Pharmaceuticals and Medical Devices Safety Information

No. 294 September 2012

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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. 294 September 2012

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
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
APTT	Activated partial thromboplastin time
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CHDF	Continuous hemodiafiltration
CK (CPK)	Creatine kinase (Creatine phosphokinase)
CRP	C-reactive protein
CT	Computed tomography
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
IU	International unit
JCS	Japan Coma Scale
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
PE	Phenoxyethanol
PLT	Platelet
PS	Performance status
PT	Prothrombin Time
RBC	Red blood cell count
WBC	White blood cell count
XELOX	A regimen consisting of capecitabine plus oxaliplatin
γ-GTP	gamma-glutamyl transpeptidase

1

Proper Use of Contact Lenses and Prevention of Eye Disorders

1. Introduction

Corrective contact lenses have been regulated as "specially controlled medical devices" in accordance with the Pharmaceutical Affairs Law (Law No. 145, 1960) to ensure safety and quality. Non-corrective, decorative/cosmetic contact lenses (used mainly among young people in recent years) have been designated as "specially controlled medical devices" since November 2009[1)], in response to reports of eye disorders due to improper use and product quality problems[2,3)]

This section reports cases of eye disorders associated with contact lenses. Healthcare providers are requested to warn users thoroughly on the proper use of contact lenses.

2. Contact lens-related eye disorders

(1) Reports of eye disorders from healthcare providers

Based on the Drugs and Medical Devices Safety Information Reporting System[4)], a total of 69 contact lens-related eye disorder events were reported from healthcare providers to MHLW during the 3 years from FY 2009 through FY 2011 Reported eye disorders are shown in Table 1. Most of the disorders are corneal disorders, such as corneal infiltrates and corneal erosion, and conjunctival disorders. The major causes of reported eye disorders include insufficient lens care, improper use such as improper continuous wearing and non-consultation of ophthalmologists, which is required before use. One of the problems that has also been pointed out is that users have not been given a detailed explanation of information about the risk of eye disorders and proper use upon purchasing contact lenses, as well as users' low awareness of the risk of eye disorders and proper use.

Of the 69 cases reported, the product was identified in 43 cases (excluding products unappoved in Japan), and non-corrective, decorative/cosmetic contact lenses were used in 20 cases.

Table 1 Common eye disorders reported

Eye disorders	Reported number of cases
Corneal infiltrates	21
Corneal erosion	14
Keratitis	10
Conjunctivitis	18
Allergic conjunctivitis	5
Hyperaemia	6

*1 Each health hazard is counted if multiple events are included in a report. Health hazards reported in at least 5 cases are presented.

(2) Results of questionnaire survey conducted by the Japan Ophthalmologists Association

The Japan Ophthalmologists Association released the results of the questionnaire survey[5)] conducted among ophthalmology institutions concerning contact lens-related eye disorders. According to the survey, some patients who visited a medical institution due to contact lens-related eye disorders

had serious corneal ulcers and corneal infiltrates. In recent years, the number of cases of eye disorder associated with non-corrective, decorative/cosmetic contact lenses has been increasing. The major causes of eye disorders are improper use such as improper continuous wearing and insufficient cleaning. The survey also reported that there are a number of users who purchased the product without consultation of ophthalmologist, and those who received no periodic eye check-ups at all during use, especially among users who purchased contact lenses via mail-order or the Internet.

3. Reinforcement for provision of information upon selling contact lenses

To prevent contact lens-related eye disorders, it is important to use contact lenses properly in addition to ensuring the safety of products.

MHLW has been instructing MAHs of contact lenses to provide information about proper use to users and to disseminate and educate users about proper use. In response to the wide use of decorative contact lenses and diversified marketing channels including the Internet in recent years, MHLW issued a notification ("Required procedures upon Selling Contact Lenses," PFSB Notification No. 0718-16 of Pharmaceutical and Food Safety Bureau, MHLW) dated July 18, 2012 to request the relevant parties to ensure the following so that adequate information is provided to users upon purchasing contact lenses:

- Confirm consultation of ophthalmologist to the consumer, and record and retain the name of the medical institution.
- If the consumer has not consulted an ophthalmologist at the time of purchasing, inform him/her of the risk of health hazards associated with contact lenses, and recommend consultation with an ophthalmologist to the consumer.
- Provide the consumer with information necessary for proper use, including possible serious eye disorders caused by improper use of contact lenses.
- When receiving an inquiry from the user about eye disorders, provide information concerning the details of the health hazards, etc. as necessary to the medical institution the user visited before purchasing.
- The sales supervisor of the distributors should thoroughly provide recommendations on the operations of the sales office to the distributors, in order to avoid health hazards.

4. Requests to healthcare providers

(1) Dissemination and education of proper use of contact lenses

Procedures of usage and care of the contact lenses are performed by the users. To prevent eye disorders, dissemination and education of proper use should be continued while the contact lenses are in use, not only at the time of purchasing. Healthcare providers are requested to continue to instruct users thoroughly about the importance of proper use and the necessity of periodic eye check-ups, at the start of use and at regular examinations.

The relevant associations, such as the Japan Contact Lens Society and Japan Ophthalmologists Association, have set up the websites to provide information about proper use of contact lenses, and educational posters and leaflets are available for downloading. Please utilize the information and materials.

PMDA has posted a Q&A page regarding contact lenses on its website for the public (http://www.info.pmda.go.jp/mdevicesqa/mdevicesqa.html [only available in Japanese language]), and a consultation service for medical devices is available (Phone No. 03-3506-9436, from 9:00 to 17:00, Monday through Friday [except for public holidays, year-end and New Year holidays]) for consultation about usage of contact lenses. Please utilize these services for providing information to contact lens users.

Website of the Japan Contact Lens Society
- Proper care of contact lenses
  http://www.clgakkai.jp/general/study.html
- Proper procedures for soft contact lens care
  http://www.clgakkai.jp/general/scl_care.html

Website of the Japan Ophthalmologists Association
- Let's use contact lenses properly and safely.
  http://www.gankaikai.or.jp/contact-lens/safety.html

Website of the Japan Contact Lens Association
- Checklist for proper use
  http://www.jcla.gr.jp/menu/index.asp?patten_cd=12&page_no=6
- Precautions for safe use
  http://www.jcla.gr.jp/menu/index.asp?patten_cd=12&page_no=11

Educational poster by the Japan Contact Lens Association
http://www.jcla.gr.jp/menu/index.asp?patten_cd=12&page_no=27

(2) Reports according to Drugs and Medical Devices Safety Information Reporting System

If healthcare providers consider that it is necessary to report a case of contact lens-related eye disorder to prevent the occurrence or spread of a health hazard, please report the case to the MHLW in accordance with the Drugs and Medical Devices Safety Information Reporting System. When reporting, please include as much information obtained from the user as possible so that the product can be identified, including the brand name, the MAH, and lot number of the contact lenses used, since such information is necessary to investigate and implement the safety measures.

When additional information is necessary to investigate the safety measures, the MAH of the reported product may conduct a detailed investigation at the medical institution, etc. In this case, healthcare providers are encouraged to cooperate for the investigation.

<References> (including provisionally translated titles)

1) Website of the Ministry of Health, Labour and Welfare. "Decorative Contact Lenses" http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/colorcontact/index.html (only available in Japanese language)
2) National Consumer Affairs Center of Japan. "Safety of decorative contact lenses - contact lenses not designed to correct vision" (published in February 2006) http://www.kokusen.go.jp/news/data/n-20060203_1.html (only available in Japanese language)
3) National Institute of Technology and Evaluation. "Results of survey of non-corrective colored contact lenses" (published in July 2008) http://www.nite.go.jp/jiko/press/prs080710.html (only available in Japanese language)
4) Drugs and Medical Devices Safety Information Reporting System http://www.info.pmda.go.jp/info/houkoku.html (only available in Japanese language)
5) "Report of questionnaire survey on contact lens-related eye disorders (FY 2011)." The Journal of the Japan Ophthalmologists Association 83:4 (2012) (only available in Japanese language)

2

Summary of Report on Adverse Reactions to the Influenza Vaccine in the 2011 Season

1. Introduction

This section describes the adverse reactions to the influenza vaccines reported from October 2011 through the end of March 2012.

Vaccination with trivalent influenza vaccine (including 2009 influenza [H1N1] and influenza A/H3N2 and B) was started in October 2011. Adverse reactions considered to meet the Adverse Reaction Reporting Criteria[1)] are to be directly reported to the MHLW regardless of causality. The reported adverse reactions were tabulated and evaluated by PMDA as appropriate, and deaths and serious cases were also evaluated with regard to causality based on opinions from experts.

These adverse reaction reports are investigated and reviewed on a regular basis at the joint meeting of the Subcommittee on Drug Safety, Committee on Drug Safety under Pharmaceutical Affairs and Food Sanitation Council and the Influenza Vaccine Adverse Reaction Review Committee to determine the necessity of safety measures. The results of the discussions are discribed below.

In addition, adverse reaction reports associated with the influenza vaccines, which had been collected from April 1, 2009 through March 31, 2012, were indentified and reviewed by PMDA to determine whether an alert including a package insert revision should be issued. Details of the safety measures are also presented.

2. Reports of adverse reactions to influenza vaccines (October 1, 2011 to March 31, 2012)

(1) Number of reported adverse reactions and reporting frequency

Table 1 shows the number of reported adverse reactions to the influenza vaccines and the reporting frequency calculated from the estimated number of vaccinated persons based on the amount of vaccines distributed to medical institutions.

Table 1 Number of reported adverse reactions and estimated number of vaccinated persons

	Adverse reactions reported by medical institutions			Adverse reactions reported by MAHs (Serious adverse reaction report)*	
Estimated number of vaccinated persons (number of vaccinations)	Number of reported adverse reactions (reporting frequency)	Number of reported serious cases (reporting frequency)	Number of reported deaths	Number of reported serious cases (reporting frequency)	Number of reported deaths
50,325,537 (as of March 31, 2012)	554 (0.0011%)	96 (0.00019%)	7 (0.000014%)	83 (0.00016%)	1 (0.000002%)

* The adverse reactions reported by MAHs were those cases determined to be serious in accordance with the Pharmaceutical Affairs Law Article 77-4-2 and may overlap some other cases of adverse reaction reports by the medical institutions.

(2) Outline of reported adverse reactions by sex, age group

The number of reported adverse reactions to the influenza vaccine is shown by sex and age group in Tables 2 and 3, respectively.

Table 2 Number of reports by sex

Sex	Number of adverse reactions reported by medical institutions	Number of adverse reactions reported by MAHs
Male	291	41
Female	261 (pregnant women 0)	39 (pregnant woman 1)
Unknown	2	3
Total	554	83

Table 3 Number of reports by age

Age	Number of adverse reactions reported by medical institutions			Number of adverse reactions reported by MAHs	
	Number of reported adverse reactions	Number of reported serious cases		Number of reported serious cases	
			Number of reported deaths		Number of reported deaths
0-9 years	263	37	0	28	0
10-19 years	33	4	0	11	0
20-29 years	39	6	0	5	0
30-39 years	38	4	0	10	0
40-49 years	42	5	0	6	0
50-59 years	20	3	0	2	0
60-69 years	35	10	1	3	0
70-79 years	46	11	1	6	1
≥80 years	35	15	5	8	0
Unknown	3	1	0	4	0
Total	554	96	7	83	1

(3) Specific topics of reported adverse reactions

Adverse reactions to the influenza vaccines reported for the 2011 season are presented by System Organ Class in the rightmost column of Table 4. No marked difference was noted in comparison with the reports for the 2010 season.

Nine cases of post-vaccination death were reported up to May 21, 2012. Experts assessed that all of these cases were likely caused by exacerbation or recurrence of underlying diseases, and that none of these deaths had a direct, clear causality to the vaccination.

A total of 60 cases of adverse reactions were identified as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis.[Note 1)] Among the 60 cases, according to the expert assessment, the possibility of Guillain-Barre syndrome for 1 case and acute disseminated encephalomyelitis for 8 cases could not be ruled out.

Note 1) Includes cases reported using the adverse reaction terms such as numbness, feeling of weakness, neuropathy, muscular weakness and difficult swallowing

A total of 51 cases of adverse reactions were reported as possible anaphylaxis.[Note 2)] Of these, 35 cases (including 23 serious cases) were assessed as anaphylaxis of Level 3 or higher of the Brighton Criteria.[2)] Cases of at least Level 3 of the Brighton Criteria were reported at a frequency of 0.3 out of 100,000 vaccinations.

Of the 51 cases reported as possible anaphylaxis, vaccines manufactured by the Chemo-Sero-Therapeutic Research Institute (hereinafter, "Kaketsuken") were used in 43 cases. The reporting frequency of the cases of at least Level 3 of the Brighton Criteria by lot was up to 1.4 per 100,000 vaccinations, which was higher than the frequency for the other companies' vaccines (up to 0.4 per 100,000 vaccinations). Investigations were performed to determine the cause. The results revealed no problems about the Kaketsuken's product based on the national assay and in-house tests performed by the MAH, and no specific problems were found for the manufacturing control or quality control at the production plant. On the other hand, phenoxyethanol (hereinafter, "PE"), a preservative contained only in the Kaketsuken's influenza vaccine, was examined for its influence on the occurrence of anaphylaxis. As a result, especially in the basophil activation test using blood from patients with anaphylaxis, expression level of CD203c increased in some cases after stimulation by an influenza vaccine containing PE, while no increase in the CD203c expression level was observed after stimulation by PE alone. Stimulation by Kaketsuken's influenza vaccine without PE and stimulation by the other companies' influenza vaccines containing thimerosal resulted in no difference in the CD203c expression level. Based on these results, the preservative of Kaketsuken's influenza vaccine has been, changed from PE to thimerosal for the 2012 season as a preliminary and precautionary measure.

With regard to anaphylaxis after influenza vaccination, caution should be exercised for the following points for all the vaccine products in the 2012 season:

(1) Vaccine recipients should be closely monitored for about 30 minutes after vaccination.
(2) If any symptom suggesting anaphylaxis is observed, appropriate measures should be taken.
(3) Vaccine recipients and their guardians should be instructed to consult a physician immediately if any abnormalities are observed after vaccination.

Note 2) Includes cases reported using the adverse reaction terms of anaphylaxis, anaphylactic reaction, anaphylactic shock and anaphylactoid reaction.

Table 4 Comparison of adverse reaction reports for the 2010 season and the 2011 season

	2010 season		2011 season	
	Trivalent influenza vaccine (seasonal bivalent and H1N1)		Trivalent influenza vaccine (seasonal bivalent and H1N1)	
System Organ Class of adverse reaction*	Adverse reactions reported by medical institutions	Adverse reactions reported by MAHs	Adverse reactions reported by medical institutions	Adverse reactions reported by MAHs
Blood and lymphatic system disorders	2	8	5	3
Cardiac disorders	3	3	1	1
Ear and labyrinth disorders	0	0	0	1
Eye disorders	1	3	1	2
Gastrointestinal disorders	5	2	5	2
General disorders and administration site conditions	48	31	32	28
Hepatobiliary disorders	5	6	2	3
Immune system disorders	21	5	17	13
Infections and infestations	11	6	7	5
Investigations	4	2	2	6
Metabolism and nutrition disorders	1	4	2	1
Musculoskeletal and connective tissue disorders	6	5	2	11
Nervous system disorders	51	35	31	32
Psychiatric disorders	1	1	0	0
Renal and urinary disorders	2	5	0	2
Respiratory, thoracic and mediastinal disorders	11	13	15	11
Skin and subcutaneous tissue disorders	16	23	21	15
Endocrine disorders	0	0	1	0
Pregnancy, puerperium and perinatal conditions	2	0	0	1
Vascular disorders	3	6	1	1
Injury, poisoning and procedural complications	0	0	1	0
Total	193	158	146	138

* Adverse reaction terms were coded in accordance with the MedDRA/J Ver. 15.0.

* Adverse reactions assessed by the reporting physician as serious were tabulated as adverse reactions reported by the medical institutions.

3. Discussion about safety measures

Adverse reactions to the influenza HA vaccines reported to the PMDA from April 1, 2011 through March 31, 2012 were identified and reviewed by PMDA to determine whether the Precautions section should be revised.

Based on the accumulated adverse reaction reports and the causality assessment, alerts against nephrotic syndrome and interstitial nephritis were considered to be necessary.

Because 3 cases of nephrotic syndrome for which a causality to the vaccines could not be ruled out have been reported in Japan during the most recent 3 fiscal years, MHLW considered it appropriate on the basis of experts' opinions to include nephrotic syndrome in the Precautions section. The MAHs were instructed to revise the Precautions section on July 10, 2012. As for interstitial nephritis, the causality could not be clearly assessed due to a limited number of cases serving as the basis.[3)] MHLW therefore considered that the Precautions section should not be revised at this time and that close attention should be continuously payed to further reports.

4. Safety measures hereafter

Medical institutions are requested to continue to exercise caution for the following points concerning anaphylaxis in the 2012 season:

(1) Vaccine recipients should be closely monitored for about 30 minutes after vaccination.
(2) If any symptom suggesting anaphylaxis is observed, appropriate measures should be taken.
(3) Vaccine recipients and their guardians should be instructed to consult a physician immediately if any abnormalities are observed after vaccination.

Besides anaphylaxis, please also promptly report any adverse reaction meeting Adverse Reaction Reporting Criteria.

MHLW/PMDA will continue to collect safety information including the adverse reaction reports and to investigate the necessity of safety measures. Healthcare professionals are requested to continue reporting adverse reactions.

<References> (including provisionally translated titles)

1) Ministry of Health, Labour and Welfare: Report on Adverse Reactions to the Influenza A (H1N1) Vaccines
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/inful_05.html
(only available in Japanese language)

2) Ministry of Health, Labour and Welfare: Reference materials 1-2 for the 2012 Subcommittee on Drug Safety of Committee on Drug Safety (the first meeting) and the Influenza Vaccine Adverse Reaction Review Committee (the first meeting) and the Vaccine Adverse Reaction Review Committee for Carcinoma of the Uterine Cervix (the first meeting)
http://www.mhlw.go.jp/stf/shingi/2r9852000002c06s-att/2r9852000002c0c4.pdf
(only available in Japanese language)

3) Pharmaceuticals and Medical Devices Agency: Summary of the investigation result for revision of Precautions section for influenza HA vaccines
http://www.info.pmda.go.jp/kaitei/file/20120710frepno3.pdf
(only available in Japanese language)

3

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated August 7, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Oxaliplatin

Brand Name (name of company)	ELPLAT I. V. INFUSION SOLUTION 50 mg, 100 mg (Yakult Honsha Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Incurable, unresectable, advanced/recurrent colorectal cancer Postoperative adjuvant chemotherapy for colon cancer

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored, and if symptoms including myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

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, 2009 to May 8, 2012)

- Rhabdomyolysis: 1 case (1 fatal case)

The number of patients using this drug per year estimated by MAHs: approximately 35,000 (FY 2011)

Launched in Japan: June 2010 (ELPLAT I.V. INFUSION SOLUTION)
* April 2005 - March 2011 (ELPLAT FOR INJECTION)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Colon cancer (diabetes mellitus)	99 mg/m^2 3 times (Days 1, 22, 43)	**Rhabdomyolysis, dehydration** Day 1 of administration: The patient had colon cancer (recurrence after resection, with metastases to the peritoneum and para-aortic lymph nodes), performance status (PS) of 0, concomitant diabetes mellitus, and no history of intake of psychotropic drugs, etc. A XELOX regimen of oxaliplatin 99 mg/m^2 combined with capecitabine 3000 mg/day (everyday administration until Day 15) was given. Day 22 of administration: The XELOX regimen of oxaliplatin combined with capecitabine (everyday administration until Day 36) was given. Day 43 of administration: The XELOX regimen of oxaliplatin combined with

				capecitabine (everyday administration until Day 49) was given. Day 48 of administration: Diarrhoea (non-serious) and pyrexia (38°C range) occurred. Day 49 of administration: As pain occurred from both shoulders to the lower back, the patient visited this hospital. Diarrhoea remitted, but pyrexia (39°C range) and dehydration occurred, and then the patient was admitted to the hospital. Bolus transfusion (2500 mL/14 hours) was started. The patient had urination without a red-brown color (occurrence of rhabdomyolysis). Day 50 of administration: Snoring-like breathing and a decreased level of consciousness (Japan Coma Scale [JCS] 100) were noted from the morning. After administration of glucose, the patient's level of consciousness improved. Blood tests showed an abnormally high level of creatine kinase (creatine phosphokinase) (CK [CPK]) 15658 IU/L, urine myoglobin 73000 ng/mL, blood myoglobin 15000 ng/mL, and increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), and increased lactate dehydrogenase (LDH). A decrease in activation of the coagulation system was noted and the platelet count decreased to $2.2 \times 10^4/mm^3$. Consequently the patient was diagnosed with rhabdomyolysis. As systolic blood pressure decreased to the 60 - 80 mmHg range, administration of a vasopressor was started. The patient developed nearly anuria from the early afternoon, and did not respond to administration of furosemide. Systolic blood pressure decreased to the 60 mmHg range from the night despite administration of a vasopressor. Since a decreased level of consciousness was noted, intubation was performed, and the patient was put under mechanical ventilation. Day 51 of administration: As a state of hepatic/renal failure was noted, continuous hemodiafiltration (CHDF) was performed, but the patient died of rhabdomyolysis.
	Concomitant medications: capecitabine, dexamethasone sodium phosphate, granisetron hydrochloride, pyridoxal phosphate hydrate, heparinoid			

Laboratory Examination

	Day 1 of administration	Day 12 of administration	Day 22 of administration	Day 43 of administration	Day 49 of administration	Day 50 of administration	Day 51 of administration
Body temperature (°C)	-	-	-	-	39°C range	-	-
CRP (mg/dL)	0.04	0.16	0.05	0.07	4.90	21.57	18.56
Hemoglobin (g/dL)	13.6	13.3	13.4	12.7	14.4	14.1	11.8
RBC ($\times 10^4/mm^3$)	462	463	461	435	478	471	380
PLT ($\times 10^4/mm^3$)	24.8	19.5	16.8	15.3	5.9	2.2	1.9
WBC ($/mm^3$)	5640	4970	4790	3850	4990	10880	18070
Neutrophil count ($/mm^3$)	3340	-	-	1500	-	-	-
AST (GOT) (IU/L)	27	33	130	50	52	405	2094
ALT (GPT) (IU/L)	30	31	109	49	49	131	773
LDH (IU/L)	161	158	249	175	242	717	2764
Total bilirubin (mg/dL)	0.4	0.4	0.5	0.5	0.9	1.3	1.8
BUN (mg/dL)	14.7	15.4	12.5	11.6	23.6	34.0	42.0
Creatinine (mg/dL)	1.27	1.13	1.11	1.15	2.39	2.36	3.61
Na (mEq/L)	140	-	138	139	138	134	137

K (mEq/L)	4.4	-	4.3	4.2	4.2	5.1	7.7
Cl (mEq/L)	107	-	104	103	97	95	97
Albumin (g/dL)	4.3	4.2	4.5	4.1	3.8	3.2	2.0
CK (CPK) (IU/L)	104	-	77	73	267	15658	12258
PT (%)	>100	-	>100	-	64	41	-
APTT (sec)	24.0	-	23.4	-	-	-	-
Myoglobin (ng/mL)	-	-	-	-	-	15000	-
Urine myoglobin (ng/mL)	-	-	-	-	-	73000	-

4

Revision of Precautions (No. 239)

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 August 7, 2012 (excluding those presented in "3. Important Safety Information" of this Bulletin).

1 Skeletal muscle relaxants

Suxamethonium Chloride Hydrate

Brand Name	Suxamethonium Injection 20 "AS," 40 "AS," 100 "AS" (Astellas Pharma Inc.) RELAXIN Injection 200 mg (Kyorin Pharmaceutical Co., Ltd.)
Contraindications	Patients with a history of hypersensitivity to ingredients of this drug
Important Precautions	In patients who developed an anaphylactic reaction to a non-depolarizing muscle relaxant in the past, caution should be exercised since a similar anaplylatic reaction may occur.
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylactoid symptoms**: Shock or anaphylactoid symptoms (increased airway pressure, decreased blood pressure, tachycardia, generalised redness, etc.) 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.

2 Miscellaneous metabolism agents-Miscellaneous

Pamidronate Disodium Hydrate

Brand Name	Aredia for i.v. infusion 15 mg, 30 mg (Novartis Pharma K.K.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Acute renal failure, nephrotic syndrome (due to focal segmental glomerulosclerosis, etc.), interstitial nephritis**: Acute renal failure, nephrotic syndrome (due to focal segmental glomerulosclerosis, etc.), or interstitial nephritis may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. **Interstitial pneumonia**: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

3 Antiparkinsonian agents

Ropinirole Hydrochloride (extended release tablets)

Brand Name	ReQuip CR Tablets 2 mg, 8 mg (GlaxoSmithKline K.K.)
Important Precautions	This drug is designed to release the active ingredient and be dissolved over 24 hours. If the residence time of this drug in the digestive tract seems to have shortened due to previous intestinal resection, colostomy, diarrhoea, etc. or if a residue of this drug is confirmed in stool, the patients may not sufficiently respond to this drug.

4 Miscellaneous metabolism agents-Miscellaneous

Diazoxide

Brand Name	AROGLYCEM Capsules 25 mg (MSD K.K), DIAZOXIDE Capsules 25 mg "MSD" (MSD K.K)
Adverse Reactions (clinically significant adverse reactions)	**Decreased platelets**: Decreased platelets may occur. Patients should be carefully monitored through blood tests, etc. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

5 Miscellaneous metabolism agents-Miscellaneous

Zoledronic Acid Hydrate

Brand Name	ZOMETA for i.v. infusion 4 mg (Novartis Pharma K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Acute renal failure, interstitial nephritis**: Renal disorder such as acute renal failure and interstitial nephritis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. **Interstitial pneumonia**: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

6 Antimetabolites

Nelarabine

Brand Name	ARRANON G Injection 250 mg (GlaxoSmithKline K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Rhabdomyolysis**: Rhabdomyolysis may occur. Patients should be carefully monitored, and if symptoms such as myalgia, feeling of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin are observed, administration of this drug should be discontinued, and appropriate measures should be taken. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

7 Non-main therapeutic purpose agents-Miscellaneous

Varenicline Tartrate

Brand Name	CHAMPIX Tablets 0.5 mg, 1 mg (Pfizer Japan Inc.)

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

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 September 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Inactivated Poliomyelitis Vaccine (Salk Vaccine) IMOVAX POLIO subcutaneous	Sanofi Pasteur K.K.	August 31, 2012
Axitinib Inlyta Tablets 1 mg, 5 mg	Pfizer Japan Inc.	August 30, 2012
Ropinirole Hydrochloride ReQuip CR Tablets 2 mg, 8 mg	GlaxoSmithKline K.K.	August 28, 2012
Atomoxetine Hydrochloride Strattera Capsule 5 mg, 10 mg, 25 mg, 40 mg*1	Eli Lilly Japan K.K.	August 24, 2012
Sulbactam Sodium/Ampicillin Sodium UNASYN-S for Intravenous Use 0.75 g, 1.5 g, 3 g, UNASYN-S KIT for Intravenous Use 1.5 g, 3 g*2, 3	Pfizer Japan Inc.	August 10, 2012
Perflubutane SONAZOID FOR INJECTION 16 μL*4	Daiichi Sankyo Company, Limited	August 10, 2012
Sunitinib SUTENT Capsule 12.5 mg*5	Pfizer Japan Inc.	August 10, 2012
Apomorphine Hydrochloride Hydrate Apokyn subcutaneous injection 30 mg	Kyowa Hakko Kirin Co., Ltd.	July 27, 2012
Rotavirus Vaccine, Live, Oral, Pentavalent RotaTeq Oral Solution	MSD K.K.	July 20, 2012
Gabapentin Enacarbil Regnite Tablets 300 mg	Astellas Pharma. Inc.	July 10, 2012
Bixalomer Kiklin Capsules 250 mg	Astellas Pharma. Inc.	June 26, 2012
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg ZITHROMAC 250 mg*6	Pfizer Japan Inc.	June 22, 2012
Aprepitant EMEND Capsules 125 mg, 80 mg, EMEND Capsules Set*7	Ono Pharmaceutical Co., Ltd.	June 22, 2012
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg*8	AstraZeneca K.K.	June 22, 2012

Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg*[9]	Pfizer Japan Inc.	June 22, 2012
Lidocaine Penles Tape 18 mg*[10]	Nitto Denko Corporation	June 22, 2012
Dornase Alfa (Genetical Recombination) PULMOZYME Inhalation Solution 2.5 mg	Chugai Pharmaceutical Co., Ltd.	June 8, 2012
Rilpivirine Hydrochloride EDURANT Tablets 25 mg	Janssen Pharmaceutical K.K.	June 8, 2012
Miglustat BRAZAVES Capsule 100 mg	Actelion Pharmaceuticals Japan Ltd.	May 30, 2012
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg	Ferring Pharmaceutical Co., Ltd.	May 29, 2012
Mogamulizumab (Genetical Recombination) POTELIGEO Injection 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 29, 2012
Azilsartan AZILVA Tablets 20 mg, 40 mg	Takeda Pharmaceutical Company Limited	May 28, 2012
Oxycodone Hydrochloride Hydrate OXIFAST Injection 10 mg, 50 mg	Shionogi & Co., Ltd.	May 28, 2012
Thalidomide THALED CAPSULE 50, 100*[11]	Fujimoto Pharmaceutical Corporation	May 25, 2012
Doripenem Hydrate FINIBAX for Intravenous Infusion 0.25 g, 0.5 g, FINIBAX Kit for Intravenous Infusion 0.25 g*[12, 13]	Shionogi & Co., Ltd.	May 25, 2012
Thyrotropin Human Alfa (Genetical Recombination) THYROGEN for Intramuscular Injection 0.9 mg*[14]	Sato Pharmaceutical Co., Ltd.	May 25, 2012
Mometasone Furoate Hydrate NASONEX Nasal 50 μg 56 sprays, NASONEX Nasal 50 μg 112 sprays*[13]	MSD K.K.	May 25, 2012
Lidocaine/Propitocaine EMLA CREAM	Sato Pharmaceutical Co., Ltd.	May 14, 2012
Brimonidine Tartrate AIPHAGAN OPHTHALMIC SOLUTION 0.1%	Senju Pharmaceutical Co., Ltd.	May 11, 2012
Alendronate Sodium Hydrate Bonalon Bag for I.V. Infusion 900 μg	Teijin Pharma Limited	May 10, 2012
Caspofungin Acetate CANCIDAS for Intravenous Drip Infusion 50 mg, 70 mg	MSD K.K.	April 19, 2012
Eszopiclone Lunesta Tablets 1 mg, 2 mg, 3 mg	Eisai Co., Ltd.	April 18, 2012
Rivaroxaban Xarelto Tablets 10 mg, 15 mg	Bayer Yakuhin Ltd.	April 18, 2012
Atovaquone SAMTIREL Oral Suspension 15%	GlaxoSmithKline K.K.	April 17, 2012
Denosumab (Genetical Recombination) RANMARK SUBCUTANEOUS INJECTION 120 mg	Daiichi Sankyo Company, Limited	April 17, 2012
Crizotinib XALKORI Capsules 200 mg, 250 mg	Pfizer Japan Inc.	March 30, 2012

*1 An additional indication for “treatment of patients with attention deficit/hyperactivity disorder (AD/HD) in adulthood”

*2 An additional indication for “Streptococcus pneumonia, Moraxella (Branhamella) catarrhalis”

*3 An additional administration for “severe infections”

*4 An additional indication for “contrast enhanced imaging for breast mass lesion in mammary ultrasonography”

*5 An additional indication for “treatment of patients with pancreatic neuroendocrine tumour”

*6 An additional indication for “treatment of patients with pelvic inflammatory disease”

*7 An additional administration for “pediatrics (aged 12 and older)”

*8 An additional indication for “treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low-doses aspirin”

*9 An additional indication for “treatment of pain in patients with fibromyalgia”

*10 An additional indication for “relief of pain at removal of molluscum contagiosum”

*11 An additional indication for “erythema nodosum leprosum”

*12 An additional indication for “pyogenic meningitis”

*13 An additional administration for “pediatrics”

*14 An additional indication for “adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of metastatic thyroid cancer”