Pharmaceuticals and Medical Devices Safety Information

No. 280 June 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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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

ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BCG	Bacille Calmette-Guerin
BUN	Blood urea nitrogen
CD4	Cluster of differentiation 4
CHDF	Continuous hemodiafiltration
CHOP	Cyclophosphamide-Hydroxydaunorubicin-Vincristine (Oncovin)-Prednisolone
CLL	Chronic lymphocytic leukaemia
CMV IgM	Cytomegalovirus-Immunoglobulin M
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
CVP	Cyclophosphamide-Vincristine-Prednisolone
DLST	Drug lymphocyte stimulation test
DPT	Diphtheria-Pertussis-Tetanus
ECG	Electrocardiogram
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
GVHD	Graft-versus-host disease
HBc	Hepatitis B core
HBe	Hepatitis B envelope
HBs	Hepatitis B surface
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV RNA	Hepatitis C virus ribonucleic acid
Hib	Haemophilus Influenzae Type b
HIV	Human immunodeficiency virus
HIV RNA	Human immunodeficiency virus ribonucleic acid
HUS	Haemolytic uraemic syndrome
ICU	Intensive care unit
IgG	Immunoglobulin G
IgM-HA	Immunoglobulin M-Hepatitis A
IgM-HBc	Immunoglobulin M-Hepatitis B core
IU	International unit
JC virus	John Cunningham virus
JCS	Japan Coma Scale
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LC	Log copies
LDH	Lactate dehydrogenase
LKM	Liver-kidney microsome
MAH	Marketing authorization holder
MR	Measles-Rubella
MRI	Magnetic resonance imaging
OHSS	Ovarian hyperstimulation syndrome
PCR	Polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PD	Progressive disease
PML	Progressive multifocal leukoencephalopathy
PR	Partial remission
PT	Prothrombin Time
SI	Stimulation index
SIDS	Sudden infant death syndrome
$SatO_2$	Oxygen saturation
TBI	Total body irradiation
TEN	Toxic epidermal necrolysis
TTP	Thrombotic thrombocytopenic purpura
VCA IgM	Viral capsid antigen-Immunoglobulin M
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

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Safety Measures for Pediatric Pneumococcal Conjugate Vaccine and Haemophilus Influenzae Type b (Hib) Vaccine

1. Introduction

In November 2010, the project for urgent vaccination promotion regarding pediatric pneumococcal conjugate vaccine, haemophilus influenzae type b (Hib) vaccine, and human papillomavirus vaccine for prevention of cervical cancer was started. The "Procedures for Urgent Vaccination Promotion*" stipulated that adverse reactions to the vaccines that occur during the project must be reported to MHLW regardless of the causality.[1)]

Four fatal cases have been reported from March 2 to 4, 2011 in infants who simultaneously received multiple vaccinations including pediatric pneumococcal conjugate vaccine and Hib vaccine, which were subject to the project. MHLW temporarily suspended the use of these vaccines on March 4.[2)]

To review the causality between the vaccinations and infant deaths (including those reported after March 4) as well as the safety of these vaccines when they are given simultaneously, the joint meeting of Subcommittee on Drug Safety of Committee on Drug Safety and Vaccine Adverse Reaction Review Committee for Carcinoma of the Uterine Cervix (hereinafter referred to as "The Joint Meeting") was held on March 8 and 24. The review results were summarized on March 24,[3)] and vaccinations was resumed on April 1. The review process that led up to the resumption of vaccinations and details of safety measures are described below.

*Provisional Translation: Procedures for Urgent Vaccination Promotion

2. Review of fatal cases

Seven fatal cases were reported from March 2 to 24, 2011 in infants who simultaneously received multiple vaccinations including pediatric pneumococcal conjugate vaccine and Hib vaccine. The causality between the deaths and the vaccinations were reviewed at the Joint Meeting held on March 8 and 24 based on as much detailed information as possible, including post-vaccination course and the severities of the underlying diseases described in the autopsy reports and medical records. The results were described below. (**Table 1**)

(1) All the 7 fatal cases were 0- to 2-year-old infants. Three of them had underlying diseases, and it was not confirmed whether the other 4 cases had underlying diseases.
(2) Three infants died on the day following the vaccination, 1 died two days later, 2 died three days later, and 1 died 7 days later.
(3) Having reviewed the seven cases based on the post-vaccination course and findings currently available, it is considered that there is no clear or direct causality with the vaccinations in the 7 fatal cases. Meanwhile, some of the fatal cases involved infants with underlying heart disease. Therefore, sufficient precautions should be taken for patients with serious underlying disease, such as severe congenital heart disease, depending on their disease conditions.

Table 1 Summary of fetal cases

No.	Vaccine (1) Lot	Vaccine (2) Lot	Vaccine (3) Lot	Age, sex (female/male), underlying disease	Date of vaccination, post-vaccination course	Results of review
1	Prevenar (first dose) 10G03A	ActHIB (first dose) E1235	-	2 Y old, male	February 28, 2011 He died the day after the vaccination. He was found with his face down in a state of cardiorespiratory arrest.	The autopsy report suggested that he died of respiratory failure due to aspiration. The causality between the vaccination and his death is unclear.
2	Prevenar (first dose) 10G03A		Diphtheria-Pertussis-Tetanus (DPT) combined vaccine (Kitasato) (fourth dose) AC014D	1 Y old, female, no underlying diseases	March 1, 2011 She died the day after the vaccination. At midnight, she developed hyperthermia. On the following day, she was found lying with her face down in a state of respiratory arrest during a nap.	The autopsy report shows neither clear cause of death nor causality with the vaccination. Human metapneumovirus was identified by polymerase chain reaction (PCR) in her throat swab. This suggested that she died of acute infection.
3	Prevenar (second dose) 10E02A	ActHIB (second dose) E1065	DPT (Kitasato) (first dose) AM009B	< 6 M old, female, no underlying diseases	She died 3 days after the vaccination. In the morning, she was found in a state of respiratory arrest.	
4	Prevenar (second dose) 10H01A	ActHIB (second dose) E1234	DPT (Kitasato) (second dose) AM009B	≥ 6 M,< 1 Y old, female, dextrocardia, heterotaxia, univentricular heart, pulmonary valve stenosis	March 3, 2011 He died the day after the vaccination. Ill complexion, rolling of the eyes and loss of consciousness were noted at noon.	The autopsy report shows neither clear cause of death nor causality with the vaccination.
5		ActHIB (first dose) E0770	Bacille Calmette-Guerin (BCG) (first dose) KH128	< 6 M old, male, cyanosis at birth, cardiac tumor (check-up at 3-months old showed no abnormalities), right ventricular hypertrophy etc.	February 4, 2011 He died 2 days after the vaccination. He was found in a state of respiratory arrest in the morning.	An autopsy was not performed. Neither cause of death nor causality with the vaccination is clear.

6		ActHIB (first dose) E1201	DPT (Kitasato) (second dose) AC014D	≥ 6 M, < 1 Y old, male, no underlying diseases	February 15, 2011 He died 7 days after the vaccination. In the morning, he was found lying with his face down in a state of cardiorespiratory arrest.	According to the autopsy report, the cause of death was sudden infant death syndrome. Although norovirus was identified by PCR in his stool on admission to the hospital, no symptoms associated with norovirus infections were reported. The causality between the death and infection was unclear. The causality with the vaccinations is also unclear.
7		ActHIB (first dose) E0558	DPT (BIKEN) 3E12A	< 6 M old, female, no underlying diseases	July 26, 2010 She died 3 days after the vaccination. She had tachypnoea at night 2 days after the vaccination. In the middle of the night 3 days after the vaccination, abnormal respiration occurred, followed by respiratory arrest at home.	According to the autopsy report, the cause of death was acute circulatory failure. The causality with vaccination is unclear.

3. The situation in Japan and overseas

(1) Use-result report in the U.S.[4)]

In the U.S, 31.5 million doses of pediatric pneumococcal conjugate vaccine were given during the first 2 years after launch. Adverse events were reported in 4154 cases, out of which 117 were fatal cases. The incidence of reported death was 0.37 case per 100000 doses. Out of 117 fatal cases, the cause of death was unclear in 73 cases (62.4%), which included 59 cases of documented or suspected sudden infant death syndrome (SIDS). Of the 44 cases with identified causes of death, infants died of infection in 22 cases, condition at birth including congenital abnomalies in 13 cases, and convulsion or other causes in 8 cases.

(2) Fatal case reported overseas

1) Pediatric pneumococcal conjugate vaccine

According to the data collected by the marketing authorization holders (MAHs) between August 2005 and May 2010, 166 deaths were reported in overseas children who received pediatric pneumococcal conjugate vaccine (**Table 2**). The number of vaccine shipped during the same period was 158.52 million doses, and the incidence of reported death was 0.1 case per 100000 doses. The incidence of death per 100000 doses by country is, in descending order, 0.6 case in the Netherlands, 0.5 case in Germany, and 0.4 case in Switzerland.

Table 2 Reported number of deaths in children who received pediatric pneumococcal conjugate vaccine (August 2005 to May 2010)

Details (cause of death)	Number of cases
Pneumococcal disease	58
SIDS	53
Others	25
Miscellaneous/unknown	30
Total (158 million doses)	166 (0.1 case per 100000 doses)

2) Hib vaccine

According to the data collected by the MAHs between January 2006 and March 2011, 21 deaths were reported in overseas children who received Hib vaccine (**Table 3**). The number of vaccines shipped during the same period was 53.04 million doses, and the incidence of reported death was 0.04 case per 100000 doses. The incidence of death per 100000 doses by country is, in a descending order, 1.0 case in Canada, 0.3 case in Sweden and 0.1 case in Belgium.

Table 3 Reported deaths in children who received Hib vaccine (January 2006 to March 9, 2011)

Details (cause of death)	Number of case
SIDS	4
Others	11
Unknown	6
Total (53 million doses)	21 (0.04 case per 100000 doses)

Based on the above reports, deaths have been reported at a certain level of incidence in children who received pediatric pneumococcal conjugate vaccine or Hib vaccine. The incidence of reported death was 0.1 to 1 case per 100000 doses for pediatric pneumococcal conjugate vaccine and 0.02 to 1 case per 100000 doses for Hib vaccine. In overseas, infections and SIDS accounted for most of the causes of deaths, and there is no clear causality between the vaccinations and death.

(3) Fatal cases reported in Japan

In Japan, out of 2.67 million doses of pediatric pneumococcal conjugate vaccine, 4 deaths have been reported as of March 2011. The incidence of death was 0.2 case per 100000 doses. As for Hib vaccine, 7 fatal cases out of 4.51 million doses have been reported, and the incidence of death was 0.2 case per 100000 doses.

The Joint Meeting considered that there is not much difference between the situations in Japan and overseas for the incidences and details of reported deaths, and that no specific safety concern

about the vaccination was noted.

4. Simultaneous vaccinations

(1) Status of simultaneous vaccinations

1) MHLW survey on simultaneous vaccinations

An e-mail survey was conducted at the medical institutions actively providing vaccination services, in cooperation with the Japan Medical Association and the Japan Pediatric Society, from March 10 to 12, 2011.

Based on the results from 866 responding medical institutions, 75.4% of pediatric pneumococcal conjugate vaccines and 88.0% of Hib vaccines were simultaneously given with another vaccine, among total vaccinations for the month of February, 2011 (Table 4). Overall, more than 75% of these vaccines were simultaneously administered.

Table 4 Number of simultaneous vaccinations by vaccine

	Total number of vaccination doses (Percentage)	Number of simultaneous vaccination doses (Percentage)
Pediatric pneumococcal conjugate vaccine	46,594 (100%)	35,139 (75.4%)
Hib vaccine	40,861 (100%)	35,970 (88.0%)

2) Post-marketing use-result surveys and clinical studies conducted by MAHs in Japan

(A) Table 5 shows the percentages of simultaneous vaccinations and the incidences of adverse reactions reported in the post-marketing use-result surveys conducted by the MAHs.

Table 5 Percentage of simultaneous vaccinations and incidences of adverse reactions reported in the post-marketing use-result surveys

		Hib + DPT	PCV7 + DPT[*3]	Hib + PCV7	Hib + PCV7 + DPT	Single vaccination	
						Hib	PCV7
Pediatric pneumococcal conjugate vaccine (PCV7) (1099 doses)[*1]		-	210	230	523	-	118
	Simultaneous vaccinations	-	19.1%	20.9%	47.6%	-	10.7%
	Adverse reactions	-	11.0% (23 reports)	6.5% (15 reports)	9.8% (51 reports)	-	5.1% (6 reports)
Hib vaccine (Hib) (1723 reports)[*2]		772	-	88	50	764	-
	Simultaneous vaccinations	44.8%	-	5.1%	2.9%	44.3%	-
	Adverse reactions	27.6% (213 cases)	-	39.8% (35 cases)	42.0% (21 cases)	32.3% (247 cases)	-

*1 Number of vaccination doses from September 1, 2010 to February 28, 2011

*2 Number of vaccination doses from August 1, 2009 to February 5, 2011

*3 DPT, Diphtheria-Pertussis-Tetanus combined vaccine

(B) Tables 6 and 7 show the incidences of adverse reactions reported in the post-marketing

clinical studies conducted by the MAHs.

Table 6 Incidences of adverse reactions reported in the post-marketing clinical study of pediatric pneumococcal conjugate vaccine (as of March 10, 2011)

Subjects	Single DPT vaccination		PCV7 + DPT	
	Number of subjects	Number of doses	Number of subjects	Number of doses
Number of subjects/ number of doses	158	408	159	394
Local reaction (Number of cases/number of doses analyzed)	78/158 (49.4%)	121/384 (31.5%)	126/159 (79.2%)	251/377 (66.6%)
Systemic reaction (Number of cases/number of doses analyzed)	98/158 (62.0%)	163/384 (42.4%)	117/159 (73.6%)	195/374 (52.1%)

Table 7 Incidences of adverse reactions reported in the post-marketing clinical study of Hib vaccine

Subjects	Single DPT vaccination		Hib + DPT	
	Number of subjects	Number of doses (total for 4 doses)	Number of subjects	Number of doses (total for 4 doses)
Number of subjects/ number of doses	173	673	191	746
Local reaction	143 (82.7%)	348 (51.7%)	165 (86.4%)	473 (62.6%)
Systemic reaction	100 (57.8%)	168 (25.0%)	134 (70.2%)	260 (34.4%)
Local + systemic	159 (91.9%)	418 (62.1%)	179 (93.7%)	567 (75.0%)

3) Hib/pneumococcal vaccine safety survey in Kagoshima prefecture

Nishi et al. (Kagoshima University) conducted a safety survey for Hib and/or pneumococcal vaccines in 11165 cases at 29 medical institutions in Kagoshima prefecture.[5)]

Adverse events collected in the survey included anaphylaxis, encephalitis/encephalopathy, neurologic symptoms including convulsion, sequelae associated with these symptoms, abnormal local swelling spread over the elbow, systemic rash and urticaria, pyrexia of 39 °C or higher (within 2 days of vaccination), and other symptoms requiring hospitalization. The observation period was 2 week.
The survey results as of January 31, 2011 are summarized below.

Adverse events associated with pediatric pneumococcal conjugate vaccine occurred in 11 out of 1244 cases (0.88%) in the single vaccination group and 17 out of 1802 cases (0.94%) in the simultaneous vaccination group (Hib vaccine, 44%; DPT vaccine, 30%; influenza vaccine, 11%; Measles-Rubella (MR) vaccine, 6.4%; Japanese encephalitis vaccine, 3.5%; mumps vaccine, 2.3%; BCG vaccine, 1.7%; and varicella vaccine, 1.3%). The incidence of adverse events between single and simultaneous vaccinations was comparable, and the incidence of adverse events was not significantly associated with simultaneous vaccinations (p=0.98).

Adverse events associated with Hib vaccine occurred in 31 of 5656 cases (0.55%) in the single vaccination group and 45 of 5509 cases (0.82%) in the simultaneous vaccinations group (DPT vaccine,

77%; pediatric pneumococcal conjugate vaccine, 13%; MR vaccine, 5%; influenza vaccine, 3%; varicella vaccine, 0.9%; mumps vaccine, 0.7%; Japanese encephalitis vaccine, 0.5%; and BCG vaccine, 0.5%). While the incidence of adverse events was slightly higher in the simultaneous vaccinations group, the incidence of adverse events was not significantly associated with simultaneous vaccinations (p=0.11).

The MHLW survey of simultaneous vaccinations showed that more than 75% of pneumococcal vaccinations and Hib vaccinations were simultaneously administered with other vaccine(s). Comparable results were obtained from the surveys conducted by the MAHs.

The post-marketing surveillances/clinical studies conducted by the MAHs had a tendency to a higher incidence of adverse reactions to simultaneous vaccinations than that to single vaccinations. On the other hand, the Kagoshima University survey showed no significant difference in the incidence of adverse reactions to single vaccinations and that to simultaneous vaccinations. Neither survey suggested a tendency for an increase in serious adverse reactions associated with simultaneous vaccinations.

The March 24 Joint Meeting considered that, although some studies reported that there appeared to be a higher incidence of adverse reactions to simultaneous vaccinations than that to single vaccinations, no increase in serious adverse reactions were noted and there is no safety concern based on the data presented above, as well as the vaccination records of patients with underlying diseases in Japan and the situations in the U.S. and Europe.

5. National test results of vaccines and quality control

The national test conducted by the National Institute of Infectious Diseases showed that vaccine lots given to fatal cases was within the acceptable criteria and no deviation was found.

For Hib vaccine, the recall of specific lots was conducted on March 11, 2011 because contamination was found in some of the products. The contaminated foreign matters were identified as a mixture of the nylon-like chemical substance (polyacrylamide) and glass fiber. It was assumed that in the process of connecting an injection needle to a syringe, the device supporting the injection syringe melted and adhered (contaminated) to the inside of the syringe.[6)] The safety concerns due to contamination were limited to local irritation. In addition, it was reported that no foreign matters were observed in the recalled lots of vaccines which were used in fatal cases. Thus, it is not considered that the contamination by foreign substances is associated with the fatal cases.

6. Safety measures

The Joint Meeting considered that there was no direct or clear causality between pediatric pneumococcal conjugate vaccine or Hib vaccine and the fatal cases, and that no safety concerns were noted based on the information on simultaneous vaccinations of both vaccines. Based on the above information, the following precautions should be taken when using pediatric pneumococcal conjugate vaccine and Hib vaccine.

(1) Physicians should explain that simultaneous vaccinations can efficiently achieve the preventive effect within a short period of time and that single vaccinations are also available. If simultaneous vaccinations are to be carried out, physicians should determine the necessity of the vaccination and should obtain the consent of the child's guardian.

(2) Vaccinations should be performed in infants with serious underlying diseases including severe cardiac diseases, to prevent severe infectious disorders such as meningitis, and vaccines should be carefully administered after checking the infant's clinical condition. In such cases, single vaccinations should be considered, and physicians should determine the necessity of simultaneous vaccinations.

To thoroughly inform medical institutions of the precautions, Q&As[7)] were issued and revision of Precautions sections[8)] was required on March 29, 2011. On March 31, "Implementation of the

project for urgent promotion of vaccinations including cervical cancer vaccine" was partially revised[1)] after the Joint Meeting held on the same day. Pediatric pneumococcal conjugate vaccine and Hib vaccine were resumed on April 1.

Further fatal cases within several days after vaccination may be reported. The Joint Meeting consider it is appropriate that if further post-vaccination deaths are reported, as much detailed information should be collected as possible and causality with vaccines should be quickly evaluated by experts. In addition, the Joint Meeting concluded that based on overseas post-vaccination fatal case reports, in the case where the incidence of death (regardless of causality) exceeds 0.5 per 100000 doses in 6 months, expert review meetings should be held to quickly determine appropriate actions.

References (including provisionally translated titles)

1) Procedures for Urgent Vaccination Promotion (partially revised on March 31, 2011) (MHLW)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/110331-1.pdf
2) Reports on fatal cases in children who simultaneously received vaccinations including pneumococcal conjugate vaccine and Hib vaccine and suspension of the use of the vaccines (MHLW)
http://www.mhlw.go.jp/stf/houdou/2r98520000013zvg.html
3) Safety review results of Pneumococcal conjugate vaccine and Haemophilus influenzae type b (Hib) vaccine for pediatrics (March 24, 2011)
http://www.mhlw.go.jp/stf/houdou/2r985200000167mx.html
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5) Joint meeting material "Safety survey of Hib/pneumococcal conjugate vaccines in Kagoshima prefecture" (March 24, 2011)
http://www.mhlw.go.jp/stf/shingi/2r9852000001dn2t-att/2r9852000001dn97.pdf
6) Q&A Voluntary recall of Hib vaccine (product name, ActHIB) (MHLW)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/110404.pdf
7) Q&A Resuming vaccination with the pediatric pneumococcal conjugate vaccine and the Hib vaccine (MHLW)
http://www.pmda.go.jp/english/service/pdf/20110502-1_QandA.pdf (in English)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/110329-1.pdf(only available in Japanese language)
8) Information on Revision of Precautions (instruction issued on March 29, 2011)
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2

Manuals for Management of Individual Serious Adverse Drug Reactions

1. Introduction

MHLW has been developing "Manuals for Management of Individual Serious Adverse Drug Reactions" (hereinafter referred to as "the Manuals") in cooperation with experts from relevant academic societies since FY 2005. The Manuals describes adverse drug reactions, which are crucial for ensuring their early recognition and treatment. The Manuals provide a comprehensive list of relevant initial symptoms, typical clinical cases, and diagnostics of serious adverse drug reactions. With the addition of 12 adverse drug reactions in FY 2010, the Manuals have been released for a total of 75 (including existing manuals) adverse drug reactions.

2. The Manuals

The existing safety measures have been drug-oriented. Reports of adverse drug reactions have been collected and reviewed for each drug, and relevant package inserts have been revised accordingly to alert healthcare providers. However, adverse drug reactions may occur in unaffected organs, and serious adverse drug reactions are generally infrequent and may be unfamiliar to healthcare providers. Therefore, the recognition of adverse drug reactions may be delayed, causing aggravation of related symptoms.

In addition to the existing drug-oriented safety measures, MHLW has been developing the Manuals to implement safety management that focuses on drug-induced adverse reactions.

The Manuals have been developed for both patients and healthcare providers. The manuals for patients are clearly written and include a summary of adverse drug reactions which patients and their family members should know about, as well as initial symptoms and key points for early recognition and treatment. The manuals for healthcare providers include key points for early recognition and treatment, a summary of adverse drug reactions, diagnostics, general treatment, and typical clinical cases.

The titles of the 12 newly-developed manuals in FY 2010 and common initial symptoms associated with the adverse drug reactions are shown in **Table 1**. The list of 75 currently-available manuals is shown in **Table 2**. The Manuals are available on the MHLW website (http://www.mhlw.go.jp/topics/2006/11/tp1122-1.html) and the PMDA website (http://www.info.pmda.go.jp/juutoku/juutoku_index.html).

The Manuals will be kept up to date by adding new information when necessary.

3. Request to healthcare providers

The Manuals are prepared for patients and healthcare providers separately. In addition to managing adverse drug reactions, healthcare providers such as physicians, dentists, and pharmacists are encouraged to use the Manuals to aid in-house communication and to help provide medical instructions to patients in order to ensure early recognition and treatment of serious adverse drug reactions. In addition, healthcare providers are encouraged to let their patients use the Manuals so that the patients can quickly detect symptoms themselves.

Table 1 Manuals for Management of Individual Serious Adverse Drug Reactions released in 2011

Manual title (adverse drug reaction)	Common initial symptoms
Acute pyelonephritis	"Chilliness", "Tremulousness", "Pyrexia", "Pain in the side and back"
Nephrogenic diabetes insipidus	"Significant increase of urine output", "Severe thirst", "Excessive drinking"
Tumour lysis syndrome	It is difficult to recognize early this adverse drug reaction based on initial symptoms. Blood test, urine analysis, and measurement of urine output are important to accurately identify the adverse drug reaction.
Aseptic meningitis	"Pyrexia (hyperthermia around 40°C)", "Headache", "Feeling sick", "Feeling queasy", "Difficulty of bending the head forward due to tense neck", "Decreased consciousness"
Acute disseminated encephalomyelitis	"Headache", "Pyrexia", "Vomiting", "Clouding consciousness", "Unclear vision", "Difficulty of moving hands and feet", "Difficulty of walking", "Decreased sensation"
Acute encephalopathy in children	"Convulsion lasting for more than 5 minutes", "Loss of consciousness and lying limply after convulsion stops", "Nonsensical talk and behavior or lying limply without convulsion"
Hypoglycaemia	"Cold sweat", "Feeling sick", "Sudden severe hunger", "Chilliness", Palpitation, "Treble hands and feet", "Flickering sight", "Feeling wobbly", "Feeling of weakness", "Headache", "Dopiness", "Seeing only darkness and almost falling", "Fuzzy head", "Dozing", "Abnormal or unusual behavior", "Nonsensical talk", "Inarticulateness", "Loss of consciousness", Convulsion"
Idiopathic osteonecrosis of femoral head	"Pain in the base of femoral bone", "Pain in the knee or hip"
Haemorrhagic cystitis	"Reddish urine (haematuria)", "Frequency increased micturition", "Painful micturition", "Feeling of residual urine"
Ovarian hyperstimulation syndrome (OHSS)	"Abdominal distention", "Feeling queasy", "Sudden weight gain", "Decreased urine output"
Corneal opacity	"Filmy vision", "Hyperaemia", "Sensation of foreign body", "Glare"
Drug-induced taste disturbance	"Hypogeusia", "Unpleasant taste", "Taste alteration", "Meals not tasty"

Table 2 List of Manuals for Management of Individual Serious Adverse Drug Reactions

As of May 2011

Field	Name of cooperating society	Adverse drug reactions
Dermatologicals	The Japanese Dermatological Association	Stevens-Johnson syndrome Toxic epidermal necrosis Drug-induced hypersensitivity syndrome Acute generalized exanthematous pustulosis Drug-induced contact dermatitis
Hepatic	The Japan Society of Hepatology	Drug-induced hepatic disorder
Renal	The Japanese Society of Nephrology	Acute renal failure Interstitial nephritis Nephrotic syndrome ☆ Acute pyelonephritis ☆ Nephrgenic diabetes insipidus ☆ Tumour lysis syndrome
Blood	The Japanese Society of Hematology	Aplastic anaemia Bleeding tendency Drug-induced anaemia Agranulocytosis Thrombocytopenia Thrombosis Disseminated intravascular coagulation Thrombotic thrombocytopenic purpura Heparin-induced thrombocytopenia
Respiratory system	The Japanese Respiratory Society	Interstitial pneumonia Asthmatic attack due to nonsteroidal anti-inflammatory drug Acute lung injury/Acute respiratory distress syndrome Pulmonary oedema Acute eosinophilic pneumonia Pulmonary alveolar haemorrhage Pleurisy, Pleural effusion
Alimentary tract	The Japanese Society of Gastroenterology	Paralytic ileus Peptic ulcer Pseudomembranous colitis Acute pancreatitis (Drug-induced pancreatitis) Severe diarrhoea
Cardiovascular system	The Japanese Circulation Society	Ventricular tachycardia Congestive cardiac failure
Nervous and musculo-skeletal system	The Japanese Society of Neurology	Drug-induced parkinsonism Rhabdomyolysis Leukoencephalopathy Peripheral neuropathy ☆ Aseptic meningitis ☆ Acute disseminated encephalomyelitis Guillain-Barre syndrome Dyskinesia Convulsion/Epilepsy Ataxia Headache
	The Japanese Society of Child Neurology	☆ Acute encephalopathy in children

Field	Name of cooperating society	Adverse drug reactions
Psychiatric	The Japanese Society of Clinical Neuropsychopharmacology	Neuroleptic malignant syndrome Drug-induced depression Akathisia Serotonin syndrome
	The Japan Pediatric Society	Neonatal drug withdrawal syndrome
Metabolism and endocrine	The Japan Endocrine Society	Pseudoaldosteronism Thyrotoxicosis Hypothyroidism
	The Japan Diabetes Society	☆ Hypoglycaemia Hyperglycaemia
Hypersensitivity	The Japanese Society of Allergology	Anaphylaxis Angioedema Laryngeal oedema Urticaria/Angiooedema due to nonsteroidal anti-inflammatory drug
Oral cavity	The Japanese Society of Oral and Maxillofacial Surgeons	Osteonecrosis of jaw due to bisphosphonates Drug-induced stomatitis Stomatitis due to anticancer agents
Bones	The Japanese Orthopaedic Association	Osteoporosis ☆ Idiopathic osteonecrosis of femoral head
Urinary organs	The Japanese Urological Association	Urinary retention/dysuria ☆ Haemorrhagic cystitis
Ovary	The Japan Society of Obstetrics and Gynecology	☆ Ovarian hyperstimulation syndrome (OHSS)
Sensory organs (visual)	The Japanese Ophthalmological Society	Retinal disorder/Visual field defects Glaucomas ☆ Corneal opacity
Sensory organs (auditory)	The Oto-Rhino-Laryngological Society of Japan, Inc.	Deafness
Sensory organs (mouth)	The Japanese Stomatological Society	☆ Drug-induced taste disturbance
Carcinoma	The Japan Society of Clinical Oncology	Hand and foot syndrome

Manuals with ☆ are newly published.

3

Important Safety Information

This section presents the contents of revisions and case summaries that served as the basis for these revisions to important adverse reactions included under the Precautions section of the package inserts of drugs that have been revised in accordance with the Notification dated April 20, 2011.

1 Olopatadine Hydrochloride (oral dosage form)

Brand Name (name of company)	ALLELOCK Tablets 2.5, 5, ALLELOCK OD Tablets 2.5, 5 (Kyowa Hakko Kirin Co., Ltd.)
Therapeutic Category	Allergic agents-Miscellaneous
Indications	Adult: Allergic rhinitis, urticaria, pruritus associated with skin disease (eczema/dermatitis, prurigo, cutaneous pruritus, psoriasis vugaris, erythema multiforme exudativum) Pediatrics: Allergic rhinitis, urticaria, pruritus associated with skin disease (eczema/dermatitis, cutaneous pruritus)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Fulminant hepatitis, hepatic dysfunction, jaundice: Fulminant hepatitis, hepatic dysfunction with elevations of AST (GOT), ALT (GPT), γ-GTP, LDH, and Al-P or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to March 4, 2011)

- Fulminant hepatitis: 2 cases (2 fatal cases)

The number of patients using this drug per year estimated by the MAHs:
Approximately 4.438 million (November 2009 to October 2010)
Launched into Japan: March 2001 (ALLELOCK Tablets 2.5, 5)
November 2010 (ALLELOCK OD Tablets 2.5, 5)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 90s	Eczema (hypertension)	2.5 mg for 13 days	**Fulminant hepatitis** The patient started receiving epinastine hydrochloride and topical corticosteroid for treatment of eczema at a hospital. Day 1 of administration: In the same month, treatment was switched from the above two drugs to olopatadine hydrochloride 2.5 mg/day after the first consultation at the reporting hospital. Around Day 6 of administration: Jaundice occurred. Day 13 of administration (day of discontinuation): Administration of olopatadine hydrochloride was discontinued.

				1 day after discontinuation: The patient was admitted to the hospital. Total bilirubin 14.6 mg/dL, AST (GOT) 640 IU/L, ALT (GPT) 1055 IU/L. Administration of glycyrrhizin/glycine/cysteine, heparin sodium, and omeprazole were started. 3 days after discontinuation: The liver disorder became fulminant and was complicated with renal impairment and disseminated intravascular coagulation. Administration of methylprednisolone sodium succinate and meropenem hydrate were started. 4 days after discontinuation: The patient had disturbed consciousness and was unable to communicate. 6 days after discontinuation: The patient died. Drug lymphocyte stimulation test (DLST) was negative for olopatadine hydrochloride
	Concomitant medications: epinastine hydrochloride, anti-inflammatory/analgesic/anti-itching, nifedipine, loperamide hydrochloride			

Laboratory Examination

	10 months before administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation
Total bilirubin (mg/dL)	1.3	14.6	14.2	12.6	15.1
AST (GOT) (IU/L)	16	640	280	124	124
ALT (GPT) (IU/L)	9	1055	708	312	275
γ-GTP (IU/L)	17	60	-	-	-
Prothrombin (PT) activity (%)	-	-	14	25	23

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 40s	Neurodermatitis (infertility)	Unknown for 208 days	**Fulminant hepatitis** The patient had been taking oral norgestrel/ethinylestradiol for treatment of infertility. Day 1 of administration: Administration of olopatadine hydrochloride was started for treatment of neurodermatitis. 200 days of administration: The patient had general malaise and yellow urine. Administration of norgestrel/ethinylestradiol were discontinued on the previous day. Day 208 of administration (day of discontinuation): Administration of olopatadine hydrochloride was discontinued. 1 day after discontinuation: The patient had jaundice; total bilirubin 13.2 mg/dL, AST (GOT) 123 IU/L, ALT (GPT) 140 IU/L, and PT activity 21%. She was admitted to the hospital. She was fasted, given transfusion and followed. An abdominal CT showed no liver deformity. No obstructive jaundice was noted.

				3 days after discontinuation: Administration of ursodeoxycholic acid and glycyrrhizin/glycine/cysteine were started. 4 days after discontinuation: Administration of prednisolone 40 mg was started. 5 days after discontinuation: Steroid pulse therapy was performed for 3 days. 6 days after discontinuation: The patient was moved to the intensive care unit (ICU). Plasma exchange (10 days in total) and continuous haemodiafiltration (CHDF) were started. 7 days after discontinuation: The patient had near-anuria and disturbed consciousness (grade II to III), and systemic management by mechanical ventilation using endotracheal intubation was performed. The abdominal CT showed that her liver was shrinking and increased ascites. The electroencephalography showed overall decrease in activity. PT remained 30% to 40% during the plasma exchange. Jaundice progressed. 25 days after discontinuation: Generalised convulsion occurred, but subsided with thiopental sodium. The patient's general condition continued to deteriorate. 29 days after discontinuation: The patient died. Viral test: negative for HBV-DNA, HCV-RNA, anti-VCA IgM antibody, CMV IgM antibody, IgM-HA antibody Autoimmunology test: serum IgG normal, antinuclear antibody × 40, smooth muscle antibody negative, anti-LKM-1 antibody negative DLST: positive for olopatadine hydrochloride (Stimulation Index [SI], 519%) and norgestrel/ethinylestradiol (SI, 326%)
	Concomitant medications: norgestrel/ethinylestradiol, ascorbic acid/calcium pantothenate, pyridoxal phosphate hydrate, riboflavin butyrate			

Laboratory Examination

	1 day after discontinuation	5 days after discontinuation	10 days after discontinuation	15 days after discontinuation	20 days after discontinuation	25 days after discontinuation	29 days after discontinuation
Ammonia (μg/dL)	-	84	131	248	242	397	>500
Total bilirubin (mg/dL)	13.2	33.8	42.3	26.7	31.8	29.5	21.5
AST (GOT) (IU/L)	123	101	128	61	165	123	91
ALT (GPT) (IU/L)	140	17	24	28	60	97	77
γ-GTP (IU/L)	453	253	48	33	45	32	38
PT activity (%)	21	14	31	28	19	-	-

2 Fludarabine Phosphate

Brand Name (name of company)	Fludara ORAL 10mg tablet, Fludara 50 mg for Intravenous Infusion (Genzyme Japan K.K.)
Therapeutic Category	Antimetabolites
Indications	● Chronic lymphocytic leukaemia with anaemia or thrombocytopenia ● Following relapsed or refractory diseases: Low-grade B-cell non-Hodgkin's lymphoma Mantle cell lymphoma ● Pretreatment of allogenic hematopoietic stem cell transplantation for the treatment of the following diseases (Fludara I.V. Injection 50 mg only): Acute myeloid leukaemia, myelodysplastic syndrome, chronic myeloid leukaemia, chronic lymphocytic leukaemia, malignant lymphoma, multiple myeloma.

PRECAUTIONS (underlined parts are revised)

Important Precautions

Aggravation of hepatitis or fulminant hepatitis may occur in hepatitis B virus carriers after administration of this drug. Special attention should be paid to the occurrence of signs or symptoms related to an increase in hepatitis B virus, monitoring of liver function test results and hepatitis virus marker levels during and after treatment. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures, such as administration of antivirals, should be taken immediately. Hepatitis due to the hepatitis B virus has been reported in patients who are negative for HBs antigen before starting this drug.

Adverse Reactions (clinically significant adverse reactions)

Severe opportunistic infection: Opportunistic infections such as sepsis and pneumonia may occur. Aggravation of hepatitis due to hepatitis B virus or fulminant hepatitis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued immediately, and appropriate measures, such as administration of antibiotics, antifungals, or antivirals, should be taken.

Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leucoencephalopathy (PML) may occur. Patients should be carefully monitored during and after treatment with this drug. If symptoms such as 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.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to March 18, 2011)

- Progressive multifocal leukoencephalopathy: 1 case (1 fatal case)
- Hepatitis due to hepatitis B virus: 5 cases (1 fatal case)

The number of patients using this drug per year estimated by the MAHs:
Approximately 2600 (2010)
Launched into Japan: April 2000 (Injectable dosage form)
July 2007 (oral dosage form)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Chronic lymphocytic leukaemia (hepatitis B)	40 mg (oral) for 5 days ↓ 60 mg (oral) for 15 days	**Fulminant hepatitis, hepatitis B** Approximately 7 months before administration: The patient had chronic lymphocytic leukaemia (CLL). Oral administration of cyclophosphamide hydrate 50 mg was started for treatment of airway narrowing associated with swollen cervical lymph nodes. Approximately 4 months before administration: AST (GOT) 60 IU/L, ALT (GPT) 112 IU/L. Cyclophosphamide hydrate-induced liver disorder was suspected. The dosing frequency of cyclophosphamide hydrate was decreased to alternate days. Approximately 3 months before administration: A CT showed enlarged lymph nodes. No abnormality was found in the liver, gallbladder, pancreas and kidneys. Day 1 of administration: Due to the aggravation of airway narrowing, oral administration of fludarabine phosphate (40 mg for 5 days) was started after switching from cyclophosphamide hydrate. 28 days after administration: Oral administration of fludarabine phosphate (60 mg for 5 days) was started (the second cycle). 56 days after administration: Oral administration of fludarabine phosphate (60 mg for 5 days) was started (the third cycle). 69 days after administration: Fulminant hepatitis occurred. The liver disorder alternately improved and worsened. 84 days after administration: Oral administration of fludarabine phosphate (60 mg for 5 days) was started (the fourth cycle). 88 days after administration (day of completion): Administration of fludarabine phosphate was completed. 37 days after completion: Total bilirubin 2.5 mg/dL, AST (GOT) 844 IU/L, ALT (GPT) 927 IU/L. The viral test showed Hbs antigen of 250 IU/L or higher. ALT (GPT) 1867 IU/L, total bilirubin 11.6 mg/dL and, PT activity 66%. The patient was treated in the ICU. HBe antibody positive, IgM-HBc antibody negative, HBV-DNA 8.1 LC/mL. Wild-type in core promoter region, mutant-type in pre-core promoter region. Based on the absence of bodily fluid infection in the past half year, HBV reactivation was suspected. Concomitant therapy with entecavir hydrate and adefovir dipivoxil and liver supporting therapy were started. On day 3 of hospitalization, steroid pulse therapy was performed since PT activity had decreased to 54%. PT activity temporarily improved. Liver function gradually decreased after predonine dose reduction. 44 days after completion: Enlarged lymph nodes were noted. Pelvic lymph node enlargement was not found. The size, form and image of liver were normal. Splenomegaly was not found. Mild thickening of gallbladder wall was noted. No biliary abnormality was found. 62 days after completion:

				Unclear liver margin and surface irregularity were noted. Slight atrophy was present. No space-occupying lesion was found in the liver. Ascites occurred. Splenomegaly was not found. The lymph nodes slightly shrunk. Pancreatic enlargement was not found. Hepatitis was present. Mild liver shrunk and oedematous thickening of gallbladder wall were noted. 79 days after completion: The patient died of fulminant hepatitis. Cause of death: Acute aggravation of hepatitis B
	Concomitant medications: cyclophosphamide hydrate			

Laboratory Examination

	Approx. 4 months before administration	37 days after completion	44 days after completion
AST (GOT) (IU/L)	60	844	-
ALT (GPT) (IU/L)	112	927	-
Total bilirubin (mg/dL)	-	2.5	11.6
HBs antigen (IU/mL)	-	>250	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Chronic lymphocytic leukaemia (splenomegaly, hepatitis virus carrier)	50 mg (oral) for 5 days	**Hepatitis B, abnormal hepatic function, decreased neutrophil count, sepsis** Complications: Splenomegaly, hepatitis virus carrier (exposure via parents) Medical history: appendicitis, hyperlipidaemia 10 days before administration: The patient was negative for HBs antigen and positive for HBc antibody at first consultation. The patient was diagnosed with chronic lymphocytic leukaemia based on the examination upon admission. The leukaemia was in an advanced stage. Day 1 of administration: The first cycle of oral administration of fludarabine phosphate (50 mg/day for 5 days) was started. 7 days after administration: Sepsis occurred. Filgrastim (genetical recombination) (75 μg) and cefepime dihydrochloride hydrate (4 g) were administered. 8 days after administration: Neutrophil count decreased (0). 11 days after administration: Filgrastim (genetical recombination) (300 μg) was administered for 6 days. 13 days after administration: Imipenem hydrate/cilastatin sodium (1 g/day) and vancomycin hydrochloride (1 g/day) were intravenously administered for 7 days. 18 days after administration: Sepsis improved. 25 days after administration: Neutropenia remained low due to severe bone marrow depression. Sepsis occurred concurrently. After the first cycle, administration of fludarabine phosphate was discontinued. The

				treatment was switched to Cyclophosphamide-Vincristine-Prednisolone (CVP) therapy. 60 days after administration: Neutropenia remitted. 89 days after administration: Acute hepatitis B occurred and Grade IV abnormal hepatic function developed. Detailed examinations showed that HBs antigen, which had been negative upon admission, had turned positive, and that the viral load had increased. The patient was diagnosed with acute hepatitis B. 92 days after administration: Treatment of antiviral (entecavir hydrate 0.5 mg/day) was started. 138 days after administration: An abdominal ultrasound did not show any characteristic hepatic disorder. 165 days after administration: An abdominal ultrasound did not show any characteristic hepatic disorder. Abnormal hepatic function and acute hepatitis B improved. The treatment of lymphoma resumed. 247 days after administration: The patient died due to aggravation of underlying disease.
	Concomitant medications: sulfamethoxazole/trimethoprim, fluconazole, sodium rabeprazole, prednisolone, cyclophosphamide hydrate, vincristine sulfate			

Laboratory Examination

	10 days before administration	8 days after administration	60 days after administration	89 days after administration	91 days after administration	92 days after administration	109 days after administration	165 days after administration	174 days after administration
WBC (/mm^3)	181800	17100	8300	7100	-	-	-	10100	-
Neutrophils (%)	0.5	0.0	11.5	25.0	-	-	-	1.5	-
Neutrophils (/mm^3)	909	0	955	1775	-	-	-	152	-
Lymphocytes (%)	99.0	100.0	83.0	68.0	-	-	-	98.0	-
AST (GOT) (IU/L)	18	13	11	642	-	-	-	16	-
ALT (GPT) (IU/L)	9	7	8	414	-	-	-	31	-
LDH (IU/L)	204	134	155	435	-	-	-	168	-
Al-P (IU/L)	189	150	110	109	-	-	-	217	-
γ-GTP (IU/L)	13	-	-	20	-	-	-	70	-
HBs antigen	(-)	-	-	-	-	-	>500	-	26.5
HBs antibody	(+)	-	-	-	2.2	-	1.8	-	3.8
HBc antibody	(+)	-	-	-	-	98.9	99.6	-	99.7

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 40s	Cord blood transplant therapy (swollen inguinal lymph nodes, follicular center cell	Unknown (intravenous) Unknown	**Progressive multifocal leukoencephalopathy** Approximately 8.5 years before administration: The patient was diagnosed with follicular lymphoma (Grade 2, Stage 4A). He achieved a partial remission (PR) after Cyclophosphamide-Hydroxydaunorubicin-Oncovin-Prednisolone (CHOP) therapy. Approximately 4 years before administration: The patient had progressive disease (PD). Despite various

		lymphoma)		salvage chemotherapies with rituximab (genetical recombination), the disease gradually became treatment resistant. The patient also became transfusion-dependent due to cytopenia associated with bone marrow infiltration. Day 1 of administration: Non-myeloablative cord blood transplantation was performed. Pre-transplant treatment included fludarabine phosphate, melphalan and total body irradiation (TBI) 4 Gy. Tacrolimus hydrate and short-term methotrexate were administered for prevention of graft-versus-host disease (GVHD). 35 days after administration: The patient was aware of feelings of weakness in his left arm. 42 days after administration: Somnolence and paresis in his left arm progressed. A brain CT showed a low density area in the right white matter. MRI showed T2 weighted image in the right subcortical white matter and similar multiple lesions in the left white matter. 43 days after administration: Seventh nerve paralysis occurred. Cerebrospinal fluid test (PCR method) detected JC virus, and the patient was diagnosed with progressive multifocal leukoencephalopathy (PML). 53 days after administration: Left upper and lower extremities were completely paralyzed. MRI showed expansion of existing lesions. 77 days after administration: Disturbed consciousness progressed to Japan Coma Scale (JCS) 3-300. 107 days after administration: The patient died. Autopsy showed that demyelination had spread from the right frontal lobe to the parietal lobe, countless minor demyelination in the bilateral cerebral hemisphere and brainstem, foamy macrophage infiltration, oligodendroglial intranuclear inclusion and anti-JC virus antibodies.
	Concomitant medications: rituximab (genetical recombination), cladribine, corticosteroids, melphalan, tacrolimus hydrate, methotrexate			

3 Miriplatin hydrate, iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil (MIRIPLA suspension vehicle)

(1) Miriplatin hydrate

Brand Name (name of company)	MIRIPLA for Intra-arterial Injection 70 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Lipiodolization for hepatocellular carcinoma

≪PRECAUTIONS (underlined parts are revised)≫

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored for changes in their clinical symptoms including pyrexia, cough and dyspnoea. If any abnormalities are observed, examinations including chest X-ray, chest CT scan and serum marker test should be performed. If interstitial

pneumonia is suspected, appropriate measures including administration of corticosteroids should be taken.

Acute renal failure: Serious renal disorders such as acute renal failure may occur. Patients should be carefully monitored. If any abnormalities of BUN or serum creatinine level are observed, appropriate measures should be taken.

(2) Iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil (MIRIPLA suspension vehicle)

Brand Name (name of company)	MIRIPLA suspension vehicle 4 mL (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Non-main therapeutic purpose agents-Miscellaneous
Indications	Suspension of MIRIPLA for Intra-arterial Injection 70 mg

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur after administration of miriplatin suspension. Patients should be carefully monitored for changes in their clinical symptoms including pyrexia, cough and dyspnoea. If any abnormalities are observed, examinations including chest X-ray, chest CT scan and serum marker test should be performed. If interstitial pneumonia is suspected, appropriate measures including administration of corticosteroids should be taken.

Acute renal failure: Serious renal disorders such as acute renal failure may occur after administration of miriplatin suspension. Patients should be carefully monitored, if any abnormalities in BUN or serum creatinine level are observed, 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 year (from initial marketing to March 29, 2011)

- Interstitial pneumonia: 5 cases (1 fatal case)
- Acute renal failure: 1 case (1 fatal case)

The number of patients using this drug per year estimated by the MAHs: Approximately 10000 (FY 2010)

Launched into Japan:January 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Hepatocellular carcinoma (hepatitis C, hepatic cirrhosis, hypertension)	120 mg for 1 day	**Interstitial pneumonia** The patient had hepatic artery embolization (with emulsion of iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil and gelatin) with cisplatin for treatment of hepatocellular carcinoma at 2 years and 5 months, 2 years and 3 months, 1 year and 3 months, 10 months, and 5 months prior to the administration of iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil. Urticaria appeared after the last treatment session. Day 1 of administration: Lipiodolization with iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil was performed. No urticaria occurred. The patient had pyrexia of 39.5°C after the surgery and was prescribed with loxoprofen sodium hydrate. 1 day after completion: Pyrexia of 39.3°C developed.

				2 days after completion: Pyrexia of 38.9°C developed. 3 days after completion: The patient had pyrexia of 38.1°C in the morning. Oral loxoprofen sodium hydrate was administered. Dyspnoea occurred around noon. The patient had pyrexia of 38.9°C at night. Dyspnoea and cough were present. Intranasal oxygen 3 L was administered since $SatO_2$ (oxygen saturation) had decreased to 77%. Dyspnoea disappeared. $SatO_2$ increased to 93%. (Interstitial pneumonia occurred.) 4 days after completion: Coarse crackle was heard in the right middle lung by auscultation. A CT showed panlobular ground-glass opacities in the bilateral upper lobe. The patient was diagnosed with interstitial pneumonia based on the absence of abnormality in electrocardiogram (ECG) and echocardiography. Steroid pulse therapy (methylprednisolone 1000 mg for 3 days), oral administration of antibiotic (ciprofloxacin 300 mg × 2 for 4 days) and famotidine were started. 5 days after completion: The patient had no pyrexia. $SatO_2$ remained at 96% to 99%. A small amount of bloody sputum was noted. A plain X-ray of the chest showed absence of shadow in the upper lung field. 6 days after completion: On day 3 of steroid pulse therapy, respiratory condition was improving. 7 days after completion: Steroid was switched to oral prednisolone 30 mg. Oxygen therapy was discontinued. The patient had no shortness of breath when walking to the bathroom. A plain X-ray of the chest showed decrease in shadow. 8 days after completion: The respiratory symptoms mostly disappeared but abdominal distention was noted. 9 days after completion: Furosemide 40 mg and potassium canrenoate 100 mg were intravenously administered for treatment of abdominal distention. 10 days after completion: Abdominal distention improved after urination. 11 days after completion: Furosemide 40 mg was switched to oral spironolactone 25 mg. Dose of prednisolone was reduced to 20 mg. 13 days after completion: A plain chest X-ray showed absence of ground-glass opacities, interlobular septal thickening, and bilateral pleural effusion. The dose of prednisolone was reduced to 10 mg. The patient was discharged from the hospital. (Interstitial pneumonia remitted.)
	Concomitant medications: isoleucine/leucine/valine, ursodeoxycholic acid, etizolam, glycyrrhizin/DL-methionine combination, amlodipine besilate, rebamipide, loxoprofen sodium hydrate			

Laboratory Examination

	1 day after completion	4 days after completion	5 days after completion	6 days after completion	9 days after completion	13 days after completion
KL-6 (U/mL)	-	-	-	307	-	-
CRP (mg/dL)	0.85	2.64	3.51	-	0.39	<0.30
LDH (IU/L)	247	197	189	-	234	217

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Hepatocellular carcinoma (chronic obstructive pulmonary disease, hypertension, hyperlipidaemia, proctitis)	100 mg for 1 day	**Acute renal failure** The patient had been found to have alcoholic hepatopathy in past days. About 1 month before the treatment, aggravation of hepatic dysfunction was noted at the urological department, where the patient received outpatient care after the treatment of prostate and bladder cancer. The patient visited the gastrointestinal department for the first time. An outpatient examination suggested a finding of hepatic cirrhosis. A CT showed multiple hepatocellular carcinoma. Day 1 of administration: Angiography was performed. At least 2 tumor stains were found in the back of the right lobe. Iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil were arterially administered to the right posterior segmental branch. 1 day after completion: BUN and creatinine (Cr) remained high postoperation. Urine output decreased (200 to 500 mL/day), and oedema was aggravated. Fluid replacement (1000 mL/day) was started. Human serum albumin was also administered. 2 days after completion: Acute renal failure developed. 8 days after completion: Weight was increasing, urine output decreased, appetite was impaired, and malaise was aggravated. 13 days after completion: Administration of human serum albumin 50 mL was started and continued until 22 days after completion. 15 days after completion: Administration of furosemide 40 mg/day was started and continued until 23 days after completion. 18 days after completion: BUN and Cr further increased. Urine output decreased to < 200 mL/day. Dose of diuretics was increased. 20 days after completion: Haemodialysis was considered due to anuria. 21 days after completion: BUN and Cr further increased. Hepatic failure was concurrently aggravated. Haemodialysis was performed, but terminated after 2 hours and 45 minutes due to decreased blood pressure. It was impossible to remove water. Dyspnoea occurred. 22 days after completion: The patient had respiratory failure during the second session

				of haemodialysis. A mechanical ventilator was attached. Blood pressure continued to drop and did not increase even after administration of dopamine hydrochloride and dobutamine hydrochloride. 23 days after completion: Cardiac arrest occurred in the early morning. Heartbeat resumed twice with cardiopulmonary resuscitation. Death was confirmed after the third cardiac arrest. Cause of death: Acute renal failure Autopsy: not performed
	Concomitant medications: ursodeoxycholic acid, salazosulfapyridine, solution for postoperative recovery, bezafibrate, telmisartan, tocopherol nicotinate, isoleucine/leucine/valine			

Laboratory Examination

	22 days before administration	1 day after completion	4 days after completion	7 days after completion	18 days after completion	21 days after completion
BUN (mg/dL)	21.5	23.7	47.8	53.8	66.7	103.7
Serum creatinine (mg/dL)	0.93	1.60	2.46	2.04	3.23	6.01

4

Revision of Precautions (No. 226)

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 Notification dated April 20, 2011 (excluding those presented in 3. Important Safety Information of this Bulletin).

1 Allergic agents-Miscellaneous

Ketotifen Fumarate (oral dosage form)

Brand Name	Zaditen Capsules 1mg, Zaditen Syrup 0.02%, Zaditen Dry Syrup 0.1% (Novartis Pharma K.K.)
Contraindications	Patients with past or present epilepsy
Careful Administration	Patients with past or present convulsive disorders other than epilepsy
Reference Information	Yokoyama, H., et al.: Meth. Find. Clin. Pharmacol. 1993;15(3):183-188

2 Hypnotics and sedatives, anxiolytics

Alprazolam

Brand Name	CONSTAN 0.4 mg. TABLETS, CONSTAN 0.8 mg. TABLETS (Takeda Pharmaceutical Company Limited), Solanax Tablets 0.4 mg, 0.8 mg (Pfizer Japan Inc)
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfunction with elevated AST (GOT), ALT (GPT), and γ-GTP or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

3 Antiparkinsonian agents

Pramipexole hydrochloride hydrate

Brand Name	BI・Sifrol Tablets 0.125 mg, 0.5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Precautions of Dosage and Administration	This drug is excreted as unchanged drug in the urine. When patients with renal impairment (creatinine clearance < 50 mL/min) are treated with this drug, the elimination half-life of this drug is prolonged due to decreased renal clearance. In this case, the dosing frequency should be adjusted based on the following method, and the dose should be carefully titrated by monitoring the patient's renal function. The maximum daily dose and maximum single dose in patients with renal impairment are shown in the table below. Since this drug has not been much used in dialysis patients or those with very severe renal impairment, this drug should be

carefully administered in such patients by monitoring the patient's condition.

Creatinine clearance (mL/min)			Dosage	Initial daily dose	Maximum daily dose
	Creatinine clearance	≥50	< 1.5 mg/day, twice a day	0.125 mg × 2	4.5 mg (1.5 mg × 3)
			< 1.5 mg/day, three times a day		
50>	Creatinine clearance	≥20	twice a day	0.125 mg × 2	2.25 mg (1.125 mg × 2)
20>	Creatinine clearance		once daily	0.125 mg × 1	1.5 mg (1.5 mg × 1)

4 **Antihypertensives**

Aliskiren fumarate

Brand Name Rasilez Tablets 150mg (Novartis Pharma K.K.)

Adverse Reactions (clinically significant adverse reactions) **Renal impairment**: Serious renal impairment may occur, resulting in aggravation of chronic renal failure in some cases. Patients should be carefully monitored, if any abnormalities are observed, appropriate measures should be taken.

5 **Digestive organ agents-Miscellaneous**

Infliximab (genetical recombination)

Brand Name REMICADE for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corporation)

Important Precautions Interstitial pneumonia may occur. Patients should be instructed to contact a physician immediately if symptoms such as pyrexia, cough, or dyspnoea occur after administration of this drug. If any such symptoms are observed, chest X-ray and CT examinations should be performed, and appropriate measures including administration of corticosteroids should be taken. Some cases in which interstitial pneumonia occurred and led to fatal course have been reported especially in concomitant with methotrexate.
When using this drug with methotrexate, physicians should thoroughly read the package insert of methotrexate, and this drug should be administered after consideration of risks-benefits.

6 **Antimetabolites**

Pemetrexed sodium hydrate

Brand Name Alimta Injection 100 mg, 500 mg (Eli Lilly Japan K.K.)

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

7 **Acting mainly on mold**

Micafungin sodium

Brand Name Funguard 25 mg for Infusion, Funguard 50 mg for Infusion, Funguard 75 mg for Infusion (Astellas Pharma Inc.)

Adverse Reactions (clinically significant **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Toxic epidermal necrolysis,

adverse reactions) oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

8 **Antivirals**

Darunavir ethanolate (300 mg)

Brand Name

PREZISTA Tablets 300 mg (Janssen Pharmaceutical K.K.)

Precautions of Indications

The sentence, "This drug should be used in anti-HIV drug treatment-naïve HIV infected patients" was deleted.

When patients are treated with this drug, their past treatment and, if possible, results of drug-resistance tests (genotype or phenotype analysis) should be checked.

(1) PREZISTA Tablets 300 mg

This drug should be used in anti-HIV drug treatment-experienced patients with at least one darunavir resistance associated substitution.

(2) PREZISTANAIVE Tablets 400 mg

This drug should be used in anti-HIV drug treatment-naïve HIV-infected patients or anti-HIV drug treatment-experienced patients with no darunavir resistance associated substitutions.

CD4-positive lymphocyte count and plasma HIV RNA level are indicators for starting treatment of asymptomatic HIV infection. When using this drug, physicians should check the CD4-positive lymphocyte count and plasma HIV RNA level, and read the latest guidelines.

The safety and efficacy of this drug have not been established in HIV-infected children.

Precautions of Dosage and Administration

The sentence, "See the package insert of PREZISTANAIVE Tablets 400 mg for the dosage and administration in anti-HIV drug treatment-naïve patients" was deleted.

This drug should be used in accordance with the table below.

Anti-HIV drug treatment-naïve HIV infected patients	Anti-HIV drug treatment-experienced patients	
	Patients with no darunavir resistance associated substitutions	Patients with at least one darunavir resistance associated substitution
2 tablets of PREZISTANAIVE Tablets 400 mg once daily.	2 tablets of PREZISTANAIVE Tablets 400 mg once daily.	2 tablets of PREZISTA Tablets 300 mg twice daily.

Genotype drug resistance test is recommended in anti-HIV drug treatment-experienced patients. If genotype testing cannot be performed, administration of 2 tablets of PREZISTA Tablets 300 mg twice daily is recommended.

Important Precautions

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and erythema multiforme have been reported in association with administration of this drug. In overseas clinical studies, rash, including cases with unknown causality, occurred in 10.3% of patients treated with this drug. Rash requiring treatment discontinuation occurred in 0.5% of patients, severe rash with pyrexia and increased hepatic enzyme levels occurred in 0.4% of patients, and oculomucocutaneous syndrome (Stevens-Johnson syndrome) occurred in less than 0.1% of patients. In many cases, mild to moderate rash occurred within 4 weeks of treatment but achieved remission during the treatment. If severe rash occurs, administration of this drug should be discontinued immediately, and appropriate measures should be taken. In the overseas clinical studies in treatment-experienced patients, the incidence of rash (including skin eruption with unclear causality) was higher in patients who received the treatment regimen including this drug and

raltegravir compared with those who received a treatment regimen including either this drug or raltegravir. However, there were no differences in the incidence of drug-related rash. Rash was mild to moderate in severity and did not result in treatment restriction or discontinuation.

9 **Antivirals**

Darunavir ethanolate (400 mg)

Brand Name

PREZISTANAIVE Tablets 400 mg (Janssen Pharmaceutical K.K.)

Precautions of Indications

The sentence, "This drug should be used in anti-HIV drug treatment-naïve HIV-infected patients (the safety and efficacy have not been established in patients other than anti-HIV drug treatment-naïve HIV-infected patients)" was deleted.
When patients are treated with this drug, their past treatment and, if possible, results of drug-resistance tests (genotype or phenotype analysis) should be checked.

(1) PREZISTA Tablets 300 mg
This drug should be used in HIV-infected patients with at least one darunavir resistance associated substitution.

(2) PREZISTANAIVE Tablets 400 mg
This drug should be used in anti-HIV drug treatment-naïve HIV-infected patients or anti-HIV drug treatment-experienced patients with no darunavir resistance associated substitutions.

Precautions of Dosage and Administration

The sentence, "See the package insert of PREZISTA Tablets 300 mg for the dosage and administration in anti-HIV drug treatment-experienced patients" was deleted.
This drug should be used in accordance with the table below.

Anti-HIV drug treatment-naïve HIV infected patients	Anti-HIV drug treatment-experienced patients	
	Patients with no darunavir resistance associated substitutions	Patients with at least one darunavir resistance associated substitution
2 tablets of PREZISTANAIVE Tablets 400 mg once daily.	2 tablets of PREZISTANAIVE Tablets 400 mg once daily.	2 tablets of PREZISTA Tablets 300 mg twice daily.

Genotype drug resistance test is recommended in anti-HIV drug treatment-experienced patients. If genotype testing cannot be performed, administration of 2 tablets of PREZISTA Tablets 300 mg twice daily is recommended.

Important Precautions

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and erythema multiforme have been reported in association with administration of this drug. In overseas clinical studies, rash, including cases with unknown causality, occurred in 10.3% of patients treated with this drug. Rash requiring treatment discontinuation occurred in 0.5% of patients, severe rash with pyrexia and increased hepatic enzyme levels occurred in 0.4% of patients, and oculomucocutaneous syndrome (Stevens-Johnson syndrome) occurred in less than 0.1% of patients. In many cases, mild to moderate rash occurred within 4 weeks of treatment but achieved remission during the treatment. If severe rash occurs, administration of this drug should be discontinued immediately, and appropriate measures should be taken. In the overseas clinical studies in treatment-experienced patients, the incidence of rash (including skin eruption with unclear causality) was higher in patients who received the treatment regimen including this drug and raltegravir compared with those who received a treatment regimen including either this drug or raltegravir. However, there were no differences in the incidence of drug-related rash. Rash was mild to moderate in severity and did not result in treatment restriction or discontinuation.

10 Antivirals

Ribavirin (Tablets)

Brand Name

COPEGUS Tablet 200 mg (Chugai Pharmaceutical Co., Ltd.)

Precautions of Dosage and Administration

Haematology tests should be periodically performed during the administration of this drug. If neutrophil count, platelet count or haemoglobin decreases, dose of this drug should be adjusted based on the table below.
If the administration of this drug is resumed, the laboratory test values should be checked to make sure they are over the discontinuation criteria shown in the table below. However, the dose of peginterferon alfa-2a (genetical recombination) should be reduced to 90 μg when the administration of this drug is resumed after discontinuing administration due to platelet count decrease.

11 Biological preparations-Miscellaneous

Peg-Interferon Alfa-2a (genetical recombination)

Brand Name

PEGASYS s.c. 90 μg, 180 μg (Chugai Pharmaceutical Co., Ltd.)

Precautions of Dosage and Administration

<Improvement of viraemia in patients with chronic hepatitis C who are being treated with monotherapy of this drug>
Haematology tests should be periodically performed during the administration of this drug. If neutrophil count, platelet count, or haemoglobin decreases, dose of this drug should be adjusted based on the table below.
<Improvement of viraemia in patients with chronic hepatitis C in concomitant use of ribavirin>
Haematology tests should be periodically performed during the concomitant use with this drug and ribavirin. If neutrophil count, platelet count, or haemoglobin decreases, dose of this drug should be adjusted based on the table below.
If the administration of this drug is resumed, the laboratory test values should be checked to make sure they are over the discontinuation criteria shown in the table below. However, the dose of peginterferon alfa-2a (genetical recombination) should be reduced to 90 μg when the administration of this drug is resumed after discontinuing administration due to platelet count decrease.

Important Precautions

Neutropenia, thrombocytopenia, and anaemia may occur. Haematology tests should be performed periodically, e.g., at least twice a week in the first week of administration, once a week for up to 8 weeks of administration, and once every subsequent 4 weeks. Tests should be periodically performed even after completion of this drug until the test values return to normal. If significant cytopenia, etc. is observed, the tests should be performed more frequently.
Hepatic dysfunction and renal impairment may occur. Periodic biochemical tests should be performed every 4 weeks.
Patients should be thoroughly monitored for infection, haemorrhage symptom (e.g., gingival bleeding, epistaxis, subcutaneous haemorrhage and purpura), and anaemia-associated symptoms during the administration of this drug. If any abnormalities are observed, haematology tests should be performed, and appropriate measures such as dose reduction or discontinuing administration should be taken.

12 Biological preparations-Miscellaneous

Peg-Interferon Alfa-2b (genetical recombination)

Brand Name

PEGINTRON Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL (MSD K.K.)

Adverse Reactions (clinically significant adverse reactions)	**Haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP)**: Haemolytic uraemic syndrome (HUS) characterized by thrombocytopenia, anaemia and renal failure, and thrombotic thrombocytopenic purpura (TTP) may occur. Patients should be carefully monitored by performing periodic blood tests (platelet count, red blood cell count, haemogram, etc.) and renal function analyses. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

13 **Over-the-counter drugs**

Ketotifen Fumarate (oral dosage form)

Brand Name	Zaditen AL Rhinitis Capsule (Novartis Pharma K.K.), Jikina Rhinitis Tablet (Fuji Yakuhin co., Ltd.), Pabron Rhinitis Capsule-Z (Taisho Pharmaceutical Co., Ltd.), Histomin Rhinitis Capsule Z (Kobayashi Pharmaceutical Industries. Ltd.)
When not to use the product	This product should not be used in the following persons. Persons who have experienced epilepsy or convulsive seizure.
Consultation	The sentence, "Consult a physician or a pharmacist if you have been diagnosed with epilepsy" was deleted.

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 June 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
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
Repaglinide SUREPOST Tablets 0.25 mg, 0.5 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 16, 2011
Febuxostat Feburic Tablet 10 mg, 20 mg, 40 mg	Teijin Pharma Limited.	May 17, 2011
Levonorgestrel NORLEVO 0.75 mg Tablet	Sosei Co. Ltd.	May 24, 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”