Pharmaceuticals and Medical Devices Safety Information

No. 368 November 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 (https://www.mhlw.go.jp, only in Japanese).

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

Register here

Published by
Ministry of Health, Labour and Welfare

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Pharmaceuticals and Medical Devices Safety Information

No. 368 November 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
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
JSHP	the Japanese Society of Hospital Pharmacists
Plt (10 000/μL)	Platelet
WBC (/μL)	White blood cell
Hb (g/dL)	Hemoglobin
RBC	Red blood cell
UIBC	Unsaturated iron binding capacity
HAE	Hereditary angioedema

1
Initiative of Revision of the Manuals for Management of Various Serious Adverse Drug Reactions (Part 3)

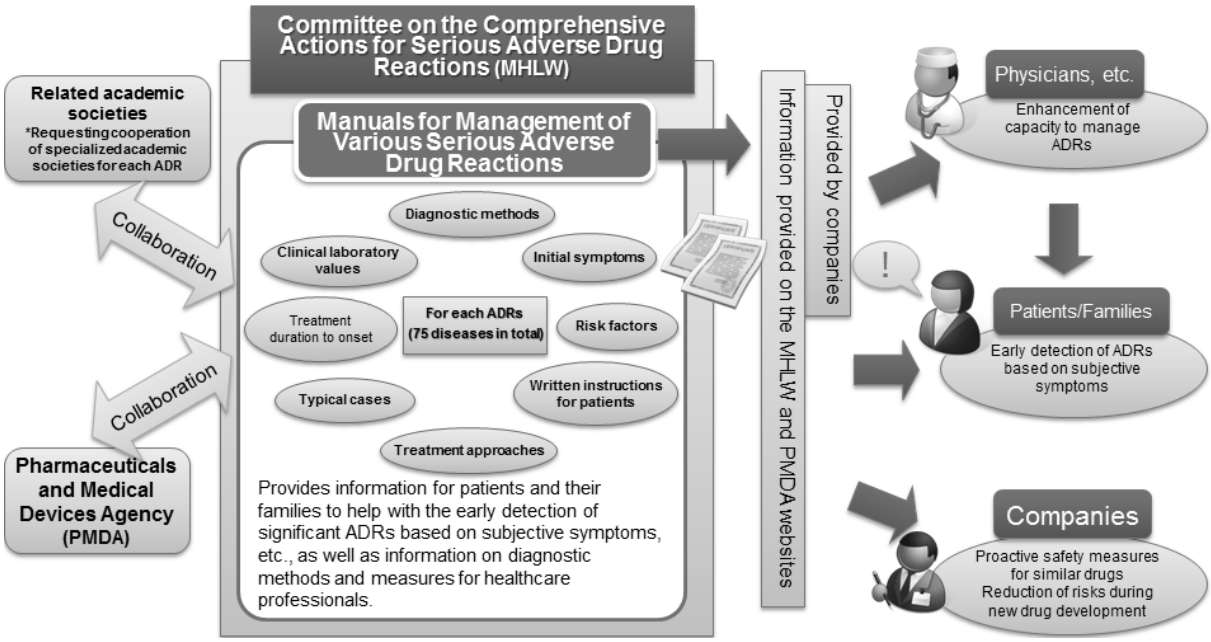
1. Revision of the Manuals for Management of Various Serious Adverse Drug Reactions

The Manuals for Management of Various Serious Adverse Drug Reactions were compiled from FY 2005 to FY 2010 by the committee on the comprehensive actions for serious adverse drug reactions (ADRs) who reviewed and compiled the drafts prepared by manual preparation committees organized in related academic societies through discussion with the Japanese Society of Hospital Pharmacists (JSHP) as entrusted by the MHLW. The drafts were prepared with reference to academic papers, various guidelines, health and labour sciences research project reports, PMDA health and welfare service reports, etc. At present, the manuals are available for a total of 75 diseases.

Since FY 2016, we have been working on the revision of the manuals based on the latest knowledge[i].

Revision of the Manuals for the Management of Various Serious Adverse Drug Reactions

The Manuals for the Management of Various Serious Adverse Drug Reactions prepared between FY 2005 and 2010 (a total of 75 diseases) will be revised/updated based on the recent knowledge to contribute to early detection and early management of ADRs in clinical settings, etc. (Manuals will be prioritized for review through a 5-year period from FY2016.)



2. Progress of Revision

In FY 2019, we completed drafting the revisions of the following manuals. The revision drafts were reported and discussed at the meeting of the Committee on the Comprehensive Actions for Serious Adverse Drug Reactions held on July 18, 2019 and the compiled final versions were published in September 2019.

Manuals revised in FY 2019

Author	Manual title	Category
The Japan Society of Hepatology	Drug-induced liver injury	Revision
The Japanese Respiratory Society	Interstitial pneumonia	Revision
The Japanese Circulation Society	Congestive cardiac failure	Revision
The Japanese Society of Child Neurology	Pediatric acute encephalopathy	Revision
Japanese Society of Allergology	Anaphylaxis	Revision
	Vascular oedema (not induced by non-steroidal anti-inflammatory agents) *the 2 manuals for Vascular oedema and Pharyngeal oedema integrated	Revision
	Urticaria/vascular oedema induced by non-steroidal anti-inflammatory agents	Revision
Japanese Ophthalmological Society	Retinal/visual pathway disorder	Revision
	Glaucoma	Revision
	Corneal opacity	Revision
Japan Society of Clinical Oncology Japanese Dermatological Association Japanese Society of Pharmaceutical Oncology	Hand and foot syndrome	Revision

An outline of revisions in each field is provided below:

(1) Hepatology

In the field of hepatology, the “Drug-induced liver injury” manual was revised.

Considering the significant shift in the trend of drug-induced liver injury driven by the recent market launch of new drugs such as molecular targeted drugs, biological preparations, and immune check point inhibitors, case examples for these drugs were added. The revision in this field was inclusive in that health foods and supplements were also mentioned regarded as important causes for liver injury.

In addition, sections for special types of liver injury were newly added considering the importance of liver injuries mediated by the hepatitis B reactivated by anti-cancer drugs etc., in addition to those directly induced by drugs.

(2) Respiratory medicine

In the field of respiratory medicine, the “Interstitial pneumonia” manual was revised.

In line with the “Drug-induced liver injury” manual, new drugs recently launched were such as immune check point inhibitors also reflected in the revision in this field.

Causative agents were tabulated with new additions, and frequencies of adverse reactions in Japan were presented specific to drugs along with clinical disease patterns representative of such adverse reactions and drugs on which such disease patterns are prone to occur.

Cases specific to adverse reactions to representative drugs were also described.

An explicit statement was added that the Japanese are more likely to develop drug-induced liver injury, as well as figures easy to understand in the information to patients and in the description of treatment approaches for healthcare professionals.

(3) Cardiovascular medicine

In the field of cardiovascular medicine, the “Congestive cardiac failure” manual was revised.

Following the revision of the Guidelines for the Diagnosis and Treatment of Acute/chronic Cardiac Failure in 2017, sections related to the onset mechanism and diagnosis were revised in accordance with the latest guidelines.

The revision also added chemotherapy drugs to the presumed causative drugs in response to the increase of cardiovascular disorders in cancer patients associated with chemotherapy, with molecular-targeting drugs specifically among others.

(4) Neuro-musculoskeletal field

In the neuro- musculoskeletal field, the “Pediatric acute encephalopathy” manual was revised. A clear definition of acute encephalopathy specific to the consciousness level was added to the section intended for medical professionals in line with the guidelines developed in 2016. The recently increased findings that antibiotics having a pivoxil group may cause acute encephalopathy depending on the risk factors on the part of patients was also reflected in the revision.

(5) Hyper sensitivity

In the field of hyper sensitivity, the “Anaphylaxis”, “Vascular oedema”, and “Urticaria/vascular oedema induced by non-steroidal anti-inflammatory agents” manuals were revised.

The revision of the “Anaphylaxis” manual added language reflecting the guidelines launched in 2014. Specifically, instructions for use an EpiPen and illustrated diagnostic criteria for anaphylaxis were added for patients and medical professionals, respectively. The importance of initial responses with respect to the early detection and early responses was also added for medical professionals. Mechanisms of 4 types of allergies were stated based on the description of the World Allergy Organization (WAO). Figures and pictures were updated as well.

The “Vascular oedema (not induced by non-steroidal anti-inflammatory agents)” manual was revised according to the classification in the 2018 guidelines. DPP-4 inhibitors, TNF-α inhibitors, and others were newly added as presumed causative drugs. The algorism introduced in the international guidelines was incorporated in the diagnosis of hereditary angioedema (HAE). Icatibant which was approved in 2017 for the indication was added for the treatment of HAE.

Wording and figures were modified in the “Urticaria/vascular oedema induced by non-steroidal anti-inflammatory agents” manual.

(6) Sensory organ (ophthalmology)

In the sensory organ (ophthalmology) field, the “Retinal/visual pathway disorder”, “Glaucoma”, and “Cornel opacity” manuals were revised.

Language concerning the requirement for monitoring with visual field tests was added related to the retinal disorder with scarce ocular fundus findings associated with vigabatrin or Sabril, an anti-infantile spasms drug. The necessity of monitoring was also noted for hydroxychloroquine, a newly approved drug for systemic lupus erythematodes. Retinal disorder associated with cardiac glycosides (digoxin etc.) was also described.

For the “Glaucoma” manual, an antiepileptic drug (topiramate) and drugs with anticholinergic effect were added to the section for causative drugs and risks.

In the “Corneal opacity” manual, Rho kinase inhibitors and anticancer agents were added as causative ophthalmic solution and as oral medicine, respectively. Corneal opacity associated with amantadine was also added. Amantadine is a drug to improve mental activities and to treat Parkinson's syndrome which is also used for Type A influenza viral infection.

(7) Cancer

In the field of cancer, the “Hand and foot syndrome” manual was revised. Following the emergence of numerous tyrosin kinase inhibitors over nearly 10 years since the launch of the manual, revision was made to reflect the characteristics of tyrosin kinase inhibitors.

The patient guidance, the key to the early responses, was updated for better understanding.

(8) Others (common to all fields)

Following the example of the manuals revised the previous fiscal year, descriptions related to the Relief System for Adverse Drug Reaction were also added. Explanations about relief for sufferers of ADRs were added at the end of the section “About this manual” at the beginning of each manual, and the manuals also provide the number of relief benefits in the past 5 years under the Relief System for Adverse Drug Reactions and information concerning the Relief System for Adverse Drug Reactions at the end of each manual.

We continue to revise manuals in FY 2019. Please also make good use of the manuals listed on the websites of MHLW and PMDA[ii]

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[i] Previous articles introducing the Initiative of Revision of the Manuals for Management of Various Serious Adverse Drug Reactions

1. Pharmaceuticals and Medical Devices Safety Information No. 348 (http://www.pmda.go.jp/files/000221054.pdf)
2. Pharmaceuticals and Medical Devices Safety Information No. 357 (http://www.pmda.go.jp/files/000226311.pdf)

[ii] MHLW website “Manuals for Management of Various Serious ADRs” (for healthcare professionals) https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html (only in Japanese)
PMDA website “Manuals for Management of Various Serious ADRs” (for healthcare professionals) http://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html (only in Japanese)

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated October 29, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Vonoprazan fumarate

Branded name (name of company)	Takecab Tablets 10 mg., 20 mg. (Takeda Pharmaceutical Company Limited.)
Therapeutic category	Peptic ulcer agents
Indications	Treatment of gastric ulcer, duodenal ulcer, reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration Adjunct therapy to *Helicobacter pylori* eradication in the following: Gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early-stage gastric cancer, or *Helicobacter pylori* gastritis

PRECAUTIONS (revised language is underlined)

[Under old instructions] **ADVERSE REACTIONS (Clinically Significant Adverse Reactions) (newly added)**	Pancytopenia, agranulocytosis, leukopenia, or 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 taken.
[Under new instructions] **11. ADVERSE REACTIONS** **11.1 Clinically Significant Adverse Reactions) (newly added)**	Pancytopenia, agranulocytosis, leukopenia, and thrombocytopenia
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 22-month period (September 2017 to June 2019) Cases involving thrombocytopenia: 2 (no patient mortalities) Cases involving agranulocytosis, leukopenia: 4 (no patient mortalities) Cases involving pancytopenia: 2 (no patient mortalities): 2 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 6 600 000 Japanese market launch: February 2015

Case summary 1 (pancytopenia)

No.	Patient: Sex/ age	Patient: Indication for use (Complication)	Daily dose and administration duration	Adverse reaction: Clinical course and treatment provided
1	Female 80s	Gastrooesophageal reflux disease (hypertension, osteoporosis, asthma, gastrointestinal motility disorder, emphysema, pneumonia, dehydration, chronic obstruction lung disease, hypertonic bladder, abdominal discomfort, chronic bronchitis, dizziness)	20 mg 7 days ↓ Discontinuation	**Pancytopenia** Medical history, predisposition etc.: the patient introduced home use oxygen therapy for chronic respiratory failure and has been visiting as outpatient since then. 11 days before administration: The patient admitted to the hospital with pneumonia. 4 days before administration: The patient was discharged from the hospital. Date unknown: The patient had suffered dizziness, nausea, poor appetite since hospital discharge. Day 1 of administration: Oral administration of vonoprazan fumarate 20 mg started as outpatient. Day 2 of administration: The patient was admitted again with dehydration and positional dizziness. Vonoprazan fumarate was continued as inpatient. Day 4 of administration: Urticaria (drug eruption) emerged over the trunk and limb and olopatadine hydrochloride (10 mg/day) was administered. Plt declined to 8.3 (10 000/μL) (pancytopenia). Day 7 of administration (Day of discontinuation): Drug-induced pancytopenia was suspected and vonoprazan fumarate was discontinued after the dosing on the previous day. 1 day after discontinuation: Plt declined to 6.4 (10 000/μL), WBC to 2 700 (/μL), Hb to 9.0 (g/dL). Drug eruption was unresolved. 4 days after discontinuation: Plt recovered to 9.0 (10 000/μL), WBC to 3 300 (/μL), Hb to 8.4 (g/dL). 8 days after discontinuation: Pancytopenia recovered. 11 days after discontinuation: The patient was discharged from the hospital. Day 12 of discontinuation: Plt was 13.4 (10 000/μL), WBC 3 700 (/μL), Hb 9.1 (g/dL).

Laboratory test values

	4 days before admin.	Day 1 of admin.	Day 2 of admin,	Day 4 of admin.	Day 5 of admin.	1 day after discon.	4 day after discon.	8 day after discon.	12 day after discon
Plt (10 000/μL)	29.6	18.9	14.9	8.3	8.3	6.4	9.0	12.2	13.4
WBC (/μL)	6 400	5 200	4 100	3 900	4 000	2 700	3 300	3 800	3 700
Hb (g/dL)	11.0	10.7	10.8	10.5	10.3	9.0	8.4	8.5	9.1

Suspected concomitant drugs: none
Concomitant drugs: Mosapride citrate hydrate, fudosteine, telmisartan/hydrochlorothiazide combination tablets, eldecalcitol, solifenacin succinate, theophylline, furosemide, adenosine triphosphate disodium hydrate, Sennoside Tablets, celecoxib, metoclopramide, levofloxacin hydrate

Case summary 2 (agranulocytosis, leukopenia)

No.	Patient		Daily dose and administration duration	Adverse reaction
	Sex/ age	Indication for use (Complication)		Clinical course and treatment provided
2	Male 70s	Gastrooesophageal reflux disease (Iron deficiency anaemia)	20 mg 5 days ↓ Discontinuation	**Neutropenia** Medical history: none Approximately 2 weeks before administration: The patient became aware of his anorexia. 7 days before administration: The patient visited Medical institution A. Anemia was noted. 1 day before administration: The patient was referred to Institution B by Institution A for detailed examination to be diagnosed with iron deficiency anaemia based on the blood tests. WBC was 5 700, RBC 325, Hb 6.8, Ht 23.2, neutrophil counts 4 700/μL, Fe 6, UIBC 33.6, ferritin 10.7. Day 1 of administration: Esophagogastroduodenoscopy was performed and esophageal hiatal hernia and GERD (LA-D) was diagnosed. Vonoprazan fumarate (20 mg/day) and ferrous fumarate (100 mg/day) were prescribed. Day 5 of administration (Day of discontinuation): The patient had chills and pyrexia and was transported by ambulance to Medical Institution C. WBC was 700, RBC 246, Hb 5.5, Ht 17.9, Plt 17.1, neutrophil count 100/μL. Neutropenia was acknowledged. The patient was diagnosed with right pneumonia based on the CT scan and admitted to the general internal medicine department at Institution C. After the dosing on this day, vonoprazan fumarate was discontinued. Date unknown: Right pneumonia was recovering with antibiotic treatment. Day 13 of administration: Neutropenia recovered, with WBC 3700, Hb 9.5, neutrophil counts 2400/μL. 16 days after discontinuation: Right pneumonia recovered. The patient was discharged from Institution C.

Laboratory test values

	1 day before admn.	Day 5 of admin.	13 days after discontinuation	23 days after discontinuation
WBC	5 700	700	3 700	4 800
Neutrophil (/μL)	4 700	100	2 400	2 700
Eosinophil	0	0	100	80
Basophil	0	0	100	-
Lymphocyte	410	200	800	-
Monocyte	570	400	400	-
RBC	325	246	-	410
Hb	6.8	5.5	9.5	10.4
Ht	23.2	17.9	-	33.9
Plt	14.2	17.1	23.3	20.9

Suspected concomitant drugs: none
Concomitant drugs: ferrous fumarate

Case summary 3 (thrombocytopenia)

No.	Patient		Daily dose and administration duration	Adverse reaction
	Sex/ age	Indication for use (Complication)		Clinical course and treatment provided
3	Male 80s	Gastric ulcer (chronic renal disease, Type 2 diabetes mellitus, benign prostatic hypertrophy, diarrhea, liver disorder, insomnia, edema)	20 mg 20 days ↓ Discontinuation	**Thrombocytopenia** Medical history: none 9 days before administration: Plt was 10.4 (10 000/μL) Day 1 of administration: The patient was switched to vonoprazan fumarate at Institution B from famotidine (40 mg/day, morning and evening) prescribed at Institution A. Plt was 13.3 (10 000/μL). DAY 14 of administration: Plt declined to 5.3 (10 000/μL) (thrombocytopenia) Day 20 of administration (Day of discontinuation): Vonoprazan fumarate was discontinued after the dosing on this day. 1 day after discontinuation: Plt was 2.0 (10 000/μL). 5 day after discontinuation: Plt was 1.8 (10 000/μL). Platelet transfusion was performed (20 units). 12 day after discontinuation: Plt was 5.0 (10 000/μL). 16 day after discontinuation: Plt was 7.1 (10 000/μL). 19 day after discontinuation: Plt increased to 8.8 (10 000/μL). The patient recovered.

Laboratory test values

	9 days before admin.	Day 1 of admin.	Day 8 of admin.	Day 14 of admin.	Day 15 of admin.	1 day after discon.	5 day after discon.	12 day after discon.	16 day after discon.	19days after discon.
Plt (10 000/μL)	10.4	13.3	8.4	5.3	5.4	2.0	1.8	5.0	7.1	8.8

Suspected concomitant drugs: none

Concomitant drugs: Tamsulosin hydrochloride, sitagliptin phosphate hydrate, ursodeoxycholic acid, triazolam, furosemide

3

Revision of Precautions (No.308)

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 October 29, 2019.

1 Peptic ulcer agents
Vonoprazan fumarate

Branded name	Takecab Tablets 10 mg, 20 mg (Takeda Pharmaceutical Company Limited.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	Pancytopenia, agranulocytosis, leukopenia, or 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 taken.
[Under New instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions <common to all indications> (newly added)	Pancytopenia, agranulocytosis, leukopenia, and thrombocytopenia

2 Urinary organ agents
D-Sorbitol (urologic irrigating solution)

Branded name	UromaticS urologic irrigating solution 3% (Baxter Limited)
[Under Old instructions]	
Contraindications (newly added)	Patients with *hereditary fructose intolerance

*Hereditary fructose intolerance is very rare in Japan. Only 5 cases from 3 families have been reported to date (For hereditary fructose intolerance, please refer to PMDSI 362.)

3 Miscellaneous metabolism agents-miscellaneous
Belimumab (genetical recombination)

Branded name	Benlysta for I.V. infusion 120 mg, 400 mg, Benlysta for S.C. injection 200 mg auto-injector, 200 mg syringe (Glaxo Smith Kline K.K.)
[Under Old instructions]	
Important Precautions (newly added)	Depression, suicidal ideation, or suicide attempt may occur. Patients and their families or other caregivers should be fully informed of the risk of these events and instructed to contact the attending physician immediately if any changes occur in the psychiatric status of patients such as insomnia or anxiety.
Adverse Reactions (Clinically Significant Adverse Reactions)	**Depression, suicidal ideation, and suicide attempt**: Depression, suicidal ideation, and suicide attempt may occur. Patients should be closely monitored and appropriate measures such as discontinuing

(newly added)	this drug should be taken if any abnormalities are observed.

4 Antibiotics-miscellaneous

[1] Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
[2] Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Branded name	[1] Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited.) [2] Vonopion Pack (Takeda Pharmaceutical Company Limited.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	Pancytopenia, agranulocytosis, leukopenia, or 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 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 31 October, 2019)

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

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Quizartinib hydrochloride Vanflyta Tablets 17.7 mg, 26.5 mg	Daiichi Sankyo Co., Ltd.	October 10, 2019
	Insulin degludec (genetical recombination)/liraglutide (genetical recombination) Xultophy combination Injection FlexTouch	Novo Nordisk Pharma Ltd.	September 26, 2019
	Belimumab (genetical recombination) Benlysta for I.V. infusion 120 mg, 400 mg	Glaxo Smith Kline K.K.	September 20, 2019
	Apremilast*1 Otezla Tablets 10 mg, 20 mg, 30 mg	Celgene K.K.	September 20, 2019
	Desmopressin acetate hydrate*2 Minirinmelt OD Tablets 25 μg, 50 μg	Ferring Pharmaceuticals Co., Ltd.	September 20, 2019
	Azithromycin hydrate Azimycin Ophthalmic Solution 1%	Senju Pharmaceutical Co., Ltd.	September 11, 2019
	Blonanserin Lonasen Tape 20 mg, 30 mg, 40 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 10, 2019
	Patisiran sodium Onpattro infusion 2 mg/mL	Alnylam Pharmaceuticals, Inc.	September 9, 2019
	Glycopyrronium bromide/formoterol fumarate hydrate Bevespi Aerosphere 28 inhalations	AstraZeneca K.K.	September 4, 2019
	Budesonide/glycopyrronium bromide/formoterol fumarate hydrate Breztri Aerosphere 56 inhalations	AstraZeneca K.K.	September 4, 2019
	Entrectinib Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	September 4, 2019
	Defibrotide sodium Defitelio Injection 200 mg	Nippon Shinyaku Co., Ltd.	September 4, 2019
	Ravulizumab (genetical recombination) Ultomiris Intravenous Infusion 300 mg	Alexion Pharmaceuticals, Inc.	September 4, 2019

	pH4-treated normal human immunoglobulin Privigen 10% I.V. Drip Infusion 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	CSL Behring K.K.	August 19, 2019
	Freeze-dried inactivated tissue culture rabies vaccine Rabipur for intramuscular injection	Glaxo Smith Kline K.K.	July 26, 2019
	Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate Symtuza Combination Tablets	Janssen Pharmaceutical K.K.	July 26, 2019
	Peficitinib hydrobromide Smyraf Tablets 50 mg, 100 mg	Astellas Pharma Inc.	July 10, 2019
	Ceftolozane sulfate/tazobactam sodium Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	June 25, 2019
	Guanfacine hydrochloride*3 Intuitive Tablets 1 mg, 3 mg	Shionogi & Co., Ltd.	June 18, 2019
	Romiplostim (genetical recombination)*4 Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Inc	June 18, 2019
	Tocilizumab (genetical recombination)*5 Actemra Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	June 12, 2019
	Sodium selenite Aselend Injection 100 μg	Fujimoto Pharmaceutical Corporation	June 6, 2019
	Apalutamide Erleada Tablets 60 mg	Janssen Pharmaceutical K.K.	May 30, 2019
	Thiotepa Rethio Intravenous Infusion 100 mg	Sumitomo Dainippon Pharma Co., Ltd.	May 28, 2019
	Risankizumab (genetical recombination) Skyrizi Subcutaneous Injection 75 mg Syringe 0.83 mL	AbbVie GK	May 24, 2019
	Fluticasone furoate/vilanterol trifenatate/umeclidinium bromide Trelegy 100 Ellipta 14 doses, 30 doses	Glaxo Smith Kline K.K.	May 22, 2019
	Esaxerenone Minnebro Tablets 1.25 mg, 2.5 mg, 5 mg	Daiichi Sankyo Co., Ltd.	May 13, 2019

*1 Oral ulcers associated with Behçet's disease with inadequate response to local therapies

*2 Nocturia due to nocturnal polyuria in males

*3 Attention deficit/hyperactivity disorder (AD/HD) in adult patients

*4 Aplastic anemia inadequately controlled with existing therapies

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