when they encounter patients who develop rhabdomyolysis, skin disorders

(SJS/TEN), or ILD following administration of drugs. Such cooperation is essential in advancing prevention style safety measures through further accumulation of such findings.

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2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated February 12, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Trastuzumab (genetical recombination) and other follow-on biologics

Branded name (name of company)	Herceptin Intravenous Infusion 60, 150, and other follow-on biologics (Chugai Pharmaceutical Co., Ltd., and the others)
Therapeutic category	Antineoplastics-miscellaneous
Indications	HER2-overexpressing breast cancer HER2-overexpressing, advanced/recurrent gastric cancer not amenable to curable resection

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Tumour lysis syndrome:** Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels and renal function, etc. If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g. administration of physiological saline solution and/or hyperuricaemia therapeutics, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms is observed.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 42-month period (April 2015 to September 2018). Cases involving tumour lysis syndrome: 2 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 26 000 Japanese market launch: Herceptin Intravenous Infusion 60: August 2004 Herceptin Intravenous Infusion 150: June 2001

Case summary

No.	Patient		Daily dose/treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Breast cancer (abnormal hepatic function)	8 mg/kg for 1 day ↓ 6 mg/kg once every 3 weeks for 165 days	**Tumour lysis syndrome** Metastases sites: liver, lung, bone, and lymph nodes Recurrent sites: conserved breast (left) Prior treatments for breast cancer: none Day 1 of administration: Administration of trastuzumab and pertuzumab was initiated for the treatment of metastatic and relapsed breast cancer. 1 day after administration: The patient experienced vomiting. The patient stayed out overnight after that. 3 days after administration: The patient returned to the hospital. The patient experienced poor meal ingestion and vomiting on 2 occasions during the stay out, and vomiting on 1 occasion after returning to the hospital. 4 days after administration (day of onset): A prompt shrinkage of tumor was observed after administration of trastuzumab. Transient hyperkalaemia and elevation in liver enzymes were observed in association with this. Tumour lysis syndrome (TLS) occurred. High K (7.0 mmol/L), low Ca (7.3 mg/dL), High P (6.2 mg/dL), and increased Cre (1.21 mg/dL) were observed and treated with glucose/insulin (GI) therapy and diuretics (furosemide and spironolactone) etc. 5 days after administration: Malaise persisted. 7 days after administration: The patient's appetite improved. The deterioration of hepatic function peaked out by 7 days after the administration of trastuzumab. The patient's systemic condition gradually improved. 8 days after administration: GI therapy was terminated. The patient recovered from TLS. 21 days after administration: Administration of the second course of trastuzumab was initiated. TLS did not occur. 25 days after administration: Further shrinkage of tumor was observed following the second administration of trastuzumab. Jaundice and hepatic function were improved in line with the shrinkage. Hepatic function disorder improved to Grade 1. 185 days after administration: Administration of trastuzumab and pertuzumab continued on an outpatient basis.

Laboratory Examination

	18 days before administration	1 day before administration	4 days after administration	4 days after administration	4 days after administration	4 days after administration	6 days after administration	6 days after administration	8 days after administration	10 days after administration	13 days after administration
Ca (mg/dL)	9.0	9.3	7.3	7.3	-	-	-	7.8	7.4	7.5	7.6
Urine bilirubin (qualitative) (-)	(+)	-	-	-	-	-	-	-	-	-	-
AST (GOT) (IU)	154	327	-	370	-	-	370	217	103	64	80
ALT (GPT) (IU)	94	114	-	233	-	-	233	180	132	92	96
LDH (IU)	479	627	-	1 031	-	-	-	1 056	659	578	472
Al-P (IU)	1 321	1 611	-	2 460	-	-	3 013	-	2 901	2 680	2 326
γ-GTP (IU)	574	-	-	471	-	-	560	-	502	454	539
Serum creatinine (mg/dL)	0.68	0.79	1.21	1.13	-	-	-	1.21	1.01	0.78	0.68
Uric acid (mg/dL)	5.1	-	-	-	-	-	-	-	-	-	-
K (mmol/L)	4.1	4.3	7.0	-	6.9	6.4	-	6.8	5.8	5.0	5.8
P (mg/dL)	3.4	3.3	6.2	4.1	-	-	-	6.2	4.3	3.3	2.9
Total bilirubin (mg/dL)	2.5	11.6	-	14.7	-	-	17.9	-	16.0	11.4	7.8
CRP (mg/dL)	2.39	5.11	-	3.05	-	-	-	1.52	0.98	1.55	2.66

Suspected concomitant drug: pertuzumab
Concomitant medications: granisetron hydrochloride, dexamethasone sodium phosphate

2 Nivolumab (genetical recombination)

Branded name (name of company)	Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Malignant melanoma Unresectable advanced or recurrent non-small cell lung cancer Unresectable or metastatic renal cell carcinoma Relapsed or refractory classical Hodgkin lymphoma Relapsed or metastatic head and neck cancer Unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy Unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Serious blood disorder:** Serious blood disorder such as immune thrombocytopenic purpura, haemolytic anaemia, and agranulocytosis 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. **Haemophagocytic syndrome:** Haemophagocytic 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 taken.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 43-month period (April 2015 to October 2018). Cases involving haemophagocytic syndrome: 3 (no patient mortalities), haemolytic anaemia: 3 (no patient mortalities), neutropenia (including agranulocytosis): 12 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 17 000 Japanese market launch: September 2014

Case summary

No.	Patient		Daily dose/treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	Non-small cell lung cancer (metastasis to lymph nodes, metastasis to lung, and smoking history)	3 mg/kg twice every 2 weeks	**Haemophagocytic syndrome, drug eruption, interstitial pneumonia**	
				Day 1 of administration	Administration of nivolumab (3 mg/kg) was initiated for the treatment of unresectable, advanced or relapsed non-small cell lung cancer upon aggravation of tumour (histology: squamous cell carcinoma; treatment site: left upper lobe; stage 4: TNM stage, T3N3M1b [metastasized organs: left lower paratracheal lymph nodes, PUL]; ALK fusion genes, negative; EGFR gene mutations, negative). PS:1
				14 days after administration (day of termination)	The patient received the second dose of nivolumab. A chest computed tomography (CT) examination revealed obvious growth and rapid progress of the tumour after the administration of nivolumab.
				7 days after termination	The patient developed pyrexia of 39°C, malaise, impaired appetite, and decreased blood pressure. PS:3
				10 days after termination	The patient was admitted to the hospital due to severe general malaise and pyrexia of 39°C (the highest body temperature was 40°C). The pyrexia led to a pattern of spiking fever after the admission, and an infection was suspected. Antibiotic and antipyretic (naproxen) were administered. PS decreased. Effects associated with tumour progression was considered. Common bacteria (blood culture) was negative (blood culture was performed twice).
				13 days after termination	The patient was diagnosed with pancytopenia based on decreased white blood cell, hemoglobin, and platelet count compared to at the time of admission. Increased ferritin and drug eruption were observed. The size of the tumour was reduced. Bone marrow aspiration was requested to the department of hematology of the hospital for detailed examination of pancytopenia. [Overall findings] Hypoplastic marrow and cells that were at each maturation stage were confirmed. No increase of blast or atypical cells. Haemophagocytosis was confirmed. [Diagnosis] Hypoplastic marrow and haemophagocytic syndrome The patient developed generalized red rash and erosion like mucositis symptoms in the mouth (enanthema and erosion). Administration of nivolumab was discontinued. Steroid pulse therapy (methylprednisolone sodium succinate, 500 mg/day) and administration of tazobactam sodium/piperacillin sodium (4.5 g 3 times/day) were initiated. A chest CT examination revealed diffuse ground glass opacities in whole lung lobes around dorsal side of both lungs. The patient had a complication of interstitial pneumonia. Antinuclear antibody test was negative.
				14 days after termination	AST/ALT increased. The patient had no subjective symptoms. The patient developed acute interstitial pneumonia. The dosage of methylprednisolone sodium succinate was increased to 1 000 mg/day.
				Date unknown	General symptoms, skin eruption, and laboratory test values improved by the steroid pulse therapy in 24 hours.

				15 days after termination	Administration of tazobactam sodium/piperacillin sodium (4.5 g/3 times/day) was terminated. The dosage of steroid was tapered off from the following day. Administration of prednisolone was initiated (40 mg/day) 26 days after termination of nivolumab.
				Date unknown	Subjective symptoms, pancytopenia, imaging findings were improved. Rash disappeared and oral erosion alleviated. The size of the primary tumour that showed a tendency of rapid growth was reduced.
				31 days after termination	Increased AST/ALT resolved.
				37 days after termination	The dosage of prednisolone was decreased (20 mg/day), and the administration was terminated 43 days after termination of nivolumab.
				90 days after termination	Haemophagocytic syndrome resolved.
				91 days after termination	Acute interstitial pneumonia and drug eruption resolved.

Laboratory Examination

	6 days before administration	1 day before administration	10 days after termination	13 days after termination	14 days after termination	90 days after termination
PLT (10 000/μL)	37.2	33.9	19.0	8.3	8.8	28.6
Hb (g/dL)	11.5	—	10.4	9.6	10.8	11.2
WBC (10 000/μL)	0.617	—	0.420	0.141	0.143	0.997
Ferritin (ng/mL)	—	—	—	6 912.7	3 002.7	113.1

Concomitant medications: codeine phosphate hydrate, brotizolam, pregabalin, sennoside

3 Palbociclib

Branded name (name of company)	Ibrance Capsules 25 mg, 125 mg (Pfizer Japan Inc.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Unresectable or recurrent breast cancer

PRECAUTIONS (revised language is underlined)

Important precautions	Interstitial lung disease may occur. When using this drug, patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. A chest CT scan or serum marker test, etc. should be performed as necessary.
Adverse reactions (clinically significant adverse reactions)	**Interstitial lung disease:** Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration of this drug should be taken.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 44-month period (April 2015 to November 2018). Cases involving interstitial lung disease: 6 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 7 000 Japanese market launch: December 2017

Case summary

No.	Patient		Daily dose/treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Recurrent breast cancer (metastases to lymph nodes)	125 mg for 15 days, 100 mg for 14 days, and 100 mg for 6 days ↓ discontinued	**Interstitial lung disease** Day 1 to Day 15 of administration: Administration of palbociclib was initiated at a dosage of 125 mg/day. Day 36 to Day 49 of administration: The dosage of palbociclib was reduced to 100 mg/day. Day 57 of administration: Salicylamide/acetaminophen/anhydrous caffeine/chlorpheniramine maleate combination product was prescribed to treat cold symptoms (cough, nasal discharge, and pharyngodynia). Administration of palbociclib was resumed at a dosage of 100 mg/day. Day 62 of administration (day of discontinuation): Cough exacerbated and codeine phosphate hydrate was additionally administered. Administration of palbociclib was discontinued. 12 days after discontinuation: A chest computed tomography (CT) examination revealed increased patchy sporadic shadows in the predominantly aerated right lung (upper, middle and lower lobes). The patient was diagnosed with interstitial lung disease based on the findings of the chest CT, and results of KL-6 and SP-D. Administration of prednisolone was initiated at a dosage of 30 mg/day. 19 days after discontinuation: The symptoms such as cough improved and the dosage of prednisolone was reduced to 20 mg/day. 26 days after discontinuation: Cough disappeared. CRP became normal at 0.13 mg/dL. The dosage of prednisolone was reduced to 10 mg/day. 33 days after discontinuation: The dosage of prednisolone was reduced to 5 mg/day. 40 days after discontinuation: Interstitial lung disease remitted. Administration of prednisolone was terminated. A chest CT examination revealed that shadows in the right lung field mostly disappeared.

Laboratory Examination

	4 days before administration	Day of discontinuation	9 days after discontinuation	26 days after discontinuation	40 days after discontinuation	86 days after discontinuation	96 days after discontinuation
Body temperature (°C)		–	35.7	–	–	–	–
CRP (mg/dL)	0.19	–	2.53	0.13	0.14	1.50	–
WBC (cells/mm^3)	6 460	–	5 140	12 540	7 530	8 920	–
Neu (%)	–	–	67.5	70.0	59.2	71.5	–
KL-6 (IU/mL)	–	–	1 960	2 640	–	–	2 110
SP-D (ng/mL)	–	–	196	71.3	–	–	95.0
Influenza A/B	–	Negative	–	–	–	–	–

Concomitant medications: fulvestrant, medroxyprogesterone acetate, digoxin, vildagliptin, glimepiride, magnesium oxide, salicylamide/acetaminophen/anhydrous caffeine/chlorpheniramine maleate combination product, codeine phosphate hydrate

4 Pembrolizumab (genetical recombination)

Branded name (name of company)	Keytruda Injection 20 mg, 100 mg (MSD K.K.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Malignant melanoma Unresectable advanced or recurrent non-small cell lung cancer Relapsed or refractory classical Hodgkin lymphoma Unresectable urothelial carcinoma exhibiting progression after chemotherapy Advanced or recurrent, microsatellite instability-high (MSI-H) solid tumours exhibiting progression after chemotherapy (only when management cannot be achieved with standard therapies)

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Serious blood disorder:** Serious blood disorder such as immune thrombocytopenic purpura, haemolytic anaemia, pure red cell aplasia, and agranulocytosis 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. **Haemophagocytic syndrome:** Haemophagocytic 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 taken.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 43-month period (April 2015 to October 2018). Cases involving haemophagocytic syndrome: 7 (no patient mortalities), neutropenia (including agranulocytosis): 4 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 9 000 Japanese market launch: February 2017

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>1</td><td>Male
70s</td><td>Lung adenocarcinoma (diabetes mellitus, hospitalisation, metastases to liver, and metastases to adrenals)</td><td>200 mg/course once every 3 weeks</td><td>
Haemophagocytic syndrome
Medical history: former smoker
Medication history: carboplatin, pemetrexed
Day 1 of administration (day of termination): The first course of pembrolizumab therapy was initiated (final administration).
9 days after termination: The patient developed pyrexia of over 40°C.
10 days after termination: Administration of prednisolone was initiated at a dosage of 40 mg/day.
11 days after termination: Pyrexia resolved.
13 days after termination: The patient developed hepatic function disorder (the worst grade: 3). The patient experienced diarrhoea and skin eruption. The symptoms improved through methylprednisolone sodium succinate pulse therapy. Administration of prednisolone was maintained at a dosage of 60 mg/day.
Date unknown: The symptoms relapsed after the dosage of prednisolone was reduced to 55 mg/day. Decreased platelets (44 000/μL) and increased ferritin level (11 273 ng/ml) were observed.
45 days after termination (day of onset): Bone marrow aspiration confirmed haemophagocytosis. The patient was diagnosed with haemophagocytic syndrome (the worst grade: 3). Methylprednisolone sodium succinate pulse therapy was initiated.
55 days after termination: The steroid pulse therapy was effective, and platelet count promptly improved.
</td></tr>
</table>

Laboratory Examination

	8 days before administration	1 day before administration	13 days after termination	20 days after termination	45 days after termination	47 days after termination	51 days after termination	55 days after termination	62 days after termination
ALT(U/L)	–	14	41	–	114	–	–	–	40
AST(U/L)	–	30	62	–	126	–	–	–	27
Platelet count (/μL)	–	228 000	–	–	53 000	83 000	127 000	185 000	–
white blood cell count (/μL)	–	6 200	–	–	4 200	10 000	7 100	5 800	–
Anti-DNA antibody (IU/mL)	4.9	–	–	2.7	6.4	–	–	–	–
Antinuclear antibody (fold-increase)	Less than 40-fold	–	–	Less than 40-fold	Less than 40-fold	–	–	–	–
antimitochondrial antibody (fold-increase)	–	–	–	–	20-fold	–	–	–	–

Suspected concomitant drug: vonoprazan fumarate, rebamipide, difenidol hydrochloride
Concomitant medications: ezetimibe

3

Revision of Precautions (No. 301)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated February 12, 2019.

1 Miscellaneous metabolism agents-miscellaneous

Eliglustat tartrate

Branded name

Cerdelga 100 mg capsule (Sanofi K.K.)

Contraindications

Patients at risk of experiencing marked elevation in the plasma concentration of this drug depending on their status as a CYP2D6 metabolizer:

1) Patients who are extensive metabolizers (EMs) of CYP2D6 and who meet any of the following criteria:
   - Patients with moderate or severe hepatic impairment (Child-Pugh class B or C)
   - Patients with mild hepatic impairment (Child-Pugh class A) and who are receiving a moderate or strong CYP2D6 inhibitor
   - Patients with mild hepatic impairment (Child-Pugh class A) and who are receiving a weak CYP2D6 inhibitor concomitantly with a moderate or strong CYP3A inhibitor
   - Patients with normal hepatic function and who are receiving a moderate or strong CYP2D6 inhibitor concomitantly with a moderate or strong CYP3A inhibitor
2) Patients who are intermediate metabolizers (IMs) of CYP2D6 and who meet any of the following criteria:
   - Patients with any degree of hepatic impairment (Child-Pugh class A, B, or C)
   - Patients with normal hepatic function and who are receiving a moderate or strong CYP3A inhibitor
3) Patients who are poor metabolizers (PMs) of CYP2D6 and who meet any of the following criteria:
   - Patients with any degree of hepatic impairment (Child-Pugh class A, B, or C)
   - Patients with normal hepatic function and who are receiving a moderate or strong CYP3A inhibitor

Precautions concerning Dosage and Administration

The CYP2D6 genotype, hepatic function, and concomitant medications of the patient should be confirmed prior to the initiation of this drug. Patient hepatic function and the status of concomitant medications should also be carefully monitored during use of this drug.

For EMs of CYP2D6, the dosage and administration of this drug should be adjusted based on the table below, at 100 mg per dose. This drug should not be administered to patients with moderate to severe hepatic impairment (Child-Pugh class B or C).

Patients with normal hepatic function

		Co-administration of a CYP3A inhibitor [Note)]		
		No co-administration	Weak inhibitor	Moderate or strong inhibitor
Co-administration of a CYP2D6 inhibitor [Note)]	No co-administration	Twice daily	Twice daily	Once daily
	Weak inhibitor	Twice daily	Twice daily	Once daily
	Moderate or strong inhibitor	Once daily	Once daily	Contraindicated

Patients with mild hepatic impairment (Child-Pugh class A)

		Co-administration of a CYP3A inhibitor [Note)]		
		No co-administration	Weak inhibitor	Moderate or strong inhibitor
Co-administration of a CYP2D6 inhibitor [Note)]	No co-administration	Twice daily	Once daily	Once daily
	Weak inhibitor	Once daily	Once daily	Contraindicated
	Moderate or strong inhibitor	Contraindicated	Contraindicated	Contraindicated

For IMs of CYP2D6, the dosage and administration of this drug should be adjusted based on the table below, at 100 mg per dose. This drug should not be administered to patients with hepatic impairment (Child-Pugh class A, B, or C).

Patients with normal hepatic function

		Co-administration of a CYP3A inhibitor [Note)]		
		No co-administration	Weak inhibitor	Moderate or strong inhibitor
Co-administration of a CYP2D6 inhibitor [Note)]	No co-administration	Twice daily	Twice daily	Contraindicated
	Weak inhibitor	Twice daily	Twice daily	Contraindicated
	Moderate or strong inhibitor	Once daily	Once daily	Contraindicated

Administration of this drug should ideally be avoided in PMs of CYP2D6, due to the risk of elevation of the plasma concentration of eliglustat. When determined to be absolutely necessary, this drug should be administered carefully, and generally at a dosage of 100 mg once daily. This drug should not be given to any patient with hepatic impairment (Child-Pugh class A, B, or C) or any patient receiving a moderate or strong CYP3A inhibitor.

Note: Refer to the Interactions section regarding CYP2D6 and CYP3A inhibitors and confirm the applicability of any contraindicated drugs or drugs requiring adjustment of dosage and administration.

Interactions (contraindication for co-administration)	Patients who are EMs of CYP2D6 with mild hepatic impairment (Child-Pugh class A): Moderate or strong CYP2D6 inhibitors Co-administration of a weak CYP2D6 inhibitor and a moderate or strong CYP3A inhibitor Class IA antiarrhythmic agents (quinidine, procainamide, etc.), Class III antiarrhythmic agents (amiodarone, sotalol, etc.), bepridil hydrochloride

2 **Antineoplastics-miscellaneous**

Trastuzumab (genetical recombination) and other follow-on biologics

Branded name	Herceptin Intravenous Infusion 60, 150, and other follow-on biologics (Chugai Pharmaceutical Co., Ltd., and the others)
Adverse reactions (clinically significant adverse reactions)	**Tumour lysis syndrome:** Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels and renal function, etc. If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g. administration of physiological saline solution and/or hyperuricaemia therapeutics, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms is observed.

3 **Antineoplastics-miscellaneous**

Nivolumab (genetical recombination)

Branded name	Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Serious blood disorder:** Serious blood disorder such as immune thrombocytopenic purpura, haemolytic anaemia, and agranulocytosis 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. **Haemophagocytic syndrome:** Haemophagocytic 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 taken.

4 **Antineoplastics-miscellaneous**

Palbociclib

Branded name	Ibrance Capsules 25 mg, 125 mg (Pfizer Japan Inc.)
Important precautions	Interstitial lung disease may occur. When using this drug, patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. A chest CT scan or serum marker test, etc. should be performed as necessary.
Adverse reactions (clinically significant adverse reactions)	**Interstitial lung disease:** Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration of this drug should be taken.

5 **Antineoplastics-miscellaneous**

Pembrolizumab (genetical recombination)

Branded name	Keytruda Injection 20 mg, 100 mg (MSD K.K.)
Adverse reactions (clinically significant adverse reactions)	**Serious blood disorder:** Serious blood disorder such as immune thrombocytopenic purpura, haemolytic anaemia, pure red cell aplasia, and agranulocytosis 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. **Haemophagocytic syndrome:** Haemophagocytic 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 taken.

6 **Antivirals**

Glecaprevir hydrate/pibrentasvir

Branded name	Maviret Combination Tablets (AbbVie GK)
Important precautions	Hepatic impairment and jaundice may occur. Patients should be carefully monitored through methods such as periodic liver function tests.
Adverse reactions (clinically significant adverse reactions)	**Hepatic impairment, jaundice:** Hepatic impairment accompanied with elevation in AST, ALT, or bilirubin levels, and jaundice may occur. If these or any other abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of January 31, 2019)

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Secukinumab (genetical recombination) *1 Cosentyx for s.c. injection 150 mg syringe	Novartis Pharma K.K.	December 21, 2018
Ipragliflozin L–proline *2 Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	December 21 2018
Dolutegravir sodium/rilpivirine hydrochloride Juluca Combination Tablets	Viiv Healthcare K.K.	December 20, 2018
Gilteritinib fumarate Xospata Tablets 40 mg	Astellas Pharma Inc.	December 3, 2018
Abemaciclib Verzenio Tablets 50 mg, 100 mg, 150 mg	Eli Lilly Japan K.K.	November 30, 2018
Dexmedetomidine hydrochloride a. Precedex Intravenous Solution 200 μg [Pfizer], b. Precedex Intravenous Solution 200 μg/50 mL syringe [Pfizer], c. Precedex Intravenous Solution 200 μg [Maruishi], d. Precedex Intravenous Solution 200 μg/50 mL syringe [Maruishi]	a, b Pfizer Japan Inc. c, d Maruishi Pharmaceutical Co., Ltd.	November 29, 2018
Macrogol 4000/sodium chloride/sodium bicarbonate/potassium chloride Movicol Combination Powder	EA Pharma Co., Ltd.	November 29, 2018
Omidenepag isopropyl Eybelis Ophthalmic Solution 0.002%	Santen Pharmaceutical Co., Ltd.	November 27, 2018
Vibegron Beova Tablets 50 mg	Kyorin Pharmaceutical Co.,Ltd.	November 27, 2018
Blinatumomab (genetical recombination) Blincyto I.V. Infusion 35 μg	Amgen Astellas BiPharma K.K.	November 27, 2018
Lorlatinib Lorbrena Tablets 25 mg, 100 mg	Pfizer Japan Inc.	November 20, 2018
Icatibant acetate Firazyr subcutaneous injection 30 mg syringe	Shire Japan KK	November 20, 2018
Vedolizumab (genetical recombination) Entyvio for I.V. Infusion 300 mg	Takeda Pharmaceutical Company Limited.	November 7, 2018

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Nonacog beta pegol (genetical recombination) Refixia I.V. Injection 500, 1000, 2000	Novo Nordisk Pharma Ltd.	November 1, 2018
Levonorgestrel/ethinylestradiol Jemina Tablets	Nobelpharma Co., Ltd.	October 4, 2018
Spiramycin Spiramycin 1.5M IU Tablets [Sanofi]	Sanofi K.K.	September 25, 2018
Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate Odefsey Combination Tablets	Janssen Pharmaceutical K.K.	September 20, 2018
Fidaxomicin Dafclir Tablets 200 mg	Astellas Pharma Inc.	September 18, 2018
Obinutuzumab (genetical recombination) Gazyva Intravenous Infusion 1000 mg	Chugai Pharmaceutical Co., Ltd.	August 29, 2018
Durvalumab (genetical recombination) Imfinzi Injection 120 mg, 500 mg	AstraZeneca K.K.	August 29, 2018
Ipilimumab (genetical recombination) *3 Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	August 21, 2018
Nivolumab (genetical recombination) *4 Opdivo I.V. Infusion 20 mg, 100 mg, 240 mg	Ono Pharmaceutical Co., Ltd.	August 21, 2018
Tedizolid phosphate Sivextro Tablets 200 mg, Sivextro for iv infusion 200 mg	Bayer Yakuhin, Ltd.	August 21, 2018
Condoliase Hernicore 1.25 Units for Intradiscal Inj.	Seikagaku Corporation	August 1, 2018

*1 Ankylosing spondylitis that does not adequately respond to existing treatments

*2 Type 1 diabetes mellitus

*3 Radically unresectable or metastatic renal cell carcinoma

*4 Radically unresectable or metastatic renal cell carcinoma