Pharmaceuticals and Medical Devices Safety Information

No. 279 May 2011

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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).

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Pharmaceuticals and Medical Devices Safety Information

No. 279 May 2011

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

[Outline of Information]

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

ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
Anti-AchR	Anti-acetylcholine receptor
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BiPAP	Bilevel positive airway pressure
BUN	Blood urea nitrogen
CD4	Cluster of differentiation 4
CHDF	Continuous hemodiafiltration
CK (CPK)	Creatine kinase (Creatine phosphokinase)
Cl	Chloride
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computed tomography
CY	Cyclophosphamide
ECG	Electrocardiogram
EPPV	Early Post-marketing Phase Vigilance
FLAIR	Fluid-attenuated inversion recovery
FN	Febrile neutropenia
FY	Fiscal year
GVHD	Graft-versus-host disease
HBs	Hepatitis B surface
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HIV	Human immunodeficiency virus
HIV-1 RNA	Human immunodeficiency virus type 1 ribonucleic acid
HLA	Human leukocyte antigen
HLGT	High level Group Term
HR	Heart rate
ICU	Intensive care unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IPSS	International Prognostic Scoring System
IU	International unit
JDIIP	Japan Drug Information Institute in Pregnancy
K	Potassium
KIR	Killer immunoglobulin-like receptor
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MRI	Magnetic resonance imaging

Na	Sodium
NCCHD	National Center for Child Health and Development
NCCN	National Comprehensive Cancer Network
Nel	Nelarabine
OTC	Over-the-counter drug
PLT	Platelet
PML	Progressive multifocal leukoencephalopathy
PS	Performance status
PT	Preferred Term
PT	Prothrombin time
QOL	Quality of life
RBC	Red blood cell count
RIST	Reduced-intensity stem cell transplantation
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SpO_2	Oxygen saturation
TEN	Toxic epidermal necrolysis
VP-16	Etoposide
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Project of Japan Drug Information Institute in Pregnancy

1. Project of Japan Drug Information Institute in Pregnancy

When using drugs during pregnancy, sufficient attention should be paid to their influence on the fetus as well as the mother.

On the other hand, because of excessive anxiety about drug-related risks, some physicians withhold necessary drug therapies or some patients stop taking medications without physician's advice, although few drugs have been confirmed to have teratogenic effects on humans. Suspension of necessary medication may result in aggravation of the mother's condition and adversely affect the fetus. Some patients even give up trying to get pregnant because they are on medication for treatment of chronic diseases.

To prevent such occurrences, MHLW established Japan Drug Information Institute in Pregnancy (JDIIP) (http://www.ncchd.go.jp/kusuri) in the National Center for Child Health and Development (NCCHD) on October 2005 to collect and evaluate the latest evidence of effects of drugs on fetuses and provide consultation services for women who wish to become pregnant and those who are already pregnant, based on the evaluated information.

As part of the project, pregnancy outcome is also collected and evaluated from women who have received consultations to enhance future pregnancy consultation services .[1)]

In addition to JDIIP, cooperating hospitals are participating in this project. To improve the access to the services, 4 hospitals have joined the project along with 16 cooperating hospitals nationwide in fiscal year (FY) 2011. This further enhances the project's consultation services and information collection. The JDIIP and 20 cooperating hospitals are described in "5. Contact information."

2. Project activities

(1) Consultation services

The project provides consultation services for pregnant women who are concerned about the drug influence on the fetus or those who wish to become pregnant. Those women can receive the advice at the Institute or cooperating hospitals or through their physicians. In addition, the project started telephone consultation services in July 2007 for users of popular OTC drugs such as cold remedies, painkillers, antiallergics and gastrointestinal drugs about which inquiries are frequently made.

The JDIIP consultation services are available by following the procedure below.

1) When you wish to receive consultation services, download the "Interview Sheet" and "Application Form for Consultation Services" from the JDIIP website (http://www.ncchd.go.jp/kusuri).
2) The "Interview Sheet", used to clarify the patient's background information, should be filled out by the patient in consultation with her physician. The "Application Form for Consultation Services" should be filled out by the physician. A referral letter issued by the physician may be used in place of "Application Form for Consultation Services".
3) Send the "Interview Sheet" and "Application Form for Consultation Services" to the JDIIP by mail.
4) The document "How To Use the Consultation Services" will be sent by the JDIIP.
5) Consultation can be made in one of the following ways:

- You will receive a direct consultation from a physician or pharmacist at the outpatient department of the NCCHD or of the cooperating hospital.
- The reply from the JDIIP will be sent to your physician, who will give the explanation to you.

If consultation services are provided at the outpatient department of the NCCHD or the cooperating hospital, specialized physicians and pharmacists in the JDIIP who have prepared the documents will attend, so that consultation can be provided based on risk communication. In principle, this method is employed for consultations regarding drugs with high risk of teratogenicity or for patients who are very worried about drug-related risks.

On the other hand, consultations can be received from your physician at a nearby hospital. Therefore, it will be more convenient for patients living far from NCCHD or the cooperating hospitals as well as for those in the early stage of pregnancy who are feeling unwell and worried about traveling.

(2) Survey of newborns

For the survey for newborns (pregnancy outcome survey), JDIIP asks the women to provide post-delivery information at the time of application for consultation services.

For the research method, a questionnaire postcard will be sent from the JDIIP one month after the expected date of delivery. The mother is asked to fill out the postcard with the results of a 1-month physical examination and return it to the JDIIP.

Moreover, in order for the objective and significance of the survey to be fully understood, the women are given an explanation during the JDIIP consultation that the information provided to them had been collected in the same manner as the survey, and that returning the postcard with pregnancy outcome data will help other women who will become pregnant in the future.

3. Consultation status

Number of consultations (including telephone consultations) provided have been increasing year after year: 111 in FY 2005, 335 in FY 2006, 673 in FY 2007, 960 in FY 2008, 1016 in FY 2009 and 1092 in FY 2010.

In December 2007, the JDIIP added a section called “Drugs and Breastfeeding” on the website as “Drug Information for Mothers”, which includes information on “Drugs That Nursing Mothers May Use” and “Drugs That Nursing Mothers Should Avoid.”

In response to the H1N1 influenza epidemic, JDIIP’s basic stance on influenza treatment and vaccination during pregnancy have been introduced in the “Influenza Update Information” section since September 2009. The latest information about drugs and pregnancy is available on the website.

4. Requests to healthcare providers

It is difficult to systematically collect information about the influence of medications taken during pregnancy on the fetus, even in post-marketing surveillances conducted by pharmaceutical companies. For the JDIIP pregnancy outcome survey, JDIIP asks the women to provide post-delivery information at the time of application for consultation services. The purpose of the pregnancy outcome survey is to efficiently collect and evaluate information on drugs used by pregnant women and the effect on their infants and to promote proper drug use. Healthcare providers are encouraged to introduce the JDIIP consultation services to pregnant women who are worried about the effect of drugs they have used.

<Reference>

1) Pharmaceuticals and Medical Devices Safety Information No.235 (April 2007)

5. Contact Information

	Name of medical institution	Contact information, reception hours, etc.
1	Japan Drug Information Institute in Pregnancy	2-10-1 Okura, Setagaya-ku, Tokyo 157-8535 in National Center for Child Health and Development (NCCHD) TEL: (+81)-3-5494-7845 FAX: (+81)-3-3415-0914 Reception hours: 10:00 –12:00, 13:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.ncchd.go.jp/kusuri
Cooperating hospitals (◎: Joined since 2011)		
2	Hokkaido University Hospital	Kita 14, Nishi 5, Kita-ku, Sapporo-city, Hokkaido 060-8648 TEL: (+81)-11-716-1161 (Extension 7723 or PHS 82943) FAX: (+81)-11-706-7616 Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
3	Iwate Medical University Hospital	19-1 Uchimaru, Morioka-city, Iwate 020-8505 TEL: (+81)-19-624-5263 (Pregnancy and drugs counseling desk: Direct call) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
4	National Hospital Organization Sendai Medical Center	2-8-8 Miyagino, Miyagino-ku, Sendai-city, Miyagi 983-8520 TEL: (+81)-22−293−1111 (Please ask for “Outpatient office for pregnancy and drugs” in Pharmacy department) Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.snh.go.jp/Medicine/index.html
5	Tsukuba University Hospital	2-1-1 Amakubo, Tsukuba-city, Ibaraki 305-8576 TEL: (+81)-29-853-3630 FAX: (+81)-29-853-7025 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
6	Toranomon Hospital	2-2-2 Toranomon, Minato-ku, Tokyo 105-8470 TEL: (+81)-3-3588-1111 (Extension 3410) FAX: (+81)-3-3505-1764 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
7	St. Luke’s International Hospital	9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560 TEL: (+81)-3-5550-2412 FAX: (+81)-3-3541-1156 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)

8	◎Yokohama City University Hospital	3-9 Fukuura, Kanazawa-ku, Yokohama-city, Kanagawa 236-0004 TEL: (+81)-45-787-2800 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) HP: http://www.fukuhp.yokohama-cu.ac.jp/
9	◎Chiba University Hospital (to be opened in June 2011)	1-8-1 Inohana, Chuo-ku, Chiba-city, Chiba 260-8677 TEL: (+81)-43-226-2628 (Drug Information, Division of Pharmacy) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
10	◎Saitama Medical University Hospital	38 Morohongo Moroyama-machi, Iruma-gun, Saitama 350-0495 TEL: (+81)-49-276-1297 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours: 15:00 – 17:00 (Monday to Saturday, excluding national holidays)
11	◎Maebashi Red Cross Hospital	3-21-36 Asahi-cho, Maebashi, Gunma 371-0014 TEL: (+81)-27-224-4585 (Division of Pharmacy: Extension 7709) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays) HP: http://www.maebashi.jrc.or.jp/
12	Shinshu University Hospital	3-1-1 Asahi, Matsumoto-city, Nagano 390-8621 TEL: (+81)-263-37-3022 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-263-37-3022 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
13	Japanese Red Cross Nagoya Daiichi Hospital	3-35 Michishita-cho, Nakamura-ku, Nagoya-city, Aichi 453-8511 TEL: (+81)-52-481-5111 (Division of Pharmacy: Extension 38376) FAX: (+81)-52-482-7733 Reception hours: 13:00 – 16:00 (Monday to Friday, excluding national holidays)
14	National Hospital Organization Nagara Medical Center	1300-7 Nagara, Gifu-city, Gifu 502-8558 TEL: (+81)-58-232-7755 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-58-295-0077 Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays)

15	National Hospital Organization Kanazawa Medical Center	1-1 Shimoishibiki-machi,Kanazawa-city, Ishikawa 920-8650 TEL: (+81)-76-262-4161 Reception hours: 9:00 – 16:30 (Monday to Friday, excluding national holidays) HP: http://www.kanazawa-hosp.jp/pv/preg.htm
16	Nara Medical University Hospital	840 Shijo-cho, Kashihara-city, Nara 634-8522 TEL: (+81)-744-22-3051 (Division of Pharmacy: Extension 3565) FAX: (+81)-744-29-8027 Reception hours: 8:30 – 16:00 (Monday to Friday, excluding national holidays) HP: http://www.naramed-u.ac.jp/~gyne/kusuri.html
17	Osaka Medical Center and Research Institute for Maternal and Child Health	840 Murodo-cho, Izumi-city, Osaka 594-1101 TEL: (+81)-725-56-5537 ("Outpatient department for pregnancy and drugs") Reception hours: 9:00 – 17:45 (Monday to Friday, excluding national holidays) URL: http://www.mch.pref.osaka.jp
18	National Hospital Organization Kagawa Children's Hospital	2603 Zentsuji-cho, Zentsuji-city, Kagawa 765-8501 TEL: (+81)-877-62-0995 FAX: (+81)-877-62-5484 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
19	Hiroshima University Hospital	1-2-3 Kasumi, Minami-ku, Hiroshima-city, Hiroshima 734-8551 TEL: (+81)-82-257-5079 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
20	Kyushu University Hospital	3-1-1 Maidashi, Higashi-ku, Fukuoka-city, Fukuoka 812-8582 TEL: (+81)-92-642-5900 Reception hours: 14:00 – 17:00 (Monday to Friday, excluding national holidays)
21	Kagoshima City Hospital	20-17 kajiya-cho, Kagoshima-city, Kagoshima 892-8580 TEL: (+81)-99-224-2101 (Pharmacy department: Extension 2603) (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-99-224-9916 Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays)

2

Safety Measures related to Lenalidomide Hydrate

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Lenalidomide Hydrate	Revlimid Capsules 5 mg (Celgene K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous	
Indications	Relapsed or refractory multiple myeloma Myelodysplastic syndrome associated with a chromosome 5q deletion	

1. Introduction

Lenalidomide hydrate, a thalidomide derivative, was approved in concomitant use of dexamethasone for the indication for treatment of patients with relapsed or refractory multiple myeloma in June 2010 in Japan. In August 2010, the additional indication for treatment of myelodysplastic syndrome associated with a chromosome 5q deletion was approved.

Multiple myeloma is a poor-prognosis hematological malignancy that presents various symptoms including anaemia, haemorrhage, infection, renal impairment and fracture. Patients with multiple myeloma are treated with chemotherapy mainly including antineoplastic agents, but it is difficult for the patients to remit completely, and almost all of them relapse after initial treatment.[1,2)] Therefore, the treatment goal for multiple myeloma will be prolongation of survival and preservation of quality of life (QOL) by alleviation of the symptoms and complications. It is reported in the literature that the median survival period of patients with relapsed or refractory multiple myeloma is 6 to 9 months.[3)] The treatment options of those patients include the concomitant use of lenalidomide hydrate and dexamethasone, thalidomide, bortezomib, or dexamethasone.[1)]

Myelodysplastic syndrome is also a hematological malignancy associated with dysplasia of white blood cells, platelets, and red blood cells. It is a group of diverse diseases that presents various symptoms including anaemia, infection, and haemorrhage. The therapeutic goal of lenalidomide hydrate is withdrawal from blood cell transfusion dependence in patients with myelodysplastic syndrome associated with a chromosome 5q deletion who have low or intermediate-1 risk according to the International Prognostic Scoring System (IPSS).[4)]

The post-marketing surveillance in all patients treated with lenalidomide hydrate (all-case surveillance) included 2,483 patients registered within half a year of initial marketing.[5)] A number of infection and hepatic dysfunction cases were reported during the half-year surveillance period. In Europe, arterial thromboembolism such as cerebral infarction was added to the European Summaries of Product Characteristics(SmPC) in January 2011.

Based on adverse reactions collected in Japan and relevant overseas regulatory measures, the safety measures related to infection, hepatic dysfunction, and cerebral infarction were reviewed, and further safety measures were taken. The details are presented below.

2. Review based on adverse reactions collected in Japan

(1) Infection

One hundred cases of infections[Note)] (27 fatal cases) were reported during the Early Post-marketing Phase Vigilance (EPPV) period (July 20, 2010 to February 19, 2011). The primary diseases of the fatal cases are shown in Table 1.

Note) Preferred Terms (PTs) under the System Organ Class (SOC) of "Infections and infestations" in the MedDRA ver.13.1 were used.

Table 1 Adverse reaction reports related to infection (fatal cases)

Primary diseases (Reason for use)	Number of cases Note1)
Multiple myeloma	24 (9)
Myelodysplastic syndrome	2 (0)
Plasmacytic leukemia	1 (1Note2))
Total	27 (10)

Note 1) The number in the parentheses shows the number of fatal cases where PMDA considered the causality between the death and lenalidomide hydrate could not be ruled out.
Note 2) A case of off-label use

The primary diseases of infection-related fatal cases included multiple myeloma in 24 cases, myelodysplastic syndrome in 2 cases and plasmacytic leukemia in 1 case. Multiple myeloma patients, which mainly consist of lenalidomide users, treated with lenalidomide hydrate are known to have higher risk of infection due to depressed normal immunoglobulins and decreased neutrophils.[6] Infection is the major cause of death in multiple myeloma patients. The incidence of sepsis in multiple myeloma patients is 0.8 to 1.4 per person-year. In addition, the incidence of infection in the disease progression phase (treatment-requiring) is 4 times higher than that in the stable disease phase (plateau phase).[7] Patients for whom lenalidomide hydrate is indicated are therefore already susceptible to infections because of their primary diseases and have high potential life-threatening risk of infections. The risk is further increased by concomitant use with high-dose dexamethasone or certain patient factors including advanced age and poor general condition.

Other factors apart from lenalidomide hydrate cannot be ruled out even in the 10 cases where PMDA considered the causality between lenalidomide hydrate and death could not be ruled out. However, it is appropriate to provide the information concerning possible infections in patients treated with lenalidomide hydrate to healthcare professionals, to alert them by adding descriptions about infection risk in the package insert, and to once again call for thorough infection control, for the following reasons:

- Although marrow depression occurring after administration of lenalidomide hydrate induced infection in some cases, there is a possibility that lenalidomide hydrate may directly increase susceptibility to infection without causing bone marrow depression.
- MHLW alerted in the "Warnings" section of package insert, that lenalidomide hydrate should be used by physicians with adequate knowledge and experience of treating patients with hematological malignancy. MHLW considers that physicians using lenalidomide hydrate should completely understand the importance of infection control. However, it would still be meaningful to once again call for thorough infection control.

(2) Hepatic dysfunction

During the EPPV, 30 cases (1 fatal case) of hepatic dysfunction[Note)] were reported, including 14 cases of Grade 3 hepatic dysfunction and 16 cases of Grade 1 or 2.[8] The primary diseases of Grade 3 hepatic dysfunction cases are shown in Table 2.

Note) PTs under the SOC of "Hepatobiliary disorders" or those under the High Level Group Terms (HLGTs) of "Hepatobiliary investigations" under the SOC of "Investigations" in the MedDRA ver.13.1 were used.

Table 2 Adverse reaction reports related to hepatic dysfunction (Grade 3)

Primary diseases (Reason for use)	Number of cases Note 1)
Multiple myeloma	13 (10)
Myelodysplastic syndrome	0 (0)
Plasmacytic leukemia	1 (1 Note 2))
Total	14 (11)

Note 1) The number in the parentheses shows the number of fatal cases where PMDA considered the causality between death and lenalidomide hydrate could not be ruled out
Note 2) A case of off-label use

Since the adverse reaction reports showed that many of the patients with Grade 3 hepatic dysfunction concomitantly used antimicrobials or antifungals, it is difficult to evaluate the causality between hepatic dysfunction and lenalidomide hydrate. Nevertheless, the causality with lenalidomide hydrate could not be ruled out in 11 cases (10 multiple myeloma patients and 1 plasmacytic leukemia patient). Therefore, it is appropriate to provide the information concerning hepatic dysfunction in patients treated with lenalidomide hydrate to healthcare professionals and to alert them by adding descriptions about hepatic dysfunction and jaundice in the package insert.

(3) Cerebral infarction

In January 2011, the European SmPC was revised to include arterial thromboembolism after a certain number of cases had been reported. The section of Clinically Significant Adverse Reactions in the Japanese package insert already includes myocardial infarction, which is classified into arterial thromboembolism, but proper safety measures against cerebral thromboembolism including cerebral infarction should be reviewed.

During the EPPV in Japan, 6 cases (no fatal case) of cerebral infarction or transient ischemic attack were reported. The primary diseases of cerebral infarction cases are shown in Table 3.

Table 3 Adverse reaction reports related to cerebral infarction

Primary diseases (Reason for use)	Number of cases Note)
Multiple myeloma	6 (4)
Myelodysplastic syndrome	0 (0)
Total	6 (4)

Note) The number in the parentheses shows the number of fatal cases where PMDA considered the causality between death and lenalidomide hydrate could not be ruled out

Since the causality between cerebral infarction and lenalidomide hydrate could not be ruled out in 4 cases (all patients with multiple myeloma), it is appropriate to add an alert about cerebral infarction and transient ischemic attack in the package insert.

3. Safety measures and future actions

Based on the review described above, it was concluded that alerts about "infection", "hepatic

dysfunction and jaundice", and "cerebral infarction and transient ischemic attack" should be added in the section of "Clinically Significant Adverse Reactions" of the package insert.

The marketing authorization holders (MAHs) were required to provide information concerning infection–related deaths and occurrence of hepatic dysfunction to healthcare professionals. The provision of the information was started on February 25, 2011 prior to the package insert revision.[5)]

Healthcare professionals are advised to closely monitor patients for these events and provide appropriate treatment if any abnormalities are observed. Please continue to ensure proper use of lenalidomide hydrate.

Specific revisions of the Precautions in the package inserts are described below. (The underlined parts are revised.)

Lenalidomide Hydrate

[Adverse Reactions (clinically significant adverse reactions)]

Cerebral infarction, transient ischaemic attack: Cerebral infarction or transient ischaemic attack may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Infection: Serious infections including pneumonia and sepsis 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.

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

Bone marrow depression: Neutropenia, thrombocytopenia, and/or anaemia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as dose reduction, drug suspension or discontinuation of administration should be taken. Some cases of platelet decrease resulting in haemorrhage (e.g., gastrointestinal haemorrhage) have been reported.

4. Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Multiple myeloma (myeloma kidney, peripheral neuropathy, hypertension, hyperlipidaemia, reflux oesophagitis)	10 mg for 5 days	**Pneumonia** Approximately 1.5 years before administration: The patient developed multiple myeloma. Day 1 of administration: Administration of lenalidomide hydrate was started. Baseline Performance Status (PS): 1. No infectious complication. Day 5 of administration (day of onset): SpO_2 suddenly decreased. An X-ray showed cardiomegaly. Wheezing and ST change on electrocardiogram (ECG) were noted, the patient was diagnosed with cardiac failure. No cardiac enzymes increased. Day 6 of administration (day of discontinuation): Administration of lenalidomide hydrate and dexamethasone were discontinued. Pyrexia gradually worsened. The patient was diagnosed with pneumonia based on an X-ray showing infiltrative and

				interstitial shadows mainly in the bilateral lower-lobes and a chest CT showing a reticular shadow in the right middle lung field. Sputum culture identified *Neisseria* species. Administration of antibiotics was started. The patient was under mechanical ventilation due to rapid deterioration in oxygen saturation. Bloody sputum was also observed. 2 days after discontinuation: Urine output continued to decrease in spite of administration of diuretics. The patient's haemodynamics became unstable. 3 days after discontinuation: The patient died.
	Concomitant medications: dexamethasone, etodolac, omeprazole, magnesium oxide, mecobalamin, gabapentin, warfarin potassium, itraconazole, sulfamethoxazole, trimethoprim, heparin sodium			

Laboratory Examination

	4 days before administration	Day 5 of administration (day of onset)	1 day after discontinuation	2 days after discontinuation
WBC (/mm^3)	2800	-	-	2200
Neutrophil count (/mm^3)	43.0	-	-	-
CRP (mg/dL)	0.06	2.69	-	11.67
Creatinine (mg/dL)	1.1	-	3.0	6.0
BUN (mg/dL)	-	-	40	80

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Multiple myeloma (none)	25 mg for 21 days	**Abnormal liver function tests** Approximately 3 years before administration: The patient developed multiple myeloma. Day 1 of administration: Administration of lenalidomide hydrate was started. Day 15 of administration (day of onset): Liver function test showed abnormality. Day 22 of administration (day of discontinuation): Administration of lenalidomide hydrate was suspended. 14 days after discontinuation: Abnormal liver function test values were improved.
	Concomitant medications: dexamethasone, lansoprazole, warfarin potassium			

Laboratory Examination

	Day 1 of administration	Day 15 of administration (day of onset)	1 day after discontinuation	14 days after discontinuation
AST (GOT) (IU/L)	19	39	657	29
ALT (GPT) (IU/L)	14	42	360	25
Al-P (IU/L)	199	180	815	282

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 70s	Multiple myeloma (Renal impairment)	20 mg for 5 days ↓ (administration suspended for 1 day) ↓ 10 mg (alternate-day) for 15 days ↓ (administration suspended for 7 days) ↓ 15 mg (alternate-day) for 19 days ↓ (administration suspended for 21 days) ↓ 10 mg (alternate-day)	**Cerebral infarction** Approximately 8 years before administration: The patient developed multiple myeloma. Day 1 of administration: Administration of lenalidomide hydrate was started (Cycle 1). Day 6 of administration (day of discontinuation): Administration of lenalidomide hydrate was suspended due to slight increase in creatinine (1-day drug withdrawal). 1 day after discontinuation (day of readministration): Administration of lenalidomide hydrate was resumed at 10 mg on alternate days. Day 13 of readministration: Erythematous papules appeared in the extremities and trunk. The patient complained about pruritus. Eosinophilia was also noted. Methylprednisolone and prednisolone were administered. Day 16 of readministration (day of discontinuation): Administration of lenalidomide hydrate was suspended (7-day drug withdrawal). Day 1 of administration: Administration of lenalidomide hydrate was resumed at 15 mg on alternate days (Cycle 2). Day 20 of administration (day of discontinuation): Administration of lenalidomide hydrate was suspended (21-day drug withdrawal). 3 days after discontinuation (day of onset): Generalized weakness and gait disturbance were noted. Magnetic resonance imaging (MRI) showed multiple cerebral infarction. Heparin and warfarin potassium were administered. 21 days after discontinuation: Generalized rash and eosinophilia resolved. Day 1 of administration: Administration of lenalidomide hydrate was resumed at 10 mg on alternate days (Cycle 3). Administration of warfarin potassium was continued. 31 days after onset: Multiple cerebral infarction remitted.
	Concomitant medications: dexamethasone, lansoprazole, rebamipide, valaciclovir hydrochloride, zoledronic acid hydrate			

<References> (including provisionally translated titles)

1) National Comprehensive Cancer Network (NCCN) Clinical practice guideline version 1. 2011
2) Mayo Clinic Proceedings 1994;69:781-6
3) Hematology 2007 American Society of Hematology Education Program Book
4) Review report of lenalidomide (July 6, 2010)
5) http://www.revlimid-japan.jp/professional/product/pdf/tks/tks_rev_201102.pdf
6) Clinical Oncology Update*, the second revised edition (Japanese Society of Medical Oncology, 2009)
7) WINTROBE'S CLINICAL HEMATOLOGY 12th EDITION
8) PAB/SD Notification No. 80, by the Director of safety Division, Pharmaceutical Affairs Bureau "Criteria for seriousness classification of adverse drug reactions"* (June 29, 1992)

*provisional translation

3

Important Safety Information

This section presents the contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the Precautions section of package inserts of drugs that have been revised in accordance with the Notification dated March 22, 2011.

1 Aripiprazole

Brand Name (name of company)	ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1% (Otsuka Pharmaceutical Co., Ltd.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

≪PRECAUTIONS (underlined parts are revised)≫

[Important Precautions]

Hypoglycaemia may occur. During administration of this drug, caution should be exercised regarding the onset of symptoms of hypoglycaemia such as feelings of weakness, malaise, cold sweat, tremor, somnolence, and disturbed consciousness. Patients should be carefully monitored, e.g. by measuring blood glucose levels. Patients and their families should be given adequate information about the possibility of the occurrence of the above adverse reactions and to watch for symptoms of hyperglycaemia (thirst, excessive drinking, polyuria, pollakiuria, hyperphagia, feelings of weakness, etc.) and symptoms of hypoglycaemia (feeling of weakness, malaise, cold sweat, tremor, somnolence, disturbed consciousness, etc.) before iniation of administration . Patients should be instructed to discontinue this drug and consult a physician immediately when such symptoms are observed,.

[Adverse Reactions (clinically significant adverse reactions)]

Hypoglycaemia: Hypoglycaemia may occur. If symptoms of hypoglycaemia such as feelings of weakness, malaise, cold sweat, tremor, somnolence, and disturbed consciousness are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

[Use in Pregnant, Parturient And Nursing Women]

Pregnant women or women who may be pregnant should only be administered when the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Withdrawal symptoms and extrapyramidal disorder such as feeding disorder, somnolence, respiratory disorder, tremor, hypotonia, and irritability have been reported in neonates of mothers who were treated with antipsychotics in late pregnancy.]

<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, 2007 to February 9, 2011)

- Hypoglycaemia: 1 case (no fatal case)
- Withdrawal symptom, extrapyramidal disorder: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 190,000 (2010)

Launched into Japan: June 2006

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Schizophrenia (diabetes mellitus, chronic renal failure)	6 mg for 16 days	**Hypoglycaemia** The patient had been receiving dialysis 3 times a week for over 5 years. Blood glucose had been controlled at 100 to 150 mg/dL for several months before administration of aripiprazole. Day 1 of administration: Administration of aripiprazole was started at 6 mg/day. Day 12 of administration: Blood glucose was measured in the morning. The patient was dozing. Blood glucose was 25 mg/dL around noon. Hypoglycaemic symptoms were noted, 50% glucose 40 mL was administered intravenously. Blood glucose increased to 299 mg/dL 5 minutes later. The patient was unable to eat lunch. Blood glucose was 175 mg/dL 30 minutes later. Blood glucose decreased to 84 mg/dL 1 hour later. 5% glucose injection 200 mL was intravenously administered. Blood glucose was 33 mg/dL 3 hours later. 50% glucose injection 20 mL was intravenously administered. 50% glucose injection 20 mL was mixed to the drip infusion. Blood glucose was 64 mg/dL 4.5 hours later. The infusion rate was accelerated. Administration of insulin human (genetical recombination) scheduled for the evening was discontinued. The patient had only thick liquid food for dinner. Day 13 of administration: Blood glucose was 81 mg/dL in the early morning. Drip infusion was completed. Blood glucose was 116 mg/dL around noon. Blood glucose was 247 mg/dL in the evening. The patient had all three meals. Day 15 of administration: Blood glucose was 34 mg/dL around noon. The patient had sugar 5 g. Day 16 of administration (day of discontinuation): Blood glucose was 61 mg/dL around noon. The patient barely ate her meal. 1 day after discontinuation: Blood glucose was 45 mg/dL in the morning. The patient had granulated sugar 10 g. Blood glucose was 30 mg/dL around noon. 5% glucose injection 200 mL was intravenously administered. Administration of aripiprazole was discontinued. (Day of last administration: Day 16) 2 days after discontinuation: Since this time, blood glucose has been controlled at 100 to 150 mg/dL. No hypoglycaemic symptoms were observed. The patient had received dialysis as usual during the follow-up period. 7 days after discontinuation:

				The patient recovered from hypoglycaemia.
	Concomitant medications: insulin human (genetical recombination), aspirin/dialuminate, carvedilol, sennoside, famotidine, nifedipine, rebamipide, mecobalamin, risperidone			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male Under age of 1	Mother Schizophrenia (none)	(Transplacental) 18 mg for 107 days (Trans-breast milk) 18 mg for 6 days	**Somnolence** (Clinical course of mother) Smoking: 10 cigarettes/day <during pregnancy: quit> Alcohol consumption: none Pregnancy history: none 134 days before administration: (Clinical course of mother) The first day of the last menstruation period. Day 1 of administration: (Clinical course of mother) The patient's mother started receiving aripiprazole 18 mg/day. She was 22 weeks + 6 days of gestation. (Clinical course of mother) Course of pregnancy: normal Day 107 of administration (the day of birth): She delivered a baby by elective caesarean section due to breech presentation. Her baby was a sleeping baby with no spontaneous respiration (for about 1 minute after birth). Temporary somnolent tendency was noted. Apgar score at 1 minute was 2. Spontaneous respiration started after positive pressure ventilation with an oxygen mask. Spontaneous respiration continued with no further problems. Apgar score at 5 minute was 9. Her baby was fed well. Aripiprazole blood concentration (first cord blood sampling): 96.4 ng/mL Aripiprazole blood concentration (second cord blood sampling): 93.7 ng/mL (Clinical course of mother) She delivered a baby. She was 38 weeks + 0 day of gestation. Delivery method: caesarean section Course of delivery: normal. Mother's condition: normal Aripiprazole blood concentration (mother's blood immediately after caesarean section): 181 ng/mL (Course of neonate) Sex: male, Apgar score: 2 (1 minute), 9 (5 minutes), Height: 53 cm, Weight: 2866 g, Head circumference: 32.5 cm, Congenital anomaly: none. Other abnormality: temporary somnolent tendency was noted. Day 112 of administration: (Course of mother) Aripiprazole concentration (breast milk): 29.5 ng/mL Day 113 of administration:

				(Course of neonate) Breast feeding status: fed (duration: Day 108 to 113 of administration). Recurrence of adverse events: none Aripiprazole blood concentration (infant' blood): 7.59 ng/mL (Course of mother) Aripiprazole concentration (breast milk): 38.7 ng/mL (Course of mother) Administration of aripiprazole is being continued.
	Concomitant medications: magnesium oxide, killed escherichia coli/hydrocortisone, sodium picosulfate hydrate, azithromycin hydrate, sodium ferrous citrate, ritodrine hydrochloride			

2 Freeze-dried Live Attenuated Mumps Vaccine

Brand Name (name of company)	Freeze-dried Live Attenuated Mumps Virus Vaccine "Kitasatodaiichisankyo" (Kitasato Daiichi Sankyo Vaccine Co., Ltd.), DRIED LIVE ATTENUATED MUMPS VACCINE (TORII STRAIN) "Takeda" (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Vaccines
Indications	Use for prevention of mumps.

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Acute disseminated encephalomyelitis (ADEM): Acute disseminated encephalomyelitis (ADEM) may occur. Pyrexia, headache, convulsion, movement disorder, and disturbed consciousness generally occur within 2 weeks. If ADEM is suspected, diagnosis should be made by MRI etc., and appropriate measures should be taken.

Encephalitis, encephalopathy: Encephalitis or encephalopathy may occur. Patients should be carefully monitored. If any abnormalities are observed, diagnosis should be made by MRI etc., and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2007 to December 31, 2010)

- Acute disseminated encephalomyelitis: 4 cases (no fatal cases)
- Encephalitis, encephalopathy: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 800,000 (2010)

Launched into Japan: May 1982

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female Under age of 10	Immunization (none)	0.5 mL Once	**Acute disseminated encephalomyelitis** Day of vaccination: The patient received a mumps vaccination at a nearby hospital. 7 days after vaccination: The patient started to get excited easily, repeat the same words and sleep badly. The symptoms gradually worsened. 11 days after vaccination: The patient visited the nearby hospital for worsened symptoms. The patient had changes of facial expression, and severe

				excitatory symptoms t Post-vaccination ADEM was suspected. The patient was referred to another hospital. The patient was excited and had echolalia at the other hospital. ADEM was suspected. Brain MRI (T2-weighted/Fluid-attenuated inversion recovery [FLAIR]) showed sporadic high intensity areas in the subcortical white matter mainly in bilateral occipital lobes. Spinal fluid cell count increased to 57/3. IgG also increased (IgG, 18; IgM, 0). ADEM was diagnosed based on the clinical course and findings, steroid pulse therapy was started on the same day. 13 days after vaccination: **Excitatory symptoms** improved. The patient was quiet and would not speak. Steroid pulse therapy was completed on the same day. 14 days after vaccination: Oral administration of steroid (prednisolone) was started. 15 days after vaccination: **Excitatory symptoms** started late at night and continued. Automatism of the mouth and a wriggling motion of the hands and feet appeared. Upward conjugate deviation of the eyes was noted. 16 days after vaccination: Conjugate deviation of the eyes in multiple directions was noted. Automatism and restlessness persisted. The intensity areas shown by brain MRI were less intense compared to the image taken 11 days after vaccination; however, some areas intensified. Since the symptoms had not improved with steroid pulse therapy alone, administration of human immunoglobulin (400 mg/kg) was started for 5 days. 20 days after vaccination: **Excitatory symptoms** gradually subsided. The patient started to say a few words. 27 days after vaccination: The patient was discharged from the hospital.
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male Under age of 10	Immunization (none)	0.5 mL Once	**Encephalitis, viral meningitis** Day of vaccination: The patient received a mumps vaccination at nearby hospital. 17 days after vaccination: The patient vomited. 18 days after vaccination: Pyrexia of over 38.0°C persisted. 20 days after vaccination: Febrile convulsion appeared in the early morning. The patient was referred and admitted to another hospital due to poor general condition. The patient was diagnosed with viral meningitis based on the spinal fluid examination upon admission. Virus was isolated from the spinal fluid. Administration of intracranial pressure reducing agent, antibiotic, and fluid replacement were started. 22 days after vaccination: The spinal fluid examination showed decreased cell counts,

				suggesting that the patient was improving. 24 days after vaccination: Because pyrexia and nuchal rigidity persisted, brain MRI and electroencephalogram were performed. The patient was diagnosed with encephalitis. On the same day, steroid pulse therapy (for 3 days), administration of human immunoglobulin (for 1 day) and aciclovir (for 7 days) were started. 28 days after vaccination: Pyrexia and general condition improved after treatment. Electroencephalographic findings also showed an improvement. 30 days after vaccination: Brain MRI showed no abnormality. 39 days after vaccination: The patient was discharged from the hospital after the post-treatment examination showed no abnormality. Periodic electroencephalogram and physical examinations have been performed as an outpatient, the patient had no apparent sequelae. 91 days after vaccination: Mumps virus was detected in the spinal fluid at the time of admission. The symptoms were determined as adverse reactions to the mumps vaccine because an identification test showed the consistency of the detected virus with the vaccine strain.
	Concomitant medications: none			

3 Anti-human Thymocyte Immunoglobulin, Rabbit

Brand Name (name of company)	Thymoglobuline for Intravenous Infusion 25 mg (Genzyme Japan K.K.)
Therapeutic Category	Biological preparations-Miscellaneous
Indications	1. Moderate to severe aplastic anaemia 2. Conditioning regimen prior to hematopoietic stem cell transplantation 3. Acute graft versus host disease after hematopoietic stem cell transplantation 4. Treatment of acute rejection following renal transplantation

≪PRECAUTIONS (underlined parts are revised)≫

[Important Precautions]

Pyrexia, chills, dyspnoea, nausea, vomiting, diarrhoea, tachycardia, hypotension, hypertension, malaise, rash, and headache may occur during the early period of the administration of this drug. The patient should be informed of possible symptoms in advance. Severe infusion-associated reaction (including cytokine release syndrome) may occur, resulting in serious cardiac or lung disorders (myocardial infarction, acute respiratory distress syndrome, pulmonary oedema). Patients should be carefully monitored during treatment. Prior treatment with corticosteroid is recommended to relieve the symptoms. Concomitant use of antipyretic or antihistamine can also relieve the symptoms frequently reported during the early period of the administration of this drug.

In hepatitis B virus carriers who receive an immunosuppressant therapy, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus has been reported in patients who were negative for HBs antigen after starting immunosuppressant therapy. Hepatitis C may be exacerbated in hepatitis C virus carriers after starting immunosuppressant therapy. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus

and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.

[Adverse Reactions (clinically significant adverse reactions)]

Severe infusion-associated reaction (including cytokine release syndrome): Severe infusion-associated reaction (including cytokine release syndrome) may occur, resulting in serious cardiac or lung disorders (myocardial infarction, acute respiratory distress syndrome, pulmonary oedema). If any abnormalities such as pyrexia, chills, dyspnea, nausea, vomiting, diarrhoea, tachycardia, hypotension, hypertension, malaise, rash, and headache are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Febrile neutropenia: Febrile neutropenia 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.

Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leucoencephalopathy (PML) may occur. Patients should be carefully monitored during and after the treatment period with this drug, and if symptoms including disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia, quadriplegia), and, language disorders are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration of this drug should be discontinued, and appropriate measures should be taken.

BK viral nephropathy: BK viral nephropathy may occur. If such symptoms occur, dose of this drug should be reduced or administration should be discontinued, and appropriate measures should be taken.

Infection (pneumonia, sepsis., etc.): Serious infections from virus (adenovirus, cytomegalovirus, herpes virus), bacteria, or fungi (aspergillus) may occur. In hepatitis B or C virus carriers who receive immunosuppressant therapy, hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years (from initial marketing to February 8, 2011)

- Severe infusion-associated reaction: 5 cases (no fatal cases)
- Febrile neutropenia: 4 cases (1 fatal case)
- BK viral nephropathy: 1 case (no fatal case)

The number of patients using this drug per year estimated by MAHs: Approximately 1200 (2010)

Launched into Japan: November 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Hematopoietic stem cell transplant (Aplastic anaemia)	125 mg for 1 day	**Cytokine release syndrome** Approximately 2 hours before administration: The patient received methylprednisolone sodium succinate (80 mg) as premedication. Approximately 1 hour before administration: Anti-human thymocyte immunoglobulin, rabbit, (2.5 mg) was administered. The patient had no symptoms. No change was noted in vital signs. Day 1 of administration: Administration of anti-human thymocyte immunoglobulin, rabbit, (125 mg) was started. 10 minutes after administration (day of discontinuation):

				Cytokine release syndrome [chills, shivering, tachycardia, increased blood pressure, and decreased SpO_2 (SpO_2 decreased from 99 to 96)] developed. Administration of anti-human thymocyte immunoglobulin, rabbit, was discontinued. Hydrocortisone sodium succinate (200 mg) and hydroxyzine hydrochloride (25 mg) were administered intravenously. 20 minutes after discontinuation: Pyrexia (38.6°C) occurred. 25 minutes after discontinuation: Intravenous infusion of methylprednisolone sodium succinate (500 mg) was administered. 6 hours after discontinuation: Body temperature did not decrease (37.9°C), and tachycardia (heart rate [HR] 104) persisted. Hydrocortisone sodium succinate (200 mg) was administered intravenously. 1 day after discontinuation: Cytokine release syndrome [chills, shivering, tachycardia, increased blood pressure and decreased SpO_2] and pyrexia resolved.
	Concomitant medications: methylprednisolone sodium succinate, fludarabine phosphate, cyclophosphamide hydrate			

Laboratory Examination

	Day 1 of administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	5 days after discontinuation
WBC (/mm^3)	1500	900	600	100	100	100
RBC (× 10^4/mm^3)	265	209	309	289	297	279
Hemoglobin (g/dL)	7.2	5.7	8.5	7.9	8.1	7.6
Hematocrit (%)	21.6	16.9	25.1	23.4	24.0	22.5
Mean cell volume (fL)	81.5	80.9	81.2	81.0	80.8	80.6
Mean corpuscular hemoglobin (pg)	27.2	27.3	27.5	27.3	27.3	27.2
Mean corpuscular hemoglobin concentration (%)	33.3	33.7	33.9	33.8	33.8	33.8
Red cell distribution width (%)	-	16.2	15.9	15.5	15.2	14.8
PLT (× 10^4/mm^3)	3.2	1.6	8.4	4.9	2.7	1.6
Mean platelet volume (fL)	-	10.4	9.6	9.4	9.5	9.6
Reticulocyte (%)	-	0.5	-	0.2	-	0.3
Segmented cell (%)	-	99.0	94.0	-	-	-
Lymphocytes (%)	-	1.0	6.0	-	-	-
AST (GOT) (U/L)	33	73	99	62	50	30
ALT (GPT) (U/L)	76	97	155	130	123	93
γ-GTP (U/L)	133	173	221	231	243	213
Cholinesterase (U/L)	-	142	-	198	-	238
CK (CPK) (U/L)	-	31	-	-	-	30
Na (mEq/L)	139	140	140	138	140	143
K (mEq/L)	3.1	3.4	3.4	3.7	3.7	3.8
Cl (mEq/L)	98	103	99	101	101	105
CRP (mg/dL)	-	4.10	2.96	1.56	-	0.58

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 10s	Acute graft versus host disease (Acute lymphocytic leukaemia, hyperglycaemia, myopathy)	62.5 mg for 1 day	**Dyspnoea, tachycardia, cytomegalovirus test positive, haemorrhagic cystitis, fluid retention, pancytopenia** Approximately 2.5 years before administration: The patient was diagnosed with acute lymphocytic leukaemia. Approximately 2 months before administration: Hematopoietic stem cell transplantation was performed (stem cell source: bone marrow, type of transplant: full transplant from an unrelated donor) Approximately 1 month before administration: The patient was diagnosed with acute graft-versus-host disease (GVHD) in skin (Stage 3). Steroids (steroid pulse therapy), tacrolimus hydrate, mycophenolate mofetil, and topical skin medication were administered. 2 days before administration: Cytomegalovirus (CMV) antigenemia occurred. Day 1 of administration (day of completion of administration) Anti-human thymocyte immunoglobulin, rabbit, 2.5 mg was administered on a trial basis, followed by 62.5 mg over 10 hours for GVHD (Skin Stage 3). Dyspnea and tachycardia occurred. Administration of anti-human thymocyte immunoglobulin, rabbit, was completed. Tachycardia resolved. Hydrocortisone sodium succinate and chlorpheniramine maleate were administered for dyspnea. 1 day after completion of administration: Pancytopenia developed. Dyspnea resolved. 5 days after completion of administration: Fluid retention developed. 20 days after completion of administration: Administration of spironolactone was started for treatment of fluid retention. 22 days after completion of administration: Administration of furosemide (oral dosage form) was started for treatment of fluid retention. 42 days after completion of administration: CMV antigenemia resolved. 55 days after completion of administration: Hemorrhagic cystitis developed. 70 days after completion of administration: Furosemide (injection) was administered for fluid retention. 77 days after completion of administration: Ceftazidime hydrate was administered for hemorrhagic cystitis for 13 days. 100 days after completion of administration: Canrenoate potassium was administered for fluid retention. 107 days after completion of administration: Administration of spironolactone and furosemide (oral dosage form) were completed. 125 days after completion of administration: Administration of furosemide (injection) for treatment of fluid retention was completed. 128 days after completion of administration: Administration of canrenoate potassium for treatment of fluid retention was completed. 131 days after completion of administration:

				The patient developed a complication of infection, brain abscess, and pneumonia induced by potent immunosuppression against acute GVHD. Dyspnea developed associated with decreased level of consciousness. The patient was under mechanical ventilation. Respiratory failure did not improve despite all possible treatment. The patient died. Resolution of hemorrhagic cystitis was confirmed at the time of death.
	Concomitant medications: acetaminophen, sertraline hydrochloride, etizolam, sulfamethoxazole/trimethoprim, ursodeoxycholic acid, brotizolam, lansoprazole, flunitrazepam, voriconazole, valaciclovir hydrochloride, amlodipine besilate, tacrolimus hydrate, mycophenolate mofetil, mirtazapine, methylprednisolone, lorazepam, epinastine hydrochloride, magnesium oxide, alfacalcidol, potassium chloride, sennoside, prednisolone, insulin human (genetical recombination), insulin lispro (genetical recombination), insulin detemir (genetical recombination), cefepime dihydrochloride hydrate, vancomycin hydrochloride, lenograstim (genetical recombination), foscarnet sodium hydrate, meropenem hydrate, minocycline hydrochloride, filgrastim (genetical recombination), phenobarbital, ganciclovir, prednisolone sodium succinate for injection, propofol, poultice, vitamin A oil, tocopherol/vitamin A oil, clobetasol propionate, white petrolatum, 1,4-dimethyl-7-isopropylazulene, triamcinolone acetonide, vidarabine, heparinoid, mometasone furoate, diphenhydramine, hydrocortisone butyrate			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 60s	Aplastic anaemia (hypertension, pruritus, sepsis, febrile neutropenia)	213 mg for 5 days	**Febrile neutropenia, septic shock, zygomycosis, sepsis, bronchitis** Day 1 of administration: The patient started receiving 2.5 mg of human thymocyte immunoglobulin, rabbit, on a trial basis, and then administration was started at 2.5 mg. Febrile neutropenia occurred. Day 2 of administration: Acetaminophen for 2 days and cefepime dihydrochloride hydrate for 10 days were administered for febrile neutropenia. Day 5 of administration (day of completion of administration): Administration of anti-human thymocyte immunoglobulin, rabbit, was completed. 5 days after completion of administration: Febrile neutropenia resolved. 6 days after completion of administration: Septic shock (causative pathogen unknown) occurred. Imipenem hydrate/cilastatin sodium was administered for 4 days. 9 days after completion of administration: Fosfomycin sodium was administered for 6 days for septic shock. 10 days after completion of administration: Dopamine hydrochloride for 3 days and linezolid for 7 days were administered for septic shock. Administration of meropenem hydrate was started. 19 days after completion of administration: Zygomycosis (suspected) occurred. Administration of amphotericin B was started. 25 days after completion of administration: Septic shock (causative pathogen unknown) resolved. Administration of meropenem hydrate was completed. 26 days after completion of administration: Biapenem was administered for 7 days for febrile neutropenia.

				45 days after completion of administration: Sepsis (causative pathogen unknown) occurred. Linezolid and biapenem were administered for 5 days, respectively. 50 days after completion of administration: Meropenem hydrate was administered for sepsis for 9 days. 58 days after completion of administration: Sepsis (causative pathogen unknown) resolved. 84 days after completion of administration: Imipenem hydrate/cilastatin sodium was administered for sepsis for 5 days. 85 days after completion of administration: Linezolid was administered for sepsis for 14 days. 93 days after completion of administration: Sepsis (causative pathogen unknown) occurred. 103 days after completion of administration: Vancomycin hydrochloride was administered for sepsis for 8 days. 105 days after completion of administration: Meropenem hydrate was administered for sepsis for 6 days. 110 days after completion of administration: Sepsis (causative pathogen unknown) resolved. 136 days after completion of administration: Bronchitis (causative pathogen unknown) occurred. Meropenem hydrate was administered for 9 days. 144 days after completion of administration: Bronchitis (causative pathogen unknown) resolved. 368 days after completion of administration: Zygomycosis (suspected) resolved.
	Concomitant medications: ciclosporin, lenograstim (genetical recombination), metenolone acetate, deferasirox, filgrastim (genetical recombination), methylprednisolone sodium succinate, d-chlorpheniramine maleate, fexofenadine hydrochloride, sulfamethoxazole/trimethoprim, prednisolone, amphotericin B, povidone-iodine			

Laboratory Examination

	3 days before administration	Day 3 of administration	4 days after completion of administration	25 days after completion of administration	94 days after completion of administration	178 days after completion of administration
WBC (/mm^3)	1800	580	2760	2140	4250	6250
Neutrophil (/mm^3)	738	516	2705	1733	3613	5250
Lymphocyte (/mm^3)	1034	-	-	214	425	438
RBC ($\times 10^4$/mm^3)	189	-	-	231	250	229
Hemoglobin (g/dL)	5.6	-	-	6.8	7.6	7.0
Reticulocyte (/mm^3)	5670	-	-	6930	17500	20610
PLT ($\times 10^4$/mm^3)	1.4	-	-	0.7	0.6	0.3
CRP (mg/dL)	0.89	11.91	1.77	-	-	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 70s	Aplastic anaemia (hypertension)	200 mg for 5 days	**Febrile neutropenia, decreased platelet count** 31 days before administration: The patient was negative for anti-platelet antibody. 25 days before administration: The patient was diagnosed with aplastic anaemia. 6 days before administration: Platelet transfusion (10 U) was performed for 3 days. 3 days before administration: Platelet transfusion (10 U) was performed every 3 days. Day 1 of administration: Administration of anti-human thymocyte immunoglobulin, rabbit, (200 mg) and ciclosporin (300 mg) were started for aplastic anaemia. Methylprednisolone (125 mg) was administered as premedication. Day 5 of administration (day of completion of administration): Administration of anti-human thymocyte immunoglobulin, rabbit, was completed. 3 days after completion of administration: Decreased platelets developed. 6 days after completion of administration: Febrile neutropenia (FN) developed. Cefepime dihydrochloride hydrate 4 g was administered. The following treatment was performed for FN since neutrophil count had been 0 after 4 days of FN onset. 10 days after completion of administration: Clindamycin hydrochloride 1200 mg for 13 days and tazobactam sodium/piperacillin sodium 13.5 g for 5 days were administered for FN. 15 days after completion of administration: Meropenem hydrate 3 g was administered for 6 days. 19 days after completion of administration: Micafungin sodium 150 mg was administered for 2 days. 20 days after completion of administration: Cefozopran hydrochloride 4 g was administered for 5 days. 22 days after completion of administration: Administration of vancomycin hydrochloride 2 g was started. 24 days after completion of administration: Doripenem hydrate 1.5 g was administered for 4 days. 28 days after completion of administration: Biapenem 1.2 g was administered for 9 days. 31 days after completion of administration: Amphotericin B 150 mg was administered for 14 days. 37 days after completion of administration: Ciprofloxacin hydrochloride 600 mg was administered for 7 days. 44 days after completion of administration: Cefepime dihydrochloride hydrate 4 g was administered for 6 days. 45 days after completion of administration: Voriconazole 400 mg was administered for 7 days. 49 days after completion of administration: Administration of vancomycin hydrochloride 2 g was completed. 50 days after completion of administration:

				Cefozopran hydrochloride 2 g was administered for 7 days. Administration of teicoplanin 200 mg was started. 52 days after completion of administration: Administration of amphotericin B 150 mg was started. 57 days after completion of administration: Doripenem hydrate 1 g was administered for 4 days. 61 days after completion of administration: Biapenem 0.6 g was administered for 4 days. 63 days after completion of administration: The test for anti-platelet antibody was positive. 64 days after completion of administration: Tazobactam sodium/piperacillin sodium 13.5 g was administered for 3 days. 67 days after completion of administration: Imipenem hydrate/cilastatin sodium 1 g was administered for 4 days. 68 days after completion of administration: Administration of amphotericin B 150 mg was completed. 69 days after completion of administration: Administration of itraconazole 200 mg was started. 71 days after completion of administration: Administration of meropenem hydrate 1.5 g was started. 73 days after completion of administration: Administration of amikacin sulfate 200 mg was started. 78 days after completion of administration: The patient died of FN. Decreased platelets had not resolved.
	Concomitant medications: itraconazole, sulfamethoxazole/trimethoprim, ciclosporin, methylprednisolone, prednisolone, lenograstim (genetical recombination), candesartan cilexetil, human platelet concentrate			

Laboratory Examination

	6 days before administration	4 days before administration	Day 1 of administration	Day 3 of administration	Day 5 of administration (day of completion of administration)	3 days after completion of administration	7 days after completion of administration	10 days after administration	47 days after completion of administration	77 days after completion of administration
WBC (/mm^3)	1400	1730	1770	80	20	10	10	110	50	140
Hemoglobin (g/dL)	7.9	-	7.9	7.6	7.2	9.1	9.3	-	-	7.6
PLT (× 10^4/mm^3)	0.9	1.8	2.5	6.2	4.5	1.2	2.0	1.4	0.3	0.4
Neutrophils (%)	-	4	-	-	-	40	40	0	0	0
Stab cell	2	-	1	5	10	-	20	-	-	-
Segmented cell	2	-	-	5	10	-	20	-	-	-
CRP (mg/dL)	1.63	1.18	1	0.86	0.4	0.33	19	25.7	17	34.52

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Male 10s	Hematopoietic stem cell transplant (Acute lymphocytic leukaemia, radiotherapy)	70 mg for 4 days	**BK virus infection, cytomegalovirus test positive, mucous membrane disorder, haemorrhoids, hypertension, respiratory disorder, renal impairment, peripheral neuropathy, overload iron** Approximately 8 years before administration: The patient was diagnosed with acute lymphocytic leukaemia. First remission was confirmed after remission induction therapy. Consolidation and maintenance therapy were completed. Approximately 4 years before administration: Bone marrow relapse occurred 2 years later. Unrelated allogenic bone marrow transplantation was performed after second remission was achieved by chemotherapy. Engraftment was confirmed on Day 21. Bone marrow relapse occurred again. Concomitant therapy with nelarabine (Nel) + cyclophosphamide (CY) + etoposide (VP16) was performed for 5 days, and third remission was achieved. Three cycles of the same regime were performed. Day 1 of administration: Administration of anti-human thymocyte immunoglobulin, rabbit, (70 mg) was started. Day 4 of administration: (day of completion of administration) Administration of anti-human thymocyte immunoglobulin, rabbit, was completed. 2 days after completion of administration: Reduced-intensity stem cell transplantation (RIST) from his mother (Human leukocyte antigen [HLA] 2-loci-mismatched, Killer immunoglobulin-like receptor [KIR] mismatch +) was performed. 9 days after completion of administration: Respiratory disorder occurred. 10 days after completion of administration: Mucous membrane disorder occurred. 11 days after completion of administration: Prednisolone succinate sodium was administered for 36 days for respiratory disorder (grade 3). 13 days after completion of administration: Internal haemorrhoids developed. 14 days after completion of administration: Renal impairment (grade 3) occurred. 17 days after completion of administration: Morphine hydrochloride hydrate was administered for 65 days for respiratory disorder. 21 days after completion of administration: Hypertension occurred. Nicardipine hydrochloride was administered for 27 days. 24 days after completion of administration: Cefepime dihydrochloride hydrate for 32 days and teicoplanin for 31 days were administered for mucous membrane disorder. 31 days after completion of administration: Internal haemorrhoids remitted. 37 days after completion of administration: BK viral cystitis occurred. Engraftment confirmed (complete chimera).

				41 days after completion of administration: Peripheral neuropathy occurred. 44 days after completion of administration: Mucous membrane disorder and respiratory disorder remitted. 47 days after completion of administration: Hypertension remitted. 75 days after completion of administration: Administration of gabapentin was started for peripheral neuropathy. 95 days after completion of administration: Cytomegalovirus (CMV) antigenemia occurred. 97 days after completion of administration: Foscarnet sodium hydrate was administered for 144 days CMV antigenemia. 138 days after completion of administration: Hyperferremia occurred. Deferasirox was administered for 107 days. 219 days after completion of administration: BK viral cystitis remitted. 249 days after completion of administration: Hyperferremia remitted.
	Concomitant medications: sulfamethoxazole/trimethoprim, clostridium butyricum preparation, fludarabine phosphate, melphalan, tacrolimus hydrate, nelarabine, cyclophosphamide hydrate, etoposide			

4 **Tacrolimus Hydrate** (oral and injectable dosage form)

Brand Name (name of company)	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 5 mg (Astellas Pharma Inc.)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous
Indications	1. Prophylaxis of organ rejection in patients receiving kidney, liver, heart, lung, and pancreas transplant 2. Prophylaxis of rejection and graft versus host disease after bone marrow transplantation 3. Myasthenia gravis (only for Prograf Capsules 0.5 mg and 1 mg, Prograf Granules 0.2 mg and 1 mg) 4. Rheumatoid arthritis (limited to patients who fail to adequately respond to conventional therapy; and only for Prograf Capsules 0.5 mg and 1 mg) 5. Lupus nephritis (limited to patients who fail to adequately respond to steroids or cannot use steroids due to adverse reactions; and only for Prograf Capsules 0.5 mg and 1 mg) 6. Refractory (steroid-resistant/steroid-dependent) active ulcerative colitis (limited to moderate to severe cases; and only for Prograf Capsules 0.5 mg, 1 mg, and 5 mg)

≪PRECAUTIONS (underlined parts are revised)≫

[Important Precautions]

<u>In hepatitis B virus carriers who receive an immunosuppressant therapy, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus has been reported in patients who were negative for HBs antigen after starting immunosuppressant. Hepatitis C may exacerbate in hepatitis C virus carriers after starting immunosuppressant therapy. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function test or hepatitis viral markers, etc.</u>

[Adverse Reactions (clinically significant adverse reactions)]

Pancytopenia, thrombocytopenic purpura, aplasia pure red cell: Pancytopenia, thrombocytopenic purpura, aplasia pure red cell may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as dose reduction or drug suspension should be taken.

Infection: Bacterial, viral, fungal or protozoal infection may occur or worsen. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, or administration of antibiotic should 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, 2007 to February 7, 2011)

- Reactivation of hepatitis B or C: 15 cases (2 fatal cases)
- Aplasia pure red cell: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 50,000 (FY 2010)

Launched into Japan: June 1993

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Rheumatoid arthritis (asymptomatic hepatitis B virus [HBV] carrier)	Unknown	**Fulminant hepatitis** Approximately 22 years before discontinuation: The patient developed severe rheumatoid arthritis. Administration of methotrexate and prednisolone were started. Approximately 1 to 8 years before discontinuation: Synovial tissue was removed from the knee (total 5 times) The patient had been negative for hepatitis B surface (HBs) antigen but turned positive for HBs antigen after the fourth surgery. The patient remained HBs antigen positive (Hepatitis B virus deoxyribonucleic acid [HBV-DNA] 3.1). The patient had a history of tuberculosis, nephrosis, and bronchiectasis. Date unknown: Administration of tacrolimus hydrate and adalimumab (genetical recombination) was started for treatment of rheumatoid arthritis (duration and dose of each drug unknown). 50 days before discontinuation: AST (GOT) 20 IU/L, ALT (GPT) 26 IU/L, total bilirubin 0.6 mg/dL. 8 days before discontinuation The patient visited the hospital complaining of cold. A Blood test was performed 2 days after the initial visit since the patient's condition had not improved. The patient was later diagnosed with fulminant hepatitis. 3 days before discontinuation AST (GOT) 1257 IU/L, ALT (GPT) 2594 IU/L, total bilirubin 3.7 mg/dL. Day of discontinuation: The patient was transferred to another hospital with jaundice and disturbed consciousness. With grade 2 hepatic encephalopathy, Prothrombin time (PT) 20% and HBV-DNA 8.6, the patient was diagnosed with HBV-induced fulminant hepatitis and admitted to the hospital. Administration of tacrolium hydrate and all concomitant drugs including

				adalimumab (genetical recombination), methotrexate, and prednisolone were discontinued. Steroid pulse therapy, continuous hemodiafiltration (CHDF), and plasma exchange were performed, and entecavir hydrate were administered. 5 days after discontinuation: Haemorrhage associated with bronchiectasis was noted. Intubation was performed because respiratory condition were uncontrolled. 11 days after discontinuation: Hepatic function did not improve. 17 days after discontinuation: The death of the patient was confirmed. The cause of death was fulminant hepatitis associated with HBV relapse.
	Concomitant medications: prednisolone, methotrexate, adalimumab (genetical recombination), salazosulfapyridine, isoniazid, calcium L-aspartate hydrate, alfacalcidol, benfotiamine/pyridoxine hydrochloride/cyanocobalamin combination capsule, teprenone, ampiroxicam, alendronate sodium hydrate, raloxifene hydrochloride, mecobalamin, clarithromycin, bromhexine hydrochloride, ambroxol hydrochloride, sodium cromoglicate, fluticasone propionate, tiotropium bromide hydrate			

Laboratory Examination

	50 days before discontinuation	3 days before discontinuation	2 days after discontinuation	6 days after discontinuation
AST (GOT) (IU/L)	20	1257	54	39
ALT (GPT) (IU/L)	26	2594	222	102
LDH (IU/L)	230	540	222	309
Al-P (IU/L)	225	396	244	244
Total bilirubin (mg/dL)	0.6	3.7	8.9	16.9

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Myasthenia gravis (thymectomy)	0.5 mg for Approx. 3 months ↓ (11-month drug withdrawal) ↓ 0.25 mg for Approx. 3 months	**Aplasia pure red cell** Approximately 9 years before administration: The patient developed diplopia and was diagnosed with myasthenia gravis (MG) based on clinical symptoms and testing positive for anti-acetylcholine receptor (anti-AChR) antibody. The patient was followed on an outpatient basis for MG (Myasthenia Gravis Foundation of America (MGFA) class IIb). Thymoma (Masaoka stage II) was found, and extended thymectomy was performed. Day 1 of administration: Administration of tacrolimus hydrate 0.5 mg was started for steroid reduction. Month 2 of administration (day of discontinuation): Haemoglobin decreased from 11.2 g/dL to 7.7 g/dL. The patient was diagnosed with aplasia pure red cell based on blood test and bone marrow findings. Administration of tacrolimus hydrate was discontinued. The patient was negative for parvovirus. 2 months after discontinuation: Aplasia pure red cell improved. 11 months after discontinuation (day of readministration): Administration of tacrolimus hydrate 0.25 mg was resumed for steroid reduction. Month 1 of readministration:

				Haemoglobin decreased from 13.2 g/dL to 11.7 g/dL. The patient was followed up. Month 3 of readministration (day of discontinuation of readministration): Administration of tacrolimus hydrate was discontinued again because haemoglobin decreased to 7.6 g/dL. 1 month after discontinuation of readministration: Haemoglobin gradually improved.
	Concomitant medications: prednisolone, ambenonium chloride, pyridostigmine bromide			

Laboratory Examination

	Before administration	Start of administration	Month 1 of administration	Month 2 of administration	Month 2 of administration (day of discontinuation):	1 month after discontinuation	2 months after discontinuation	Date unknown	Month 1 of readministration	Month 3 of readministration (day of discontinuation of readministration)
RBC ($\times 10^4/mm^3$)	420	360	345	332	-	372	431	-	-	-
Hemoglobin (g/dL)	11.2	9.7	8.7	7.8	7.7	8.3	11.6	13.2	11.7	7.6
PLT ($\times 10^4/mm^3$)	20.3	19.6	18.5	21.6	-	36.2	24.9	-	-	-
WBC ($/mm^3$)	5400	4700	4200	5100	-	7350	6616	-	-	-

5 Tolvaptan

Brand Name (name of company)	Samsca tablets 15 mg (Otsuka Pharmaceutical Co., Ltd.)
Therapeutic Category	Diuretic
Indications	Fluid retention due to heart failure in patients who are not adequately responsive to other diuretics such as loop diuretic

≪PRECAUTIONS (underlined parts are revised)≫

[Warnings]

WARNINGS

Dehydration or hypernatraemia caused by rapid water diuresis followed by disturbed consciousness have been reported in patients treated with this drug. Central pontine myelinolysis due to rapid increase in serum sodium may occur. Administration of this drug should be started or resumed while the patient is in hospital. Serum sodium should be frequently measured on the day of starting or resuming this drug.

[Important Precautions]

Intense water diuretic effect is exerted within 24 hours of administration. Serum sodium should be measured at least 4 to 6 hours and 8 to 12 hours after administration. Serum sodium should be measured everyday for about 1 week after administration and as appropriate while continuing the treatment.

[Adverse Reactions (clinically significant adverse reactions)]

Hypernatraemia: Hypernatraemia followed by haemoconcentration due to the water diuretic effect of this drug may occur. In some cases, disturbed consciousness may occur. Patients should be carefully monitored for amounts of fluid intake, urine output, serum sodium concentration, and symptoms such as thirst and dehydration during treatment. If symptoms including persistent thirst or dehydration are observed, the dose of this drug should be reduced or administration should be discontinued, and appropriate measures such as fluid replacement including

transfusion should be taken depending on the symptoms. If the serum sodium concentration increases to above the normal range, administration of this drug should be discontinued immediately, and appropriate measures such as fluid replacement including transfusion should be taken depending on the symptoms.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 4 months (from initial marketing to March 4, 2011)

- Hypernatraemia: 7 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: approximately 2000 (January to March 2011)

Launched into Japan: December 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	No urination despite diuretic use (congestive cardiac failure, sepsis, hypertension, hypoalbuminaemia)	15 mg for 3 days	**Hypernatraemia, disturbed consciousness, hypercapnia** 2 days before administration: The patient was admitted to the ICU based on a diagnosis of congestive cardiac failure. The diagnostic images showed excessive pleural effusion and ascites, anasarca, hypoalbuminaemia, and respiratory failure. Continuous IV infusion of furosemide (diuretic) 5A (100 mg) + physiological saline solution 40 mL was started. Albumin was administered for hypoalbuminaemia, but the patient had no urination. Day 1 of administration: Administration of tolvaptan 15 mg was started using tube. The patient had urination. Respiratory condition improved. Day 3 of administration (day of discontinuation): Hypernatraemia, disturbed consciousness, and hypercapnia occurred. Blood test showed that serum sodium increased to 146 mEq/L. Administration of 5% glucose solution 1500 mL/day was started. 1 day after discontinuation: Administration of tolvaptan was discontinued. 3 days after discontinuation: Drip infusion was switched to sodium-free 5% glucose solution, but serum sodium increased. Serum sodium was 157 mEq/L. The patient was transferred to the general ward. 4 days after discontinuation: Serum sodium 163 mEq/L. Blood gas analysis showed hypercapnia. The patient fell into respiratory arrest. The patient died. (The cause of death was hypercapnia. Autopsy was not performed.)
	Concomitant medications: maintenance solution (17), furosemide, physiological saline solution, human serum albumin, meropenem hydrate			

Laboratory Examination

	2 days before administration		1 day before administration	Day 1 of administration	Day 2 of administration	Day 3 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation
	After noon	Evening								
Na (mEq/L)	141	140	141	140	144	146	-	-	157	163
K (mEq/L)	4.2	4.4	4.3	5.0	4.6	4.0	-	-	3.5	3.3
Cl (mEq/L)	104	105	106	103	104	105	-	-	106	110
Urine output (mL/day)	160		347	1090	3400	3765	3750	2100	-	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 80s	Congestive cardiac failure unresponsive to other drugs. Congestive cardiac failure, pulmonary oedema with orthopnoea, mitral valve incompetence)	15 mg for 3 days	**Hypernatraemia, disturbed consciousness (drowsy)** The amount of fluid intake was restricted to < 1000 mL upon admission, but the actual daily intake was unclear since the patient was unable to communicate clearly. Day 1 of administration: Baseline serum sodium was 142 mEq/L. The patient started receiving tolvaptan 15 mg/day for congestive cardiac failure unresponsive to other drugs. Day 3 of administration (day of discontinuation): Blood test in the morning showed serum sodium was 156 mEq/L (the patient had taken tolvaptan before the test data was known). Oral administration of tolvaptan was discontinued after the morning dose (taken for 3 days in total). Disturbed Consciousness (drowsy) developed. Respiratory support with bilevel positive airway pressure (BiPAP) was started. 1 day after discontinuation: Serum sodium: 167 to 170 mEq/L (blood sampled every 4 hours). Level of consciousness was still “drowsy” with no convulsions. Physiological saline solution of all drip infusion was switched to sodium-free solution. 5% glucose solution 2500 mL/day was administered by drip infusion. Consciousness returned to the baseline level at night. 2 days after discontinuation: Serum sodium: 169 mEq/L→166 mEq/L→166 mEq/L→164 mEq/L 5% glucose solution 2000 mL/day was administered by drip infusion. Dose of furosemide was increased (40 mg/day to 160 mg/day). 3 days after discontinuation: Serum sodium: 163 mEq/L→162 mEq/L→144 mEq/L→160 mEq/L 5% glucose solution 2000 mL/day was administered by drip infusion. 4 days after discontinuation: Serum sodium 159 mEq/L 5% glucose solution 1500 mL/day was administered by drip infusion.

				5 days after discontinuation: Serum sodium 157 mEq/L 5% glucose solution 1500 mL/day was administered by drip infusion. 6 days after discontinuation: Serum sodium 153 mEq/L 5% glucose solution 1500 mL/day was administered by drip infusion. 7 days after discontinuation: Serum sodium 141 mEq/L 5% glucose solution 1000 mL/day was administered by drip infusion. Hypernatraemia resolved. Serum sodium remained around 140 mEq/L. 8 days after discontinuation: Serum sodium 144 mEq/L 10 days after discontinuation: Serum sodium 138 mEq/L
	Concomitant medications: carperitide (genetical recombination), amino acid/carbohydrates/electrolytes/vitamins (4), furosemide, human serum albumin, dopamine hydrochloride			

Laboratory Examination

	2 days before administration	1 day before administration	Immediately before administration	Day 2 of administration	Day 3 of administration (day of discontinuation)	1 day after discontinuation			
						Noon	3 hours later	7 hours later	10 and a half hours later
Na (mEq/L)	139	-	142	150	156	167	167	167	170
K (mEq/L)	3.4	-	2.9	3.6	3.9	-	-	-	4.5
Cl (mEq/L)	102	-	99	112	112	-	-	-	127
Urine output (mL/day)	2200	1050	3250	3520	4850	3800			

	2 days after discontinuation				3 days after discontinuation				4 days after discontinuation
	Time unknown	Morning	6 hours later	11 and a half hours later	Early morning	5 hours later	10 hours later	Time unknown	
Na (mEq/L)	169	166	166	164	163	162	144	160	159
K (mEq/L)	5.0	-	-	4.1	4.1	3.4	3.5	-	3.4
Cl (mEq/L)	123	-	-	119	119	115	109	-	112
Urine output (mL/day)	2370				4650				2520

	5 days after discontinuation	6 days after discontinuation	7 days after discontinuation	8 days after discontinuation	10 days after discontinuation
Na (mEq/L)	157	153	141	144	138
K (mEq/L)	3.1	3.2	3.0	-	-
Cl (mEq/L)	111	107	100	-	-
Urine output (mL/day)	1950	1450	-	-	-

6 Pioglitazone Hydrochloride, Pioglitazone Hydrochloride/Glimepiride, Pioglitazone Hydrochloride/Metformin Hydrochloride

Brand Name (name of company)	**Pioglitazone Hydrochloride** ACTOS Tablets 15, 30, ACTOS OD Tablets 15, 30 (Takeda Pharmaceutical Company Limited) **Pioglitazone hydrochloride/Glimepiride** SONIAS Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited) **Pioglitazone Hydrochloride/Metformin Hydrochloride** METACT Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Antidiabetic agents
Indications	**Pioglitazone Hydrochloride** Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments and may have insulin resistance: 1. (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies (3) α-glucosidase inhibitor along with diet and exercise therapies (4) Biguanide along with diet and exercise therapies 2. Insulin along with diet and exercise therapies **Pioglitazone hydrochloride/glimepiride** Type 2 diabetes mellitus To be used only when the concomitant use of pioglitazone hydrochloride and glimepiride is considered appropriate. **Pioglitazone hydrochloride/metformin hydrochloride** Type 2 diabetes mellitus To be used only when the concomitant use of pioglitazone hydrochloride and metformin hydrochloride is considered appropriate.

≪PRECAUTIONS (underlined parts are revised)≫

[Important Precautions]

Interstitial pneumonia may occur. If pyrexia, cough, dyspnoea or abnormal chest sound (crepitations) etc. are observed, examinations including chest X-ray, chest CT, and serum marker test should be immediately performed. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should 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, 2007 to January 27, 2011)

- Interstitial pneumonia: 7 cases (no fatal case)

The number of patients using this drug per year estimated by MAHs: Approximately 1.32 million (FY 2009)

Launched into Japan:

December 1999 (Pioglitazone hydrochloride)

July 2010 (Pioglitazone hydrochloride/metformin hydrochloride)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Diabetes mellitus Cerebral infarction, gastritis)	7.5 mg for 35 days ↓ 15 mg for 102 days	**Interstitial pneumonia** Medical history: Renal cancer surgery The patient had been taking antidiabetics for over 4 years. Day 1 of administration: Metformin hydrochloride was switched to pioglitazone hydrochloride and administration of pioglitazone hydrochloride (7.5 mg/day) was started. Day 36 of administration: Dose of pioglitazone was increased to 15 mg/day. Day 97 of administration: Crackle in the bilateral lower lungs increased. The patient was followed without additional treatment since he was asymptomatic. Day 105 of administration: Abdominal CT showed opacity in lower lungs, but no further examination was performed since the patient was asymptomatic. Day 132 of administration: The patient started to complain about cough. Day 133 of administration: SpO_2 was 89% immediately after walking (hypoxaemia). Chest x-ray showed volume loss and increased opacity in bilateral lower lungs. Interstitial pneumonia was confirmed on chest CT. Dyspnea was later confirmed. Day 134 of administration: Oral administration of prednisolone (25 mg/day) was started. Day 137 of administration (day of discontinuation): Administration of pioglitazone hydrochloride was discontinued. 1 day after discontinuation: Administration of insulin was started due to increased blood glucose. 4 days after discontinuation:Cough and crackle improved. 25 days after discontinuation: Dose of prednisolone (15 mg/day) and glibenclamide was reduced. 36 days after discontinuation: Chills and hyperthermia occurred, and administration of cefdinir was started. 39 days after discontinuation: Hyperthermia recurred, and the patient was admitted to the hospital (with suspected urinary tract infection). Diagnostic imaging performed during hospitalization showed decreased interstitial opacity. 53 days after discontinuation: The patient was discharged from the hospital. 81 days after discontinuation: Lymphocyte stimulation test was negative for pioglitazone.
	Concomitant medications: glibenclamide, voglibose, aspirin, famotidine			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Non-insulin dependent diabetes mellitus (Bronchial asthma, bronchial asthma attack , chronic respiratory tract infection, hypercholesterolaemia, hyperuricaemia, hepatic steatosis, insomnia)	15 mg for 7 days	**Drug-induced lung disorder** Smoking history (37 to 3 years before administration) 60 cigarettes/day The patient had had bronchial asthma since childhood and been treated with steroid and long-acting beta agonist inhaler. Approximately 1.5 years before administration: The patient started receiving glibenclamide and acarbose. 24 days before administration: The patient was admitted to a hospital due to poor glycemic control. Chest x-ray upon admission showed no abnormality. Diet therapy was started. 21 days before administration: Intensive insulin therapy was started. 7 days to 1 day before administration: Since bronchial asthma attack occurred, steroid was administered. Day 1 of administration: Administration of pioglitazone hydrochloride was started. The patient had pyrexia in the evening (37°C range). Day 2 of administration: Headache developed. Day 3 of administration: Acetaminophen was administered as needed for pyrexia and headache (for 5 days). Day 4 of administration: Status asthmaticus and hypoxaemia were noted. Prednisolone sodium succinate was administered by drip infusion. Day 5 of administration: Chest x-ray showed particulate opacity in bilateral lower lung fields and increased neutrophil count and CRP were noted. Concomitant respiratory tract infection was suspected, and cefotaxime sodium was administered (4 days). Day 6 of administration: Chest CT showed bilateral diffuse particulate opacity. Day 7 of administration (day of discontinuation): Based on mycoplasma antibody positive (× 80), administration of azithromycin hydrate was started. Diffuse panbronchiolitis or interstitial pneumonia was suspected based on CT findings. Administration of pioglitazone hydrochloride was discontinued. Asthmatic attack improved. 1 day after discontinuation: Headache disappeared. Drip infusion of prednisolone sodium succinate was switched to oral prednisolone. 2 days after discontinuation: Pyrexia disappeared. Mycoplasma antibody did not increase, and sputum culture was positive for mucoid *pseudomonas aeruginosa*. However CT findings could not be explained by bacterial infection or bronchial asthma. Cefotaxime sodium was switched to meropenem hydrate and amikacin sulfate. 3 days after discontinuation: Asthmatic attack disappeared. 6 days after discontinuation: Dose of prednisolone was reduced. 9 days after discontinuation: No inflammation was noted. Administration of meropenem hydrate and amikacin sulfate were discontinued. Dose of

				prednisolone was reduced. 11 days after discontinuation: Administration of prednisolone was discontinued. 12 days after discontinuation: Chest CT showed bilateral diffuse particulate opacity was slightly reduced. 15 days after discontinuation: Bronchoscopy was performed. Bronchoalveolar lavage in the right middle lobe showed total cell count 22000/mL and increased lymphocyte count. Lung biopsy showed alveolar interstitial inflammation and alveolar wall fibrosis. Interstitial lung disorder was suggested. No granulation tissue was found. Lymphocyte stimulation test showed negative for pioglitazone. 20 days after discontinuation: Chest CT showed further reduced diffuse particulate opacity. 170 days after discontinuation: Chest CT showed further reduced diffuse particulate opacity, but a small amount remained.
	Concomitant medications: acarbose, theophylline, montelukast sodium, clarithromycin, atorvastatin calcium hydrate, insulin, budesonide, sodium cromoglicate, salbutamol sulfate, prednisolone sodium succinate, prednisolone, salmeterol xinafoate, zopiclone, heparin sodium			

4

Revision of Precautions (No. 225)

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 March 22 and 29, 2011 (excluding those presented in 2. Safety Measures Related to Lenalidomide Hydrate and 3. Important Safety Information of this Bulletin).

1 < Antivirals >

Sanilvudine

[Brand Name] ZERIT CAPSULES 15, 20 (Bristol-Myers K.K.)

[Precautions of Indications] This drug should only be used when no other appropriate treatment is available, and the administration period of this drug should be as short as possible.

[Important Precautions] Anti-HIV drugs may cause redistribution/accumulation of body fat. Lipoatrophy and acquired lipodystrophy develop more frequently with this drug in comparison to other nucleoside reverse-transcriptase inhibitors (tenofovir, abacavir). The onset and severity of the diseases may be correlated with the treatment duration. Once affected, the patient may not recover even if this drug is switched to another nucleoside reverse-transcriptase inhibitor (tenofovir, abacavir). The clinical benefit should be weighed against potential risks, and alternative anti-HIV drug should be carefully considered before using this drug. The patient should be carefully monitored for signs of lipoatrophy and acquired lipodystrophy through examinations that identify signs of body fat redistribution/accumulation, and periodically interviewed to check for any changes in the patient's physical condition.

2 < Antipyretics and analgesics, anti-inflammatory agents >

Acetaminophen (without indication for osteoarthritis)

[Brand Name] Pyretinol (Iwaki Seiyaku Co., Ltd.), ALPINY SUPPOSITORIES 50, 100, 200 (Hisamitsu Pharmaceutical Co., Inc.), ANHIBA Suppositories for Pediatric Use 50 mg, 100 mg, 200 mg (Abbott JAPAN Co., Ltd.)

[Warnings]

WARNINGS

Caution should be exercised for possible serious liver disorder associated with this drug.

Serious liver disorder due to acetaminophen overdose may occur in concomitant use of other drugs containing acetaminophen (including OTC drugs). Such drugs should not be administered with this drug.

[Important Precautions] Caution should be exercised for development of possible serious liver disorders. When this drug is administered for long term, periodic liver function tests are recommended.

3

< Antipyretics and analgesics, anti-inflammatory agents >

Isopropylantipyrine/Acetaminophen/Allylisopropylacetylurea/ Anhydrous Caffeine

[Brand Name] SG Combination Granules (Shionogi & Co., Ltd.)

[Warnings]

WARNINGS

Caution should be exercised for possible serious liver disorder associated with acetaminophen contained in this drug.

Serious liver disorder due to acetaminophen overdose may occur in concomitant use of other drugs containing acetaminophen (including OTC drugs). Such drugs should not be administered with this drug.

[Careful Administration]

Heavy alcohol drinker

Patients with glutathione deficiency or dehydrated patients due to fasting, malnutrition, or eating disorder, etc.

[Overdose]

If acetaminophen detoxification (reduction of liver disorder) is performed after overdose, administration of acetylcysteine should be considered.

4

< Psychotropics >

Oxypertine
Olanzapine
Carpipramine Hydrochloride Hydrate
Carpipramine Maleate
Quetiapine Fumarate
Clocapramine Hydrochloride Hydrate
Clozapine
Chlorpromazine Hydrochloride
Chlorpromazine Hydrochloride/ Promethazine Hydrochloride/ Phenobarbital
Chlorpromazine Hibenzate
Chlorpromazine Phenolphthalinate
Spiperone
Paliperidone
Pipamperone Hydrochloride
Pimozide
Fluphenazine Decanoate
Fluphenazine Maleate
Prochlorperazine Maleate
Prochlorperazine Mesilate
Blonanserin
Propericiazine
Bromperidol
Perphenazine
Perphenazine Hydrochloride
Perphenazine Fendizoate
Perphenazine Maleate
Perospirone Hydrochloride Hydrate
Mosapramine Hydrochloride
Moperone Hydrochloride
Risperidone
Levomepromazine Hydrochloride
Levomepromazine Maleate

Sultopride Hydrochloride
Sulpiride
Zotepine
Timiperone
Trifluoperazine Maleate
Nemonapride

[Brand Name]

FORIT TABLETS 20 mg, 40 mg, FORIT POWDER 10% (Daiichi Sankyo Company, Limited)
Zyprexa Tablet 2.5 mg, 5 mg, 10 mg, Zyprexa Fine Granules 1%, Zyprexa Zydis Tablets 5 mg, 10 mg (Eli Lilly Japan K.K.)
DEFEKTON SUGAR-COATED TABLETS 25 mg, 50 mg (Mitsubishi Tanabe Pharma Corporation)
DEFEKTON POWDER 10% (Mitsubishi Tanabe Pharma Corporation)
Seroquel 25mg Tablets, Seroquel 100 mg Tablets, Seroquel 200 mg Tablets, Seroquel Fine Granules 50% (Astellas Pharma Inc.)
CLOFEKTON TABLETS 10 mg, 25 mg, 50 mg (Zensei Pharmaceutical Industries, Co., Ltd,), CLOFEKTON GRANULES 10% (Mitsubishi Tanabe Pharma Corporation)
CLOZARIL Tablets 25 mg, 100 mg (Novartis Pharma K.K.)
Wintermin Tablet 12.5 mg, 25 mg, 50 mg, 100 mg (Shionogi & Co., Ltd.), CONTOMIN SUGAR-COATED TABLETS 12.5 mg, 25 mg, 50 mg, 100 mg, CONTOMIN INTRAMUSCULAR INJECTION 10 mg, 25 mg, 50 mg (Mitsubishi Tanabe Pharma Corporation)
Vegetamin A Combination Tablet, Vegetamin B Combination Tablet (Shionogi & Co., Ltd.)
CONTOMIN Powder, 10% CONTOMIN Granule 10% (Mitsubishi Tanabe Pharma Corporation)
Wintermin Fine Granule 10% (Shionogi & Co., Ltd.)
Spiropitan Tablets 0.25 mg, 1mg, Spiropitan Powder 0.3% (Sannova Co. Ltd.)
Barnetil Tab.50, 100, 200, Barnetil Fine granule 50% (Bayer Yakuhin, Ltd.)
Abilit Tablet 50 mg, 100 mg, 200 mg, Abilit Capsule 50 mg, Abilit Fine Granule 10 %, 50% (Dainippon Sumitomo Pharma Co., Ltd.), Dogmatyl Tablets 50 mg, 100 mg, 200 mg, Dogmatyl Capsules 50mg, Dogmatyl Fine Granules 10%, 50%, Dogmatyl Intramuscular Injection 50 mg, 100 mg (Astellas Pharma Inc.)
Lodopin Tablets 25 mg, 50 mg 100 mg, Lodopin Fine Granules 10%, 50% (Astellas Pharma Inc.)
TOLOPELON TABLETS 0.5 mg, 1 mg, 3 mg, TOLOPELON FINE GRANULES 1%, TOLOPELON INJECTION 4 mg (Daiichi Sankyo Company, Limited)
TRIFLUOPERAZINE SUGAR-COATED TABLETS “YOSHITOMI” 2.5, 5 TRIFLUOPERAZINE POWDER 1% “MITSUBISHI” (Mitsubishi Tanabe Pharma Corporation)
Emilace Tablets 3 mg, 10 mg, Emilace Fine Granules 2% (Astellas Pharma Inc.)
Invega Tablets 3 mg, 6 mg, 9 mg (Janssen Pharmaceutical K.K.)
Propitan Tablets 50 mg, Propitan Powder 10% (Sannova Co., Ltd.)
Orap Tablets 1 mg, 3 mg, Orap Fine Granules 1% (Astellas Pharma Inc.)
Fludecasin INTRAMUSCULAR INJECTION 25mg, Fludecasin Kit INTRAMUSCULAR INJECTION 25mg (Mitsubishi Tanabe Pharma Corporation)
FLUMEZIN SUGAR-COATED TABLETS 0.25, 0.5, 1, FLUMEZIN POWDER 0.2% (Mitsubishi Tanabe Pharma Corporation)
Novamin Tablet 5 mg (Shionogi & Co., Ltd.)
Novamin Intramuscular Injection 5 mg (Shionogi & Co., Ltd.)
Lonasen 2 mg Tablets, Lonasen 4 mg Tablets, Lonasen 8 mg Tablets, Lonasen 2%

Powder (Dainippon Sumitomo Pharma Co., Ltd.)
Neuleptil Tablet 5 mg, 10 mg, 25 mg, Neuleptil Fine Granule 10%, Neuleptil Oral Solution 1% (Shionogi & Co., Ltd.)
Impromen TABLETS 1 mg, 3 mg, 6 mg, Impromen FINE GRANULES 1% (Janssen Pharmaceutical K.K.)
TRILAFON Tab. 2 mg, 4 mg, 8 mg, TRILAFON Powder 1% (Kyowa Pharmaceutical Industry Co., Ltd.)
PZC INTRAMUSCULAR INJECTION 2 mg (Mitsubishi Tanabe Pharma Corporation)
PZC POWDER 1% (Mitsubishi Tanabe Pharma Corporation)
PZC SUGAR-COATED TABLETS 2 mg, 4 mg, 8 mg (Mitsubishi Tanabe Pharma Corporation)
Lullan 4 mg Tablets, Lullan 8 mg Tablets, Lullan 16 mg Tablets (Dainippon Sumitomo Pharma Co., Ltd.)
Cremin TABLETS 10 mg, 25 mg, 50 mg, Cremin GRANULES 10% (Mitsubishi Tanabe Pharma Corporation)
Luvatren Tablet, Luvatren Powder (Astellas Pharma Inc.)
RISPERDAL Tablets 1 mg, 2 mg, 3 mg, RISPERDAL Fine Granules 1%, RISPERDAL Oral Solution 1 mg/mL, RISPERDAL OD Tablets 0.5 mg, 1 mg, 2 mg, RISPERDAL Consta Intramuscular Injection 25 mg, 37.5 mg, 50 mg (Janssen Pharmaceutical K.K.)
Hirnamin Intramuscular Injection 25 mg (Shionogi & Co., Ltd.), LEVOTOMIN INTRAMUSCULAR INJECTION 25 mg (Mitsubishi Tanabe Pharma Corporation)
Hirnamin Tablet 5 mg, 25 mg, 50 mg, Hirnamin Powder 50%, Hirnamin Fine Granule 10% (Shionogi & Co., Ltd.), LEVOTOMIN TABLETS 5 mg, 25 mg, 50 mg, LEVOTOMIN POWDER 10% 50%, LEVOTOMIN GRANULES 10% (Mitsubishi Tanabe Pharma Corporation)

[Use in Pregnant, Parturient And Nursing Women]

Withdrawal symptoms and extrapyramidal symptoms such as feeding disorder, somnolence, respiratory disorder, tremor, hypotonia, and irritability have been reported in neonates whose mothers were treated with antipsychotics in late pregnancy.

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5 **< Psychotropics >**

Trazodone Hydrochloride

[Brand Name]

Desyrel Tablets 25, 50 (Pfizer Japan Inc.), RESLIN Tablets 25, 50 (MSD K.K.)

[Contraindications]

Patients on treatment with saquinavir mesilate

[Interaction (contraindications for concomitant use)]

Saquinavir mesilate

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6 **< Psychotropics >**

Haloperidol

[Brand Name]

Serenace Tablet 0.75 mg, 1 mg, 1.5 mg, 3 mg, Serenace Oral Solution 0.2%, Serenace Injection 5 mg (Dainippon Sumitomo Pharma Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Ventricular fibrillation, ventricular tachycardia: Ventricular fibrillation, ventricular tachycardia (including Torsades de pointes), and prolonged QT may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as dose reduction and discontinuing administration should be taken.
Agranulocytosis, **decreased white blood cell**, **decreased platelets**:

Agranulocytosis, decreased white blood cell (initial symptoms include pyrexia, pharynx pain and general malaise) and, decreased platelets (initial symptoms include subcutaneous/submucosal haemorrhage) may occur. If any abnormalities are observed, a blood test should be performed and appropriate measures such as discontinuing administration should be taken.

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

[Use in Pregnant, Parturient And Nursing Women]

This drug should not be administrated to pregnant women or to women who may be pregnant. [Teratogenicity was suspected in some cases. Results of animal studies showed teratogenicity including cleft palate (mouse), brain malformation (hamster), decreased implantation, increased fetal resorption (mouse), and increased abortion rate (rat). Withdrawal symptoms and extrapyramidal symptoms, such as feeding disorder, somnolence, respiratory disorder, tremor, hypotonia, and irritability, have been reported in neonates whose mothers were treated with antipsychotics during late pregnancy.]

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7 **< Psychotropics >**

Haloperidol Decanoate

[Brand Name]

NEOPERIDOL Injection 50, 100 (Johnson & Johnson K.K.), HALOMONTH Injection 50 mg, 100 mg (Janssen Pharmaceutical K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Ventricular fibrillation, ventricular tachycardia: Ventricular fibrillation, ventricular tachycardia (including Torsades de pointes), and prolonged QT may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as dose reduction and discontinuing administration should be taken.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH): Syndrome of inappropriate antidiuretic hormone secretion (SIADH) accompanied by hyponatraemia, blood hyposmosis, increased urine sodium, hypersthenuria, convulsions, or disturbed consciousness may occur. In such cases, administration of this drug should be discontinued, and appropriate measures such as restricting fluid intake should be taken.

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

Agranulocytosis, decreased white blood cell, decreased platelets:
Agranulocytosis, decreased white blood cell (initial symptoms include pyrexia, pharynx pain and general malaise) and, decreased platelets (initial symptoms include subcutaneous/submucosal haemorrhage) may occur. If any abnormalities are observed, a blood test should be performed and appropriate measures such as discontinuing administration should be taken.

[Use in Pregnant, Parturient And Nursing Women]

This drug should not be administrated to pregnant women or to women who may be pregnant. [Animal studies (rat, rabbit) showed no teratogenicity but increased fetal and neonatal mortality.

For a similar compound (haloperidol), teratogenicity was suspected in some clinical cases, and also teratogenicity such as cleft palate (mouse) and brain malformation (hamster) and fetotoxicity including decreased implantation, fetal resorption (mouse) and increased abortion rate (rat) are noted in animal studies. Withdrawal symptoms and extrapyramidal symptoms such as feeding disorder, somnolence, respiratory disorder, tremor, hypotonia, and irritability have been reported in neonates whose mothers were treated with antipsychotics during late pregnancy.]

8

< Common cold drugs >

Salicynamide/Acetaminophen/Anhydrous Caffeine/ Chlorpheniramine Maleate (for adult)

Salicynamide/Acetaminophen/Anhydrous Caffeine/ Promethazine Methylenedisalicylate (for adult)

[Brand Name]

NEO-AMUNOLL Combination Powder (Sanwa Kagaku Kenkyusho Co., Ltd.),
Pelex combination granule (Taiho Pharmaceutical Co., Ltd.)
PL Combination Granules (Shionogi & Co., Ltd)

[Warnings]

WARNINGS

Caution should be exercised for possible serious liver disorder associated with acetaminophen contained in this drug.
Serious liver disorders due to acetaminophen overdose may occur in concomitant use of other drugs containing acetaminophen (including OTC drugs). Concomitant use of such drug should be avoided.

[Contraindications]

Patients with serious hepatic disorder

[Careful Administration]

Heavy alcohol drinker
Patients with glutathione deficiency or dehydrated patients due to fasting, malnutrition or eating disorder, etc.

[Overdose]

If acetaminophen detoxification (reduction of liver disorder, etc.) is performed after overdose, administration of acetylcysteine should be considered.

9

< Common cold drugs >

Salicynamide/Acetaminophen/Anhydrous Caffeine/ Chlorpheniramine Maleate (for pediatric)

Salicynamide/Acetaminophen/Anhydrous Caffeine/ Promethazine Methylenedisalicylate (for pediatric)

[Brand Name]

Pediatric Pelex combination granule (Taiho Pharmaceutical Co., Ltd.), LL COMBINATION SYRUP FOR PEDIATRIC (Daiichi Sankyo Company, Limited)
PL Combination Granules for Infant (Shionogi & Co., Ltd)

[Warnings]

WARNINGS

Caution should be exercised for possible serious liver disorder associated with acetaminophen contained in this drug.
Serious liver disorders due to acetaminophen overdose may occur in concomitant use of other drugs containing acetaminophen (including OTC drugs). Concomitant use of such drug should be avoided.

[Contraindications]

Patients with serious hepatic disorder

[Careful Administration]

Heavy alcohol drinker
Patients with glutathione deficiency or dehydrated patients due to fasting, malnutrition or eating disorder, etc.

[Interaction (precautions for concomitant use)]	Preparations containing alcohol, alcohol
[Overdose]	If acetaminophen detoxification (reduction of liver disorder, etc.) is performed after overdose, administration of acetylcysteine should be considered.

10 **< Antiarrhythmic agents >**

Amiodarone Hydrochloride (injectable dosage form)

[Brand Name]	Ancaron inj. 150 (Sanofi-Aventis K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Hyperthyroidism**: Hyperthyroidism may occur. Patients should be carefully monitored using thyroid function tests, if necessary, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

11 **< Antihypertensives >**

Olmesartan Medoxomil
Olmesartan Medoxomil/Azelnidipine

[Brand Name]	OLMETEC TABLETS 5 mg, 10 mg, 20 mg, 40 mg (Daiichi Sankyo Company, Limited) REZALTAS COMBINATION TABLETS LD, HD (Daiichi Sankyo Company, Limited)
[Adverse Reactions (clinically significant adverse reactions)]	**Anaphylactoid symptoms**: Symptoms including pruritus, generalised redness, decreased blood pressure, and dyspnea may occur. Anaphylactic shock has been also reported. 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 **< Blood and body fluid agents-Miscellaneous >**

Beraprost Sodium

[Brand Name]	DORNER Tablets 20 μg, Careload LA Tablets 60 μg (Toray Industries, Inc.), PROCYLIN Tablets 20, BERASUS LA Tablets 60 μg (Kaken Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, syncope, loss of consciousness**: Shock, syncope, and loss of consciousness may occur. Patients should be carefully monitored, and if decreases in blood pressure, tachycardia, facial pallor, or queasy are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

13 **< Antitussives >**

Diprophylline/Dihydrocodeine Phosphate/dl-Methylephedrine Hydrochloride/Diphenhydramine Salicylate/Acetaminophen/ Bromovalerylurea
Ephedra Herb extract/Caffeine and Sodium Benzoate/ Magnesium Oxide/Acetaminophen/Scopolia Extract

[Brand Name]	Coughcode-N Combination Tablets (Mylan Seiyaku Ltd.) Asgen Granule, Asgen Tablet (Asgen Pharmaceutical Co., Ltd.)

[Warnings]

WARNINGS

Caution should be exercised for possible serious liver disorder associated with acetaminophen contained in this drug.
Serious liver disorders due to acetaminophen overdose may occur in concomitant use of other drugs containing acetaminophen (including OTC drugs). Concomitant use of such drug should be avoided.

[Careful Administration]

Patients with glutathione deficiency or dehydrated patients due to fasting, malnutrition or eating disorder, etc.

[Overdose]

If acetaminophen detoxification (reduction of liver disorder, etc.) is performed after overdose, administration of acetylcysteine should be considered.

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14 **< Respiratory organ agents-Bronchodilators >**

Tiotropium Bromide Hydrate

[Brand Name]

Spiriva Inhalation Capsules 18 μg, Spiriva 2.5 μg Respimat 60 puffs
(Nippon Boehringer Ingelheim Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Angle closure glaucoma: Angle closure glaucoma may be induced. If reduced visual acuity, eye pain, headache, or hyperaemia are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

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15 **< Dental preparations-Antibiotics >**

Minocycline Hydrochloride (dental)

[Brand Name]

PERIOCLINE Dental Ointment (Sunstar Inc.)

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored. If abnormalities including urticaria, itching, generalised flushing, laryngeal oedema dyspnoea, decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

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16 **< Miscellaneous metabolism agents-Miscellaneous >**

Azathioprine

[Brand Name]

Imuran Tablets 50 mg (GlaxoSmithKline K.K.)

[Important Precautions]

In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following the administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating the administration of an immunosuppressant. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.

[Adverse Reactions (clinically significant adverse reactions)]

Infection: Pneumonia and sepsis may occur. Hepatitis due to reactivation of hepatitis B virus or hepatitis C may occur. Patients should be carefully monitored through frequent examinations (every 1 to 2 weeks in the initial treatment stage). If any abnormalities are observed, the dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken depending on the symptoms.

Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leucoencephalopathy (PML) may occur. Patients should be carefully monitored during and after the treatment period with this drug, and if symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia, quadriplegia), and language disorders etc. are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration should be discontinued, and appropriate measures should be taken.

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17 **< Miscellaneous metabolism agents-Miscellaneous >**

Everolimus (0.25 mg, 0.5 mg, 0.75 mg)

[Brand Name] Certican Tablets 0.25 mg, 0.5 mg, 0.75 mg (Novartis Pharma K.K.)

[Important Precautions] In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following the administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating the administration of an immunosuppressant. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.

[Adverse Reactions (clinically significant adverse reactions)] **Infection**: Serious infections (pneumonia, sepsis, urinary tract infection, herpes simplex, herpes zoster, etc.) from bacteria, fungi, or viruses may concurrently occur. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur in hepatitis B or C virus carriers treated with immunosuppressant. Symptoms may rapidly become aggravated under intensified immunosuppressive therapy. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken.

Hyperglycaemia, development or exacerbation of diabetes mellitus: Hyperglycaemia or development or exacerbation of diabetes mellitus may occur. Patients should be carefully monitored by checking periodic fasting blood glucose. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken.

Pulmonary embolism, deep vein thrombosis: Pulmonary embolism or deep vein thrombosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Acute respiratory distress syndrome: Acute respiratory distress syndrome may occur. Patients should be carefully monitored, and if rapidly progressing dyspnea, hypoxia or chest X-ray abnormality including diffuse infiltrative shadow in bilateral lung are observed, administration should be discontinued, and appropriate measures should be taken.

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18 **< Miscellaneous metabolism agents-Miscellaneous >**

Gusperimus Hydrochloride

[Brand Name] Spanidin for I.V. Infusion 100 mg (Nippon Kayaku Co., Ltd.)

[Important Precautions] In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating the administration of an immunosuppressant. If this drug is administered to hepatitis

virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.

[Adverse Reactions (clinically significant adverse reactions)]

Infection: Pneumonia or sepsis may occur in patients treated with immunosuppressant. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur in hepatitis B or C virus carriers treated with immunosuppressant. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken.

19

< Miscellaneous metabolism agents-Miscellaneous >

Ciclosporin (oral and injectable dosage forms)

[Brand Name]

Sandimmun Capsules 25 mg, 50 mg, Sandimmun Oral Solution 10%, Sandimmun for i.v. infusion 250 mg, Neoral 10 mg Capsules, Neoral 25 mg Capsules, Neoral 50 mg Capsules, Neoral Solution 10% (Novartis Pharma K.K.)

[Important Precautions]

In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating the administration of an immunosuppressant. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.

[Adverse Reactions (clinically significant adverse reactions)]

Infection: Serious infections (pneumonia, sepsis, urinary tract infection, herpes simplex, herpes zoster, etc.) from bacteria, fungi, or viruses may concurrently occur. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur. Symptoms may rapidly become aggravated under intensified immunosuppressive therapy. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken.

20

< Miscellaneous metabolism agents-Miscellaneous >

Mycophenolate Mofetil

[Brand Name]

CELLCEPT Capsule 250 (Chugai Pharmaceutical Co., Ltd.)

[Important Precautions]

In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating the administration of an immunosuppressant. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.

[Adverse Reactions (clinically significant adverse reactions)]

Infection: Immunosuppressive therapy may increase the sensitivity to secondary infection, causing opportunistic infection. Cytomegalovirus infection, atypical mycobacterial infection, aspergillus infection, candida infection, mucormycosis, pneumocystis carinii infection, parvovirus infection, nocardia infection, staphylococcal infection, listeria infection, or tuberculosis may occur. In addition, pneumonia, sepsis, infective endocarditis, herpes zoster, herpes simplex, upper

respiratory tract infection, bronchitis, common cold, meningitis, wound infection, peritonitis, oesophagitis, enterocolitis, cholangitis, or abscess may occur. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, appropriate measures, such as dose reduction, drug suspension, or administration of antibiotic, should be taken.

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21 **< Miscellaneous metabolism agents-Miscellaneous >**

Mizoribine

[Brand Name]	Bredinin Tablets 25, 50 (Asahi Kasei Pharma Corporation)
[Important Precautions]	In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating the administration of an immunosuppressant. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.
[Adverse Reactions (clinically significant adverse reactions)]	**Infection**: Pneumonia, meningitis, sepsis, or herpes zoster may occur. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

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22 **< Antineoplastics-Miscellaneous >**

Everolimus (5 mg)

[Brand Name]	AFINITOR tablets 5 mg (Novartis Pharma K.K.)
[Important Precautions]	Serious renal disorder may occur. Renal function tests including serum creatinine and urinary urea nitrogen (BUN) and urine tests such as protein urine should be periodically performed before and after starting treatment.
[Adverse Reactions (clinically significant adverse reactions)]	**Renal failure**: Serious renal disorder may occur. Rapid aggravation of renal failure has been reported. Patients should be carefully monitored. If any abnormalities are observed, the dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken. **Acute respiratory distress syndrome**: Acute respiratory distress syndrome may occur. Patients should be carefully monitored, and if rapidly progressing dyspnea, hypoxia or chest X-ray abnormalities including diffuse infiltrative shadow in bilateral lung are observed, administration should be discontinued, and appropriate measures should be taken. **Pulmonary embolism, deep vein thrombosis**: Pulmonary embolism or deep vein thrombosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

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23 **< Antivirals >**

Efavirenz

[Brand Name]	STOCRIN Tablets 200 mg, 600 mg (MSD K.K.)

[Important Precautions]	Serious liver disorder has been reported. Hepatic enzyme monitoring is recommended when using this drug. The risk of serious liver disorder increases especially in patients with a history of or suspected hepatitis B or C virus infection and those treated with drugs that are known to have hepatotoxicity. This drug should be used only when the usefulness outweighs the risk of serious hepatotoxicity in patients with persistent increase in serum transaminase at not less than 5 times the normal range.

24 **< Antivirals >**

Saquinavir Mesilate

[Brand Name]	INVIRASE Capsule 200 mg, INVIRASE Tablet 500 mg (Chugai Pharmaceutical Co., Ltd.)
[Contraindications]	Patients with prolonged QT interval (e.g., congenital long QT syndrome) Patients with hypokalaemia or hypomagnesaemia Patients with complete atrioventricular block not wearing a pacemaker Patients being treated with the following drugs: Amiodarone, flecainide, propafenone, bepridil, quinidine, trazodone, pimozide, ergotamine preparation, simvastatin, midazolam, triazolam, rifampicin, vardenafil
[Careful Administration]	Patients with arrhythmia such as severe bradycardia or heart disorders (e.g., ischaemic heart disease, cardiomyopathy)
[Important Precautions]	Patients or their appropriate representative should be thoroughly informed of the following matters. Informed consent should be obtained before administration of this drug. Dose-dependent QT prolongation or PR prolongation may occur. The patients should immediately contact their physicians if any signs or symptoms suggestive of arrhythmia (e.g., palpitation and syncope) occur QT prolongation may occur in association with administration of this drug. The cardiovascular condition of patients should be carefully monitored. If any signs of arrythmia are observed during the treatment, ECG should be performed. If QT prolongation or PR prolongation are observed, appropriate measures, such as discontinuing treatment, should be taken.
[Interaction (contraindications for concomitant use)]	Amiodarone, flecainide, propafenone, bepridil, quinidine, trazodone, pimozide

25 **< Antivirals >**

Nevirapine

[Brand Name]	Viramune Tablets 200 (Nippon Boehringer Ingelheim Co., Ltd.)
[Careful Administration]	Patients with elevated CD4 (250/mm^3 or higher in female, 400/mm^3 or higher in male) and plasma HIV-1 RNA (approximately 50 copies/mL or more) or patients who has not been treated with antiretroviral agent.
[Important Precautions]	Patients with elevated CD4 (250/mm^3 or higher in female, 400/mm^3 or higher in male) and plasma HIV-1 RNA (approximately 50 copies/mL or more), or patients without medical history of antiretroviral agent have a higher incidence of hepatic dysfunction compared with patients with low CD4. Therefore, CD4 and plasma HIV-1 RNA copy count should be measured, medical history with antiretroviral agent should be confirmed, and liver function tests should be performed before treatment. If any abnormalities on liver function test results are observed, administration of this drug should be discontinued.

26 < Antivirals >

Peramivir Hydrate

[Brand Name] RAPIACTA Bag for Intravenous Drip Infusion 300 mg, RAPIACTA Vial for Intravenous Drip Infusion 150 mg (Shionogi & Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Shock**: Shock (e.g., decreased blood pressure, facial pallor, cold sweat) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

27 < Antivirals >

Laninamivir Octanoate Hydrate

[Brand Name] INAVIR DRY POWDER INHALER 20 mg (Daiichi Sankyo Company, Limited)

[Important Precautions] Syncope and shock symptoms associated with this drug have been reported. The syncope and shock symptoms might have been induced by a deteriorated general condition including pyrexia and dehydration associated with influenza virus infection. The symptoms may also be induced by strong inhalation of this drug or patients holding their breath for a long time, or it may be induced by the drug itself. Patients should be well informed and understand the inhalation method provided in the user's manual. They should be instructed to inhale in a relaxed state (e.g., while sitting in a chair). If such symptoms occur, the patient should be placed supine and kept rested, appropriate measures, such as treatment with fluid replacement, should be taken.

[Adverse Reactions (clinically significant adverse reactions)] **Shock**: Shock (e.g., decreased blood pressure, facial pallor, cold sweat) may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.

28 < Chemotherapeutics-Miscellaneous >

Itraconazole

[Brand Name] ITRIZOLE Capsules 50, ITRIZOLE Oral Solution 1%, ITRIZOLE Injection 1% (Janssen Pharmaceutical K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, exfoliative dermatitis**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, acute generalised exanthematous pustulosis or exfoliative dermatitis (erythroderma) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

29 < Biological preparations-Miscellaneous >

Basiliximab (Genetical Recombination)

[Brand Name] Simulect i.v. injection 20 mg, Simulect i.v. injection 10 mg for pediatric (Novartis Pharma K. K.)

[Important Precautions] In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following the administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating

	the administration of an immunosuppressant. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.
[Adverse Reactions (clinically significant adverse reactions)]	**Infection**: Serious infections from bacteria, fungi, or viruses (pneumonia, sepsis, urinary tract infection, herpes simplex) may occur. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

30 **< Biological preparations-Miscellaneous >**

Muromonab-CD3

[Brand Name]	Orthoclone OKT3 Injection (Janssen Pharmaceutical K. K.)
[Important Precautions]	In hepatitis B virus carriers who were administrated an immunosuppressant, hepatitis may occur due to reactivation of hepatitis B virus. In addition, hepatitis due to reactivation of hepatitis B virus following the administration of an immunosuppressant has been reported in patients who were negative for HBs antigen. Hepatitis C may be exacerbated in hepatitis C virus carriers after initiating the administration of an immunosuppressant. If this drug is administered to hepatitis virus carriers, special attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc.
[Adverse Reactions (clinically significant adverse reactions)]	**Infection**: Serious infections from bacteria, fungi, viruses, or protozoa (pneumonia, sepsis, meningitis, herpes zoster) may occur. Hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C may occur in hepatitis B or C virus carriers treated with immunosuppressant. When administering this drug, patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

31 **< Non-main therapeutic purpose agents-Miscellaneous >**

Sodium Phosphate Monohydrate/Sodium Dihydrogen Phosphate Anhydrous

[Brand Name]	Visiclear Combination Tablets (Zeria Pharmaceutical Co., Ltd.)
[Contraindications]	Patients with serious renal impairment or acute phosphate nephropathy (including dialysis patients)
[Adverse Reactions (clinically significant adverse reactions)]	**Hypocalcaemia**: Hypocalcaemia (tetany, numbness, tingling sensation, muscular weakness, and disturbed consciousness) may occur. If any of these symptoms occur, appropriate measures such as electrolyte correction should be taken.

32 **< Vaccines >**

Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed) Haemophilus Type b Conjuegate Vaccine

[Brand Name]	Prevenar Suspension Liquid for S.C. Injection (Pfizer Japan Inc.) ActHIB (Sanofi Pasteur)

[Important Precautions]

When concurrently inoculating the patient with other vaccines, the patient should be informed that each vaccination can be made separately. Especially if the patient has a serious underlying disease, the physician should consider single vaccinations and check the patient's condition carefully before the vaccination. See the MHLW website [1].

< Reference >

1) Q and A Resuming vaccination with the pediatric pneumococcal conjugate vaccine and the Hib vaccine (Tuberculosis and Infectious Disease Control Division, Health Service Bureau; Safety Division, Pharmaceutical and Food Safety Bureau; MHLW)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/index.html

33 **< Over-the-counter drugs >**

Nanpao

[Brand Name]

NANPAO (Mitsubishi Tanabe Pharma Corporation)

[Consultation]

If you experience any of the following symptoms after taking the product, immediately discontinue the use of the product, and show this document to your physician or pharmacist for consultation.

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

Hepatic dysfunction: General malaise, brown urine, jaundice (skin and whites of the eyes become yellow) etc. may occur.

5

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 May 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Drospirenone/Ethinylestradiol YAZ Combination Tablet	Bayer Yakuhin, Ltd.	November 16, 2010
Eltrombopag Olamine REVOLADE Tablets 12.5 mg, 25 mg	GlaxoSmithKline K.K.	December 10, 2010
Nepafenac Nevanac Ophthalmic Suspension 0.1%	Alcon Japan Ltd.	December 10, 2010
Bendamustine Hydrochloride TREAKISYM Injection 100 mg	SymBio Pharmaceuticals Limited	December 10, 2010
Levocetirizine Hydrochloride Xyzal Tablets 5 mg	GlaxoSmithKline K.K.	December 10, 2010
Diquafosol Sodium DIQUAS ophthalmic solution 3%	Santen Pharmaceutical Co., Ltd.	December 13, 2010
Tolvaptan Samsca tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	December 14, 2010
Sodium Hyaluronate Crosslinked Polymer/Sodium Hyaluronate Crosslinked Polymer Crosslinked with Vinylsulfone SYNVISC 2 mL (intra-articular injection)	Genzyme Japan K.K.	December 14, 2010
Exenatide Byetta Subcutaneous Injection 5 µg Pen 300, 10 µg Pen 300	Eli Lilly Japan K.K.	December 17, 2010
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg	Wakamoto Co., Ltd.	December 24, 2010
l-Menthol MINCLEA catapasm for internal use 0.8%	Nippon Pharmaceutical Co., Ltd.	January 11, 2011
Levofloxacin Hydrate CRAVIT INTRAVENOUS DRIP INFUSION BAG 500 mg/100 mL, CRAVIT INTRAVENOUS DRIP INFUSION 500 mg/20 mL	Daiichi Sankyo Company, Limited	January 11, 2011
Paliperidone Invega Tablets 3 mg, 6 mg, 9 mg	Janssen Pharmaceutical K.K.	January 17, 2011

Ciclesonide Alvesco 50 μg Inhaler 112 puffs, Alvesco 100 μg Inhaler 112 puffs, Alvesco 200 μg Inhaler 56 puffs*1	Teijin Pharma Limited.	January 21, 2011
Roxatidine Acetate Hydrochloride ALTAT CAPSULES 37.5, 75*1	ASKA Pharmaceutical Co., Ltd.	January 21, 2011
Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg	Janssen Pharmaceutical K.K.	February 4, 2011
Azacitidine Vidaza for Injection 100 mg	Nippon Shinyaku Co., Ltd.	March 11, 2011
Fondaparinux Sodium Arixtra Injection 5 mg, 7.5 mg	GlaxoSmithKline K.K.	March 11, 2011
Ustekinumab (Genetical Recombination) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	March 14, 2011
Dabigatran Etexilate Methanesulfonate Prazaxa Capsules 75 mg, 110 mg	Nippon Boehringer Ingelheim Co., Ltd.	March 14, 2011
Galantamine Hydrobromide REMINYL Tablets 4 mg, 8 mg, 12 mg, REMINYL OD Tablets 4 mg, 8 mg, 12 mg, REMINYL Oral Solution 4 mg/mL	Janssen Pharmaceutical K.K.	March 22, 2011
Eldecalcitol EDIROL Capsule 0.5 μg, 0.75 μg	Chugai Pharmaceutical Co., Ltd.	April 11, 2011
Freeze-dried, Cell Culture-Derived Japanese Encephalitis Vaccine (Inactivated) ENCEVAC Subcutaneous Injection	The Chemo-Sero-Therapeutic Research Institute	April 11, 2011
Romiplostim (Genetical Recombination) Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Ltd.	April 13, 2011
Anti-human Thymocyte Immunoglobulin, Rabbit Thymoglobuline for Intravenous Infusion 25 mg*2	Genzyme Japan K.K.	April 22, 2011
Doripenem Hydrate FINIBAX for Drip Infusion 0.25 g, FINIBAX Kit for Drip Infusion 0.25 g*3	Shionogi & Co., Ltd.	April 22, 2011
Levobupivacaine Hydrochloride POPSCAINE 0.25% inj. 25 mg/10mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL*4	Maruishi Pharmaceutical Co., Ltd.	April 22, 2011

*1 An additional administration for “pediatrics”

*2 An additional indication for “treatment of acute rejection after renal transplantation”

*3 An additional dosage and administration for “maximum daily dose, 3 g”

*4 An additional indication for “conduction anesthesia”