

Pharmaceuticals and Medical Devices Safety Information

No. 288 February 2012

rev.1*

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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) website (<http://www.pmda.go.jp/english/index.html>) and on the MHLW website (<http://www.mhlw.go.jp/>), only available in Japanese language).

Published by
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

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This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

*Correction to the list in “4. List of Products Subject to Early Post-marketing Phase Vigilance.”

Pharmaceuticals and Medical Devices Safety Information No. 288 February 2012

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	Systemic Allergy Associated with the Use of Quasi-drugs/Cosmetics	C	Cases of food-dependent exercise-induced allergies associated with transdermal or transmucosal sensitization to wheat after using quasi-drugs/cosmetics containing hydrolyzed wheat powder have been reported. In these cases, the patients developed anaphylaxis triggered by exercises after eating flour-containing foods. Case summaries of food-dependent exercise-induced allergy as well as its safety measures and diagnostic criteria provided by the Japanese Society of Allergology are presented. A planned study to investigate the details of reported cases is also introduced.	5
2	Important Safety Information	P C	Daikenchuto: Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated January 10, 2012, the contents of important revisions and case summaries that served as the basis for these revisions will be provided in this section.	10
3	Revision of Precautions (No. 233)		Galsulfase (Genetical Recombination) (and 13 others)	12
4	List of Products Subject to Early Post-marketing Phase Vigilance		Lists products subject to Early Post-marketing Phase Vigilance as of February 1, 2012.	16

D: Distribution of Dear Healthcare Professional Letters P: Revision of Precautions C: Case Reports

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the “PMDA medi-navi” a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.

See our website for details of the service. → <http://www.info.pmda.go.jp/info/idx-push.html>

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

ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BALF	Bronchoalveolar lavage fluid
CAP-RAST	Capsulated hydrophilic carrier polymer-radioallergosorbent test
CD	Cluster of differentiation
CRP	C-reactive protein
CT	Computed tomography
ELISA	enzyme-linked immunosorbent assay
EPPV	Early Post-marketing Phase Vigilance
ECG	Electrocardiogram
FAQ	Frequently asked questions
FY	Fiscal year
HCO ₃	Bicarbonate
HJ	Hugh-Jones
IgE	Immunoglobulin E
IU	International unit
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
PaCO ₂	Arterial carbon dioxide partial pressure
PaO ₂	Arterial oxygen partial pressure
SP-D	Surfactant protein D
TEN	Toxic epidermal necrolysis
Ua	Unit allergen
WBC	White blood cell count
WDEIA	Wheat-dependent exercise-induced anaphylaxis
γ-GTP	gamma-glutamyl transpeptidase

Systemic Allergy Associated with the Use of Quasi-drugs/Cosmetics

1. Introduction

In September 2010, cases of systemic allergy in users of a soap bar containing hydrolyzed wheat powder were reported from medical institutions. The cases of systemic allergy were published in October 2010 to raise an alert.¹⁾ The reported food allergy with systemic symptoms, which may be due to transdermal or transmucosal sensitization following the use of quasi-drug/cosmetics, was almost completely unknown to healthcare professionals. There are few diagnostic criteria and limited information on the clinical course available. There are concerns about health hazards including aggravation of symptoms due to continuous use of the offending quasi-drug/cosmetic without knowing that is the allergen and failure to seek appropriate treatment.

A survey on the cases of systemic allergy associated with the use of quasi-drugs/cosmetics containing hydrolyzed wheat powder will start as a project of Health and Labour Sciences Research. Summaries of reported cases, relevant safety measures, and information provided by the Japanese Society of Allergology are presented. Healthcare professionals are encouraged to report similar allergy cases and to cooperate with the survey.

2. Reported cases and safety measures

The reported systemic allergy cases involved users of a soap bar containing hydrolyzed wheat powder. These cases are characterized as anaphylaxis triggered by exercise after eating flour-containing food such as pasta or bread. The allergy is called food-dependent exercise-induced allergy. In some cases, allergies were triggered by mild exercise such as walking and shopping. Unlike in the usual well-known wheat-containing food allergy, characteristic symptoms such as eyelid and face oedema have been reported in many cases.

The cases are presented below.

Case 1

Age, sex	Medical history	Clinical course and therapeutic measures	
30s Female	Perennial rhinitis, cedar pollinosis, alder pollinosis, oral allergy to apple	Approximately 2 years ago	The patient had used a soap bar containing hydrolyzed wheat powder, and around this time she had itching in the face and around the mouth and eyes. She visited a nearby hospital and was diagnosed with atopic dermatitis. The symptoms did not improve despite the prescribed tacrolimus and steroid ointment. The patient consulted other dermatologists and ophthalmologists; however, the symptoms still did not improve. The symptoms worsened especially after taking a bath. The symptoms gradually worsened over the years.
		Day of onset	The patient started to have a symptom of severe rhinitis after taking a bath. She had itching of the eyes, swelling of eyelids and the periorbital area, and redness and swelling in the face on the way home from her workplace (details unknown).

	Approximately 2 months later	After having ramen noodles and beer and walking for 5 minutes, the patient's eyes started to itch. She subsequently had redness and swelling of eyelids, the periorbital area, and palms and generalised redness and itching.
	Approximately 3 months later	After eating bread and playing tennis for 15 minutes, itching of the eyes started followed by redness and swelling of eyelids, face, and palms, and generalised redness and wheals. The patient subsequently had decreased blood pressure, abdominal pain, and diarrhoea. She was admitted to the hospital with anaphylaxis.
	Approximately 4 months later	Wheals in the face and swelling of eyelids started after taking a bath. The patient had itching of the eyes, swelling of eyelids, and generalised redness and wheals after eating pasta and cake followed by walking.
	Approximately half a year later	The patient was diagnosed with wheat allergy and referred to a hospital. A food challenge test was performed. [Test results] Serum total IgE, 440 IU/mL <Capsulated hydrophilic carrier polymer-radioallergosorbent test (CAP-RAST)> Wheat, 14.20 Ua/mL (class 3); gluten, 15.40 Ua/mL (class 3) <Prick test; wheal diameter> The soap, 3 mm; 0.3% hydrolyzed wheat, 12 mm <Food challenge test> The patient underwent an exercise test after eating bread while she was admitted to the hospital. Anaphylaxis with initial itching of the eyes and swelling of the eyelids was induced. [Diagnosis] <ul style="list-style-type: none"> • Contact urticaria associated with hydrolyzed wheat contained in the soap bar and allergic conjunctivitis • Wheat-dependent exercise-induced anaphylaxis (WDEIA) Based on the suspected WDEIA due to sensitization to hydrolyzed wheat contained in the soap bar, exercise after eating wheat products and use of the soap bar was prohibited. All symptoms such as swelling of eyelids and itching of the face after washing the face disappeared. It is unknown whether the WDEIA has been remitted.

Case 2

Age, sex	Medical history	Clinical course and therapeutic measures	
30s Female	Perennial rhinitis	Approximately 2 years ago	The patient had been using a soap bar containing hydrolyzed wheat powder. She continued using the soap bar despite itchy skin and wheals developing after washing her face.
		Day of onset	The patient had itching of the palms, angioedema around the eyes, nasal congestion, generalised redness and wheals, and abdominal pain after eating bread followed by riding a bicycle for 5 to 6 minutes. After that, the patient had anaphylaxis every time she exercised after eating wheat products.
		Approximately 8 months ago	The patient visited the hospital for a detailed examination. [Test results] Serum total IgE, 220 IU/mL <CAP-RAST> Wheat, 2.58 Ua/mL (class 2); gluten, 4.48 Ua/mL (class 3) <Prick test; wheal diameter>

		<p>The soap, 3 mm; 0.3% hydrolyzed wheat, 9 mm; wheat, 0 mm; bread, 0 mm; histamine (10 mg/mL), 3 mm</p> <p>[Diagnosis]</p> <ul style="list-style-type: none"> • Wheat-dependent exercise induced anaphylaxis (WDEIA) • Contact urticaria induced by hydrolyzed wheat <p>The diagnosis was made based on the medical history, prick test, and CAP-RAST.</p> <p>Use of the soap bar and exercise after eating wheat products were prohibited.</p>
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Case 3

Age, sex	Medical history	Clinical course and therapeutic measures	
20s Female	Atopic dermatitis since childhood; current skin eruption; no childhood food allergy	Approximately 2 years ago	The patient started using a soap bar containing hydrolyzed wheat powder. She always had skin eruptions on the face due to atopic dermatitis. Mild itching occurred after using the soap bar (the cause is unknown due to the underlying atopic dermatitis).
		Day of onset	The patient had generalised urticaria followed by decreased blood pressure after eating spaghetti carbonara followed by walking. She had carefully avoided wheat products after being diagnosed with wheat-dependent exercise-induced anaphylaxis (WDEIA) at another hospital.
		Approximately 10 months ago	The patient walked for 15 minutes after eating sakura-mochi (japanese sweets)(she later found the food contained wheat). She subsequently had geographical wheals over her entire body.
		Approximately 11 months ago	<p>The patient visited the hospital for a food challenge test.</p> <p>[Test results] Serum total IgE, 1690 IU/mL <CAP-RAST> Wheat, 30.90 Ua/mL (class 4); gluten, 44.30 Ua/mL (class 4) <Prick test; wheal diameter></p> <p>The soap, 5 mm; 0.3% hydrolyzed wheat, 18 mm; wheat, 10 mm; bread, 16 mm; histamine (10 mg/mL), 5 mm</p> <p><Food challenge test></p> <p>The patient started coughing and sneezing immediately after eating 10 g of dinner roll. Generalized wheals developed 1 hour and 20 minutes later but were remitted with adrenaline.</p> <p>[Diagnosis]</p> <ul style="list-style-type: none"> • Wheat anaphylaxis <p>Use of the soap bar and eating any wheat products were prohibited.</p> <p>No symptoms have appeared since.</p>

Most reported cases of systemic allergy involved users of “Cha no Shizuku” soap (YUUKA FACE SOAP/OCHA FACE SOAP, hereinafter referred to as “Cha no Shizuku” soap) manufactured and distributed by Yuuka Co., Ltd. and Phoenix Co., Ltd. (only the old product sold before December 7, 2010; the current product does not contain hydrolyzed wheat powder). The reported allergy was presumably associated with transdermal or transmucosal sensitization to the specific hydrolyzed wheat powder Glupearl 19S contained in the soap bar. Similar cases have been reported in users of other products containing Glupearl 19S (Savon embellir, Savon embellir noir [Cosme Naturals, Limited], and Honey Cleansing Soap [Phoenix Co., Ltd.]). The marketing authorization holders (MAHs) have voluntarily recalled the quasi-drugs and cosmetics containing Glupearl 19S, which are listed on the

MHLW website.²⁾

Hydrolyzed wheat powder is the dried powder of a water-soluble component obtained by hydrolysis of wheat seed (Japanese Standard of Quasi-drug Ingredients 2006) and contained in many quasi-drugs and cosmetics. The wheat powder includes many types of products having different molecular weight, composition, and composition ratio depending on the hydrolysis process. A study is ongoing to identify which types of hydrolyzed wheat powder are likely to cause transdermal/transmucosal sensitization.

3. Information from the Japanese Society of Allergology

Information concerning wheat allergy associated with the use of soap bars containing Glupearl 19S provided in the Rheumatism & Allergy Information Center website³⁾ includes “FAQs (for general consumers),”⁴⁾ “Definition of the disorder and diagnostic guidelines (for healthcare professionals),”⁵⁾ and “List of institutions offering treatment for wheat allergy associated with the use of “Cha no Shizuku” soap.”⁶⁾ “Diagnostic criteria for immediate wheat allergy to the hydrolyzed wheat (Glupearl 19S) contained in “Cha no Shizuku” soap and some other products”⁷⁾ have been published by the Special Committee for the Safety of Protein Hydrolysates in Cosmetics of the Japanese Society of Allergology (See below).

Diagnostic criteria for immediate wheat allergy to the hydrolyzed wheat (Glupearl 19S)
contained in “Cha no Shizuku” soap and some other products

(Prepared by the Special Committee for the Safety of Protein Hydrolysates
in Cosmetics on October 11, 2011)

[Definitive diagnosis]

Satisfying all of the following criteria:

1. Having used “Cha no Shizuku” soap or other products containing hydrolyzed wheat (Glupearl 19S)
2. Having had at least one of the following symptoms:
 - 2-1) Itching, eyelid oedema, nasal discharge and/or wheals within several to 30 minutes after using “Cha no Shizuku” soap or other products containing hydrolyzed wheat (Glupearl 19S)
 - 2-2) General symptoms such as itching, wheals, eyelid oedema, nasal discharge, dyspnoea, nausea, vomiting, abdominal pain, diarrhoea, and decreased blood pressure within 4 hours after eating wheat products
3. Having been tested positive in at least one of the following tests:
 - 3-1) Prick test using $\leq 0.1\%$ Glupearl 19S solution
 - 3-2) Immunoassay^{Note)} such as Dot Blot, Enzyme-Linked Immunosorbent Assay (ELISA), and Western Blot to identify specific IgE antibody to Glupearl 19S in the blood
 - 3-3) Basophil activation test using Glupearl 19S as the antigen

[Exclusion criterion]

4. Tested negative in a prick test using 0.1% Glupearl 19S solution

[Suspected cases]

Satisfying Criteria 1 and 2 but not 3

- * Wheat allergy is strongly suspected if sensitization to wheat or gluten is shown in a specific IgE antibody test or a prick test but there is no hypersensitivity to $\omega 5$ gliadin or milder hypersensitivity to $\omega 5$ gliadin compared with that to wheat and gluten.

Note) Contact “the Special Committee for the Safety of Protein Hydrolysates in Cosmetics of the Japanese Society of Allergology” for immunoassay-based diagnosis. The amount of serum required for the assay is 0.5 mL.
See the diagnostic criteria⁷⁾ on the Japanese Society of Allergology website for contact information.

Note that the [Exclusion criterion], “Tested negative in a prick test using 0.1% Glupearl 19S solution,” is applied for the current allergic condition but not for past conditions because sensitivity may become lower as the patient is not exposed to Glupearl 19S by stopping use of the soap bar.

4. Reporting of serious health hazards associated with quasi-drugs/cosmetics to the MHLW

This time, reports from healthcare professionals allowed MHLW to investigate the cases of systemic allergy in users of certain quasi-drugs/cosmetics and take safety measures.

If occurrence or spread of public health hazards is suspected, healthcare professionals are encouraged to promptly report health hazards associated with quasi-drugs/cosmetics to MHLW using the form for the “Drugs and Medical Devices Safety Information Reporting System,” as with the case of health hazards associated with drugs and medical devices. The reporting form is available on the PMDA website (<http://www.info.pmda.go.jp/info/houkoku.html>).

5. Request for cooperation in the survey

Sufficient data on food-dependent, exercise-induced allergies after using quasi-drugs/cosmetics are not currently available since few relevant cases have been reported. Collection of detailed systemic allergy cases will be important to prevent future cases, establish diagnostic criteria, and understand the typical clinical course. Accordingly, a detailed survey on cases of systemic allergy associated with soap bars containing hydrolyzed wheat powder is planned as a project of Health and Labour Sciences Research. Your cooperation in the survey is requested. The survey information will be posted on the MHLW website once the survey has been initiated.

<References>

- 1) <http://www.mhlw.go.jp/bunya/iyakuhin/cyanoshizuku/> (only available in Japanese language)
- 2) <http://www.mhlw.go.jp/bunya/iyakuhin/cyanoshizuku/dl/06.pdf> (only available in Japanese language)
- 3) <http://www.allergy.go.jp/allergy/flour/index.html> (only available in Japanese language)
- 4) <http://www.allergy.go.jp/allergy/flour/001.html> (only available in Japanese language)
- 5) <http://www.allergy.go.jp/allergy/flour/002.html> (only available in Japanese language)
- 6) <http://www.allergy.go.jp/allergy/flour/003.html> (only available in Japanese language)
- 7) http://www.jsaweb.jp/modules/news_topics/index.php?page=article&storyid=114 (only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated January 10, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Daikenchuto

Brand Name (name of company)	TSUMURA Daikenchuto Extract Granules for Ethical Use (Tsumura & Co.) Kotaro Daikenchuto Extract Fine Granule (Kotaro Pharmaceutical Co., Ltd.)
Therapeutic Category	Traditional Chinese medicines
Indications	(TSUMURA Daikenchuto Extract Granules for Ethical Use) Abdominal cold feeling and pain accompanied by abdominal distension. (Kotaro Daikenchuto Extract Fine Granule) Flaccidity of the abdominal wall and stomach/intestines, abdominal cold feeling, vomiting or abdominal distension, and substantial abdominal pain with increased bowel peristalsis. Gastroptosis, gastric atony, atonic diarrhoea, atonic constipation, chronic peritonitis, abdominal pain.

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: If cough, dyspnoea, pyrexia, or abnormal chest sounds are observed, administration of this drug should be discontinued, and examinations, including chest X-ray and chest CT scan, should be performed immediately.
Appropriate measures, including administration of corticosteroids, should also be taken.

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 (April 1, 2008 to November 1, 2011)

- Interstitial pneumonia: 1 case (no fatal case)

The number of patients using this drug per year estimated by MAHs: approximately 332,300 (FY 2010).

Launched in Japan: October 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Constipation (none)	7.5 g for 73 days	Interstitial pneumonia Day 1 of administration: The patients started receiving daikenchuto for treatment of constipation. Day 69 of administration: Pyrexia and hypoxaemia developed, and the chest X-ray showed diffuse opacities in both lungs. Administration of

				<p>sublactam sodium/ampicillin sodium for injection was started at another department.</p> <p>Day 73 of administration (day of discontinuation): Administration of antibiotics was started but no improvement was seen, and the patient visited the reporting physician's department. The chest CT showed diffuse ground-glass opacities.</p> <p>Administration of daikenchuto was discontinued.</p> <p>3 days after discontinuation: Pulse therapy with methylprednisolone 1 g was performed for 3 days.</p> <p>The patient's respiratory condition improved and the chest X-ray showed improvement of the shadows.</p>
Concomitant medications: sennoside, clonazepam, sodium picosulfate hydrate, haloperidol, lansoprazole, silodosin, bethanechol chloride, distigmine bromide, torasemide, ambroxol hydrochloride				

Clinical Symptoms

	Day 69 of administration	Day 73 of administration (day of discontinuation)	3 days after discontinuation	5 days after discontinuation	9 days after discontinuation
Pyrexia	Moderate	Moderate	Severe	No	No
Sputum	No	No	No	No	No
Cough	Mild	Mild	Mild	No	No
Shortness of breath (Hugh-Jones [HJ] classification)	II	III	III	II	II

Laboratory Examination

	Day 69 of administration	Day 73 of administration (day of discontinuation)	9 days after discontinuation	16 days after discontinuation
WBC (/mm ³)	7000	7600	9200	6500
LDH (IU/L)	181	-	190	184
CRP (mg/dL)	5.85	7.32	1.03	2.27
KL-6 (U/mL)	-	1170	1600	1580
SP-D (ng/mL)	-	260	382	208

Bronchoalveolar Lavage Fluid (BALF) Findings

	1 day after discontinuation
Total cell count ($\times 10^5$ /mL)	4.6
Macrophage (%)	22
Lymphocytes (%)	73
Neutrophils (%)	4
Eosinophils (%)	1
CD4/CD8 ratio	9.67

Blood Gas Test

	1 day after discontinuation	6 days after discontinuation
pH	7.482	7.491
PaO ₂ (torr)	56.0	80.0
PaCO ₂ (torr)	34.0	33.1
HCO ₃ ⁻ (mEq/L)	24.9	24.7

3

Revision of Precautions (No. 233)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated January 10, 2012 (excluding those presented in “2. Important Safety Information” of this Bulletin).

1

Enzyme preparations

Galsulfase (Genetical Recombination)

Brand Name	Naglazyme Intravenous Drip Infusion 5 mg (Angeles MG, Inc.)
Adverse Reactions (clinically significant adverse reactions)	<u>Nephrotic syndrome (membranous nephropathy, etc.):</u> As a reaction mediated by <u>immune complexes, nephrotic syndrome (membranous nephropathy, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken. Risks and benefits should be considered when administration of this drug is continued or resumed.</u>

2

Psychotropics

Aripiprazole

Brand Name	ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1% (Otsuka Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	<u>Hepatic dysfunction:</u> <u>Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), γ-GTP, and Al-P may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.</u>

3

Psychotropics

Haloperidol (injectable dosage form)

Brand Name	Serenace Injection 5 mg (Dainippon Sumitomo Pharma Co., Ltd.) and the others
Important Precautions	<u>Ventricular fibrillation, ventricular tachycardia (including torsades de pointes), prolonged QT, etc. may occur, resulting in cardiac arrest in some cases. Caution should be exercised by monitoring of vital signs such as electrocardiogram (ECG) and respiratory conditions especially when this drug is intravenously injected.</u>
Adverse Reactions (clinically significant adverse reactions)	<u>Ventricular fibrillation, ventricular tachycardia:</u> Ventricular fibrillation, ventricular tachycardia (including torsades de pointes), prolonged QT, <u>etc. may occur, resulting in cardiac arrest in some cases.</u> Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as dose reduction and discontinuing administration should be taken.

4

Genital organ agents

Chloramphenicol (preparations for vaginal application)

Brand Name CHLOMY VAGINAL TABLETS 100 mg (Daiichi-Sankyo Company, Limited) and the others

Adverse Reactions (clinically significant adverse reactions) Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored, and if abnormalities including dyspnoea, rash, decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

5

Anticoagulants

Enoxaparin Sodium

Brand Name Clexane 2000IU S.C. Inj. Kit. (sanofi-aventis K.K.)

Adverse Reactions (clinically significant adverse reactions) Hepatic dysfunction, jaundice: Hepatic dysfunction with elevations of AST (GOT) and ALT (GPT), or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

6

Antidiabetic agents

Acarbose

Brand Name Glucobay Tablet 50, 100, Glucobay OD Tablet 50, 100 (Bayer Yakuhin, Ltd.) and the others

Adverse Reactions (clinically significant adverse reactions) Intestinal obstruction: Abdominal distension, flatulence, increased flatus, etc. may occur, and intestinal obstruction due to increased air in intestines, etc. may occur. Patients should be carefully monitored, and if symptoms including persistent abdominal pain or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

7

Antidiabetic agents

**Voglibose
Mitiglinide Calcium Hydrate/Voglibose**

Brand Name BASEN Tablets 0.2, 0.3, BASEN OD Tablets 0.2, 0.3 (Takeda Pharmaceutical Company Limited) and the others
GLUBES Combination Tab. (Kissei Pharmaceutical Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions) Intestinal obstruction: Abdominal distension, flatulence, increased flatus, etc. may occur, and intestinal obstruction due to increased air in intestines, etc. may occur. Patients should be carefully monitored, and if symptoms including persistent abdominal pain or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

8

Antidiabetic agents

Miglitol

Brand Name SEIBULE Tab. 25 mg, 50 mg, 75 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions) Intestinal obstruction: Abdominal distension, flatulence, increased flatus, etc. may occur, and intestinal obstruction due to increased air in intestines, etc. may occur.

adverse reactions) Patients should be carefully monitored, and if symptoms including persistent abdominal pain or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

9

Miscellaneous metabolism agents-Miscellaneous

Tacrolimus Hydrate (oral and injectable dosage forms)

Brand Name Graceptor Capsules 0.5 mg, 1 mg, 5 mg, Prograf Capsules 0.5 mg, 1 mg, 5 mg, Prograf Granules 0.2 mg, 1 mg, Prograf Injection 2 mg, 5 mg (Astellas Pharma Inc.)

Adverse Reactions (clinically significant adverse reactions) **Pancytopenia, thrombocytopenic purpura, agranulocytosis, haemolytic anaemia, pure red cell aplasia:** Pancytopenia, thrombocytopenic purpura, agranulocytosis, haemolytic anaemia, and pure red cell aplasia may occur. Patients should be carefully monitored through periodic tests, and if any abnormalities are observed, appropriate measures such as dose reduction and drug suspension should be taken.

Hepatic dysfunction, jaundice: Hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), γ -GTP, Al-P, and LDH, or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as dose reduction and drug suspension should be taken.

10

Antineoplastics-Miscellaneous

Lenalidomide Hydrate

Brand Name Revlimid Capsules 5 mg (Celgene K.K.)

Other Precautions The results of 3 overseas clinical trials conducted in treatment-naïve patients with multiple myeloma showed the higher incidence of malignant tumors in the groups treated with this drug as compared to the control groups. In the group treated with this drug, malignant tumors such as acute myeloid leukaemia, myelodysplastic syndrome, B-cell malignant tumors, and solid cancers occurred. In the results of 2 overseas clinical studies conducted in patients with relapsed or refractory multiple myeloma showed the higher incidence of malignant tumors in the groups treated with this drug as compared to the control groups. In the group treated with this drug, malignant tumors such as basal cell carcinomas, spinocellular carcinomas, and solid cancers occurred.

11

Kampo medicines

Saireito

Brand Name TSUMURA Saireito Extract Granules for Ethical Use (Tsumura & Co.) and the others

Adverse Reactions (clinically significant adverse reactions) **Fulminant hepatitis, hepatic dysfunction, jaundice:** Fulminant hepatitis, hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), Al-P, and γ -GTP, etc. or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

12

Synthetic antibacterials

Sitafloxacin Hydrate

Brand Name GRACEVIT TABLETS 50 mg, GRACEVIT FINE GRANULES 10% (Daiichi-Sankyo Company, Limited)

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

Anaphylactoid symptoms: Anaphylactoid symptoms may occur. Patients should be carefully monitored, and if abnormalities including dyspnoea, skin eruption, and angioedema are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

**Clinically significant
adverse reactions
(similar drug)**

Prolonged QT, ventricular tachycardia (including torsades de pointes)

13

Antivirals

Lopinavir/Ritonavir

Brand Name

KALETRA Combination Tablets, KALETRA Combination Oral Solution
(Abbott Japan Co., Ltd.)

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

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome, and erythema multiforme may occur.

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Over-the-counter drugs

Daikenchuto

Brand Name

JPS Kampo Granule 30 (JPS Pharmaceutical Co., Ltd.)

Consultation

If the following symptoms are observed after taking this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician, pharmacist, or registered salesperson for a consultation.

The following serious symptoms occur in rare cases. In such a case, immediately seek medical aid.

Interstitial pneumonia: Shortness of breath or difficulty in breathing when climbing the stairs or during light exertion, dry cough, pyrexia, etc. may occur suddenly or persist.

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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 Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of the drug in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of February 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Buprenorphine NORSPAN TAPE 5 mg, 10 mg, 20 mg	Mundipharma K.K.	August 4, 2011
Escitalopram Oxalate LEXAPRO Tab. 10mg	Mochida Pharmaceutical Co., Ltd.	August 22, 2011
Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (Yeast Origin) GARDASIL Aqueous Suspension for Intramuscular Injection, GARDASIL Aqueous Suspension for Intramuscular Injection Syringe	MSD K.K.	August 26, 2011
Pancrelipase LipaCreon Granules 300 mg Sachet, LipaCreon Capsules 150 mg	Abbott Japan Co., Ltd.	August 30, 2011
Levobupivacaine Hydrochloride POPSCAINE 0.5% inj. 50 mg/10 mL, POPSCAINE 0.5% inj. syringe 50 mg/10 mL	Maruishi Pharmaceutical Co., Ltd.	September 7, 2011
Vorinostat ZOLINZA Capsules 100 mg	MSD K.K.	September 14, 2011
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg	AstraZeneca K.K.	September 15, 2011
Landiolol Hydrochloride COREBETA for Intravenous 12.5 mg	Ono Pharmaceutical Co., Ltd.	September 15, 2011
Linagliptin Trazenta Tablets 5 mg	Nippon Boehringer Ingelheim Co., Ltd.	September 15, 2011
Golimumab (Genetical Recombination) Simponi Subcutaneous Injection Syringe 50 mg	Janssen Pharmaceutical K.K.	September 16, 2011
Minodronic Acid Hydrate Bonoteo Tablets 50 mg	Astellas Pharma Inc.	September 16, 2011
Minodronic Acid Hydrate RECALBON Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	September 16, 2011
Mirabegron Betanis Tablets 25 mg, 50 mg	Astellas Pharma Inc.	September 16, 2011

Alogliptin Benzoate/Pioglitazone Hydrochloride LIOVEL Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	September 20, 2011
Indacaterol Maleate onbrez inhalation capsules 150 µg	Novartis Pharma K.K.	September 20, 2011
Daptomycin CUBICIN IV 350 mg	MSD K.K.	September 22, 2011
Itraconazole ITRIZOLE Oral Solution 1%* ¹	Janssen Pharmaceutical K.K.	September 26, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 µg, 180 µg* ²	Chugai Pharmaceutical Co., Ltd.	September 26, 2011
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion* ³	Chugai Pharmaceutical Co., Ltd.	September 26, 2011
Olopatadine Hydrochloride ALLELOCK Granules 0.5%* ⁴	Kyowa Hakko Kirin Co., Ltd.	November 15, 2011
Live Attenuated Human Rotavirus Vaccine, Oral Rotarix Oral Solution	GlaxoSmithKline K.K.	November 21, 2011
Imiquimod BESELNA CREAM 5%* ⁵	Mochida Pharmaceutical Co., Ltd.	November 25, 2011
Teriparatide Acetate Teribone Inj. 56.5 µg	Asahi Kasei Pharma Corporation	November 25, 2011
Fulvestrant FASLODEX intramuscular injection 250 mg	AstraZeneca K.K.	November 25, 2011
Modafinil MODIODAL Tablets 100 mg* ⁶	Alfresa Pharma Corporation	November 25, 2011
Telaprevir TELAVIC Tablets 250 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride IMUSERA Capsules 0.5 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride GILENYA Capsules 0.5 mg	Novartis Pharma K.K.	November 28, 2011
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg	Pfizer Japan Inc.	December 7, 2011
Canakinumab (Genetical Recombination) ILARIS for s.c. injection 150 mg	Novartis Pharma K.K.	December 7, 2011
Fosaprepitant Meglumine PROEMEND for Intravenous Infusion 150 mg	Ono Pharmaceutical Co., Ltd.	December 9, 2011
Everolimus AFINITOR tablets 5 mg* ⁷	Novartis Pharma K.K.	December 22, 2011
Everolimus Certican Tablets 0.25 mg, 0.5 mg, 0.75 mg* ⁸	Novartis Pharma K.K.	December 22, 2011
Pranlukast Hydrate ONON drysyrup 10%* ⁹	Ono Pharmaceutical Co., Ltd.	December 22, 2011
Peginterferon Alfa-2b (Genetical Recombination) PEGINTRON Powder for Injection 50 µg/0.5 mL, 100 µg/0.5 mL, 150 µg/0.5 mL* ¹⁰	MSD K.K.	December 22, 2011
Ribavirin REBETOL Capsules 200 mg* ¹¹	MSD K.K.	December 22, 2011

Rebamipide Mucosta ophthalmic suspension UD 2%	Otsuka Pharmaceutical Co., Ltd.	January 5, 2012
Human Fibrinogen/Thrombin Fraction TachoSil Tissue Sealing sheet	CSL Behring K.K.	January 17, 2012
Fosphenytoin Sodium Hydrate Fostoin 750 mg for Injection	Nobelpharma Co., Ltd.	January 17, 2012
Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, 24 mg* ¹²	Otsuka Pharmaceutical Co., Ltd.	January 18, 2012

- *1 Additional indications for “treatment of patients with fungal infection caused by *Aspergillus*, *Cryptococcus*, *Blastomyces*, or *Histoplasma* (fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, blastomycosis, histoplasmosis)”, “treatment of patients with febrile neutropenia of suspected fungal infection”, and “prophylaxis of deep mycosis in patients with haematological malignancy possibly associated with neutropenia or patients who underwent hematopoietic stem cell transplantation”
- *2 An additional indication for “improvement of viraemia in chronic active hepatitis B
- *3 An additional indication for “treatment of patients with inoperable or recurrent breast cancer”
- *4 An additional administration for “pediatrics (aged 2 to under age of 7)”
- *5 An additional indication for “treatment of patients with actinic keratosis (limited to face or baldness)”
- *6 An additional indication for “treatment of excessive daytime sleepiness in patients with obstructive sleep apnoea syndrome who receive treatment for airway obstruction with continuous positive airway pressure (CPAP) therapy, etc.”
- *7 An additional indication for “treatment of patients with pancreatic neuroendocrine tumour”
- *8 An additional indication for “prophylaxis rejection in renal transplantation”
- *9 An additional indication for “treatment of patients with allergic rhinitis”
- *10 An additional indication for “improvement of viraemia in compensated cirrhosis C in combination therapy with ribavirin”
- *11 An additional indication for “improvement of viraemia in compensated cirrhosis C in combination therapy with peginterferon alfa-2b (genetical recombination)”
- *12 An additional indication for “improvement of manic symptoms in patients with bipolar disorder”