Pharmaceuticals and Medical Devices Safety Information

No. 292 July 2012

rev.1*

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers.
The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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

Pharmaceuticals and Medical Devices Safety Information
No. 292 July 2012

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Launch of a pilot program of "Direct Patient Reporting System for Adverse Drug Reactions"**		In March 2012, PMDA started a pilot program of "Direct Patient Reporting for Adverse Drug Reactions". This web-based system allows patients/consumers or their families to report suspected adverse drug reactions. We present an overview of the system and ask for your cooperation.	5
2	**Important Safety Information**	*P* *C*	**Ivermectin (and 2 others):** Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated June 5, 2012, the contents of important revisions and case summaries that served as the basis for these revisions will be provided in this section.	8
3	**Revision of Precautions (No. 237)**		Escitalopram Oxalate (and 6 others)	24
4	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of July 1, 2012.	27

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
Af	Atrial fibrillation
AFP	a-fetoprotein
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CHDF	Continuous hemodiafiltration
CK (CPK)	Creatine kinase (Creatine phosphokinase)
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
FDP	Fibrin/fibrinogen degradation product
FFP	Fresh frozen plasma
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBc	Hepatitis B core
HCV-RNA	Hepatitis C virus ribonucleic acid
HD	Hemodialysis
HDF	Hemodiafiltration
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IU	International unit
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
PIVK-II	Protein-induced by vitamin K absence or antagonists-II
PLT	Platelet
PT	Prothrombin Time
PT INR	Prothrombin time - international normalized ratio
RBC	Red blood cell count
TEN	Toxic epidermal necrolysis
VPC	Premature ventricular contraction
VT	Ventricular tachycardia
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

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Launch of the pilot program of “Direct Patient Reporting System for Adverse Drug Reactions”

*“Direct Patient Reporting System for Adverse Drug Reactions” are only available in Japanese language.

1. Introduction

In March 2012, PMDA launched the pilot program for Direct Patient Reporting System for Adverse Drug Reactions. This web-based system allows patients/consumers or their families to report suspected adverse drug reactions. The PMDSI No. 276 described the pilot study of the patient adverse drug reaction reporting system.

While healthcare professionals report suspected adverse drug reactions to MHLW directly or through marketing authorization holders (MAHs), this pilot system allows patients/consumers to directly report suspected adverse drug reactions to PMDA.

2. Direct Patient Reporting System for Adverse Drug Reactions

The Direct Patient Reporting System for Adverse Drug Reactions (the System) is a program to collect information from patients/consumers who experienced a suspected adverse drug reaction or their families. Collected information will be used to promote drug safety measures, for example, to understand the trends for occurrences of adverse drug reactions.

Adverse drug reactions reports are received through the System on Medical Product Information website (http://www.info.pmda.go.jp/fukusayou_houkoku/fukusayou_houkoku_attention.html) (only available in Japanese language).

To access this site, search for “患者副作用報告” (patient adverse drug reaction reporting) on an internet search engine or access the Medical Product Information website (http://www.info.pmda.go.jp/index.html) and select “一般の皆様向け” (To the Public) – “患者副作用報告” (Direct Patient Reporting System for Adverse Drug Reactions) (see the figure in page 6 for the location).

Information that you should report through the System include: (1) the reporter; (2) the patient who experienced the adverse drug reaction; (3) the adverse drug reaction; (4) the medicine(s) which might have caused the adverse drug reaction; and (5) the medical institution, etc. where PMDA can ask for adverse drug reaction information.

PMDA may investigate the reported adverse drug reaction for further details. In this case, PMDA may ask for the cooperation of a relevant medical institution, etc. as needed after, in principle, obtaining approval from the patient who experienced the adverse drug reaction.

In addition, PMDA may provide reported information, excluding personal data, to MHLW and the MAHs of the concerned drug or may release the information to the public as part of its safety measures. The privacy of the reporter, the patient, and the relevant medical institution, etc. will be fully respected.

3. Reported cases

A total of 90 reports were received from the launch of the System to the end of May 2012: 71 reports from patients/consumers and 19 reports from their families.

These reports include a total of 119 suspected drugs (116 ethical drugs and 3 over-the-counter drugs) and a total of 101 suspected adverse drug reactions. Out of these, reports of 71 (70%) reactions indicated that patients/consumers consulted medical institutions.

In addition, 66% of the cases occurred in or after 2011. Many reports were submitted relatively soon after the occurrence of adverse drug reactions.

4. Conclusion

The Direct Patient Reporting System for Adverse Drug Reactions is now operated as a pilot program but will be officially launched after reviewing the reporting system, improving it as necessary and developing the method of operation, etc. based on the reports collected during the pilot period and the results of a questionnaire survey conducted among reporters.

It is expected that many reports submitted through the System will elucidate the issues of the System and technical problems, leading to a better system development and more effective use of the System. We hope many people become aware of the System and make use of it.

Healthcare professionals are continuously encouraged to report any suspected adverse drug reactions found while they are on duty through the Drugs and Medical Devices Safety Information Reporting System (http://www.info.pmda.go.jp/info/houkoku.html) (only available in Japanese language).

<References> (including provisionally translated titles)

1) "Review on the Pharmaceutical Administration to Prevent Recurrence of Yakugai (Drug-induced suffering) (final proposal)" Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Recurrence of Yakugai Similar Sufferings, April 28, 2010
http://www.mhlw.go.jp/shingi/2010/04/s0428-8.html (only available in Japanese language)
2) "Summary on System Reform of Pharmaceutical Affairs Law, etc." Subcommittee of Pharmaceutical System Reform of the Health Sciences Council, Ministry of Health, Labour and Welfare, January 24, 2012
http://www.mhlw.go.jp/stf/shingi/2r98520000020uxm.html (only available in Japanese language)

2
Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated June 5, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Ivermectin

Brand Name (name of company)	STROMECTOL Tablets 3 mg (MSD K.K.)
Therapeutic Category	Anthelmintics
Indications	1. Strongyloidiasis of the intestinal tract 2. Scabies

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Decreased platelets: Decreased platelets 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.

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 March 31, 2012)

- Decreased platelets: 1 case (no fatal cases)

The number of patients using this drug estimated by MAHs: approximately 230,000 (April 15, 2011 to April 14, 2012)

Launched in Japan: December 2002

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Acarodermatitis (interstitial lung disease, cholelithiasis, gallbladder polyp)	12 mg Once	**Decreased platelets** 5 days before administration: Platelet count was $7.08 \times 10^4/\mu L$. Day of administration (day of completion): The patient received a single dose of ivermectin 12 mg for the treatment of scabies (acarodermatitis). 1 day after completion: The patient had pyrexia of 37.6°C. 6 days after completion (day of onset): The patient developed decreased platelets. Platelet count decreased to $0.744 \times 10^4/\mu L$, $0.676 \times 10^4/\mu L$. 10 units of platelets were transfused. 1 day after onset: 20 units of platelets were transfused. Transfusion was repeated, but the count did not increase. Methylprednisolone sodium succinate 1 g × 1 was administered (for 2 days). 2 days after onset:

				D-dimer and fibrin/fibrinogen degradation product (FDP) were not noted in the qualitative test. Anti-platelet antibody was negative. Mild splenomegaly was noted with no haemorrhagic symptoms during the clinical course. Platelet count was 5.50 × 10^4/μL. 6 days after onset: Following decreased platelets, the pathological condition of interstitial pneumonia (interstitial lung disease) became aggravated, and then she entered a state of respiratory failure, and a mechanical ventilator was attached. Endotracheal intubation was performed. Platelet count was 10.4 × 10^4/μL. 20 days after onset: The patient died. The causes of death were decreased platelets and aggravation of interstitial pneumonia (respiratory failure).
	Concomitant medications: sodium valproate, thiamazole, lamotrigine, magnesium oxide			

Laboratory Examination

	5 days before administration	6 days after completion (day of onset)		2 days after onset	6 days after onset
PLT (×10^4/μL)	7.08	0.744	0.676	5.50	10.4
RBC (×10^4/μL)	296	327		272	367
Hemoglobin (g/dL)	8.87	9.80		8.22	11.3
Hematocrit (%)	27.6	31.7		25.7	35.5
WBC (/μL)	4660	4820		4000	16800
Neutrophils (%)	46.1	22.0		43.4	75.7
Eosinophils (%)	5.53	2.12		0.251	0.147
Basophils (%)	0.815	1.49		0.450	1.81
Lymphocytes (%)	32.7	46.8		46.5	9.88
Monocytes (%)	14.9	27.7		9.36	12.5

2 Telaprevir

Brand Name (name of company)	TELAVIC Tablets 250 mg (Mitsubishi Tanabe Pharma Corporation)
Therapeutic Category	Antivirals
Indications	Improvement of the following viremia in patients with chronic hepatitis C serogroup 1 (genotype I [1a] or II [1b]): (1) Untreated patients with high blood HCV RNA load (2) Patients who did not respond to or relapsed after interferon monotherapy or combination therapy with ribavirin

PRECAUTIONS (underlined parts are revised)

Careful Administration

Patients with renal impairment

Important Precautions

Tests for hemoglobin level, white blood cell count, neutrophil count, and platelet count should be performed before administration, as well as at least every week in the first 12 weeks of administration and once every subsequent 4 weeks.

Most cases of serious renal impairment, including acute renal failure and serious hepatic dysfunction, occur within 1 week after administration. Biochemical tests

including functional tests (creatinine, urea nitrogen, uric acid, etc.), liver function test, electrolyte test, etc. should be performed at least twice in the first week of administration, and additionally, once after 2 weeks and 4 weeks of administration, and then once every subsequent 4 weeks. In addition, a thyroid function test should be performed once every 12 weeks.

Adverse Reactions (clinically significant adverse reactions)

Acute renal failure: Serious renal impairment including acute renal failure may occur. Renal function tests should be performed periodically, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Serious hepatic dysfunction: Serious hepatic dysfunction may occur. Patients should be carefully monitored through periodic liver function tests and if jaundice or hepatic dysfunction with significant elevation of transaminase levels is observed, appropriate measures such as discontinuing administration should be taken.

Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored for feelings of weakness, myalgia, increased CK (CPK), etc., and if such symptoms are observed, appropriate measures such as discontinuing administration 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 5 months (acute renal failure-associated cases: from initial marketing to May 8, 2012; serious hepatic dysfunction-associated cases and rhabdomyolysis-associated cases: from initial marketing to April 20, 2012)

- Acute renal failure-associated cases: 16 cases (no fatal cases)
- Serious hepatic dysfunction-associated cases: 4 cases (1 fatal case)
- Rhabdomyolysis-associated cases: 1 case (no fatal cases)

The number of patients using this drug estimated by MAH: approximately 4,205 (from date of initial marketing to May 2012)
Launched in Japan: November 2011

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Viraemia in chronic hepatitis C (nephrolithiasis, cholelithiasis, otitis media, autoimmune thyroiditis, asthma, chronic pancreatitis)	2,250 mg for 5 days	**Malaise, pyrexia, rash, vomiting, increased blood creatinine, increased C-reactive protein, increased blood urea** The patient was previously treated with interferon + ribavirin. Day 1 of administration: The patient started receiving telaprevir (2,250 mg/day), ribavirin (400 mg/day), and peginterferon alfa-2b (genetical recombination) (1.5 μg/kg). Laboratory examination: hemoglobin (Hb) 12.7 g/dL, blood creatinine level 0.97 mg/dL, uric acid level 8.6 mg/dL, blood urea nitrogen (BUN) 20 mg/dL. Day 2 of administration: The patient had pyrexia of around 37°C and malaise. Day 3 of administration: A rash developed. [Severity] Grade 1: 50% or less of body surface area (localized) [Pruritus] None The patient had vomiting, slight fever, malaise, and stomach discomfort. Oral administration of metoclopramide tablets 5 mg (5 mg/day as needed, until 2 days after discontinuation) was prescribed. Day 4 of administration: Vomiting occurred. Day 5 of administration (day of discontinuation): C-reactive protein (CRP) level and BUN level increased.

				Blood creatinine level increased to 5.7 mg/dL. Acute renal disorder due to telaprevir was suspected. BUN 77 mg/dL. CRP 5.79 mg/dL. Administration of peginterferon alfa-2b (genetical recombination), ribavirin, and telaprevir was discontinued. A medical examination was requested from a nephrologist. Right renal atrophy was found before, which did not require treatment. Administration of valsartan was temporarily discontinued. The dose of allopurinol was reduced from 300 mg to 100 mg. Famotidine orally disintegrating tablets were switched to lansoprazole orally disintegrating tablets. Administration of magnesium oxide preparation was temporarily discontinued. Olopatadine hydrochloride was prescribed. The clinical course was monitored with fluid replacement, measurement of urine output, etc. Glucose-electrolyte infusion 500 mL (500 mL/day, until 1 day after discontinuation) and lactated Ringer's solution 500 mL (500 mL/day) were intravenously administered. Many small erythrogenic rashes developed mainly on the thighs, legs, upper limbs, back, etc. No pain/pruritus developed. Vomiting occurred. 1 day after discontinuation: No aggravation of skin eruption was noted. Vomiting occurred. The patients had pyrexia of 37.3°C. Creatinine level and BUN increased to 5.38 mg/dL and 80 mg/dL, respectively. Olopatadine hydrochloride tablets 5 mg (10 mg/day) and olopatadine hydrochloride OD tablets 5 mg (5 mg/day, until 7 days after discontinuation) were orally administered. Physiological saline 500 mL (500 mL/day, until 4 days after discontinuation) and VITAMEDIN FOR INTRAVENOUS INJECTION (1 vial/day, until 4 days after discontinuation) were intravenously administered. 2 days after discontinuation: Urine output increased. Malaise and anorexia developed. In the morning, pyrexia of the 38°C level decreased to 36.6°C The patient recovered from vomiting. Sulbactam sodium/cefoperazone sodium for intravenous injection 1 g (1 g/day, until 7 days after discontinuation) was intravenously administered. 4 days after discontinuation: The patient recovered from pyrexia. 7 days after discontinuation: The patient recovered from the rashes and malaise. 8 days after discontinuation: Olopatadine hydrochloride OD tablets 5 mg (10 mg/day) were orally administered. 10 days after discontinuation: Both the data and general condition improved. Increased creatinine level and increased BUN level remitted. Increased CRP level resolved.
	Concomitant medications: famotidine, levothyroxine sodium hydrate, valsartan, combination drug containing clostridium butyricum, sodium ferrous citrate, camostat mesilate, zolpidem tartrate, rebamipide, dextromethorphan hydrobromide hydrate, mecobalamin, kallidinogenase, theophylline, magnesium oxide, ribavirin (suspected concomitant drug), peginterferon alfa-2b (genetical recombination) (suspected concomitant drug), allopurinol			

Laboratory Examination

	Day 1 of administra-tion	Day 5 of administration (day of discontinuation)	1 day after discontinua-tion	2 days after discontinua-tion	4 days after discontinua-tion	7 days after discontinua-tion	10 days after discontinua-tion
Serum creatinine (mg/dL)	0.97	5.70	5.38	3.19	1.71	1.23	1.22
BUN(mg/dL)	20	77	80	51	20	14	13
Uric acid (mg/dL)	8.6	9.5	9.9	9.0	5.8	6.2	6.0

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Viraemia in chronic hepatitis C (hypertension)	2,250 mg for 5 days ↓ 1,500 mg Continued	**Increased blood creatinine, increased blood urea, increased blood uric acid, rash** The patient was previously treated with interferon + ribavirin. 1 day before administration: Laboratory examination: Hb14 g/dL. Day 1 of administration: The patient started receiving telaprevir (2,250 mg/day), and peginterferon alfa-2b (genetical recombination) (1.5 μg/kg/week). The patient developed pyrexia. Loxoprofen (60 mg/day as needed) was orally administered. Day 3 of administration (day of onset): Serum creatinine, BUN, and uric acid increased. A blood test was performed. BUN and uric acid level increased to 28.1 mg/dL and 8.5 mg/dL, respectively. Pyrexia remitted. Day 4 of administration: Rashes appeared on both upper limbs. [Severity] Grade 2: 50% or less of body surface area (multiple/diffuse) [Pruritus] Present Levocetirizine hydrochloride (5 mg/day) was orally administered. Day 5 of administration: Pruritus was noted. Combination cream containing crotamiton/hydrocortisone (appropriate dose) was applied. Day 6 of administration: Blood test was performed. As the test values further increased (serum creatinine 2.04 mg/dL, BUN 41.6 mg/dL, uric acid 12.9 mg/dL), the dose of telaprevir was reduced from 2,250 mg/day to 1,500 mg/day, and 500 mL of fluid replacement was performed. Rashes spread to both upper limbs, groin, abdomen, and back. Levocetirizine hydrochloride was switched to oral olopatadine hydrochloride (10 mg/day). Mosapride citrate (15 mg/day) was orally administered. Transfusion (500 mL/day, until Day 14 of administration) was intravenously administered. Day 7 of administration: Serum creatinine, BUN, and uric acid levels decreased. Day 8 of administration: Serum creatinine, BUN, and uric acid levels further decreased. Day 9 of administration: No change was seen in the rashes. Day 36 of administration: The patient recovered from the rashes.
	Concomitant medications: telmisartan, ribavirin, peginterferon alfa-2b (genetical recombination) (suspected concomitant drug), sodium rabeprazole			

Laboratory Examination

	1 day before administra-tion	Day 3 of administration (day of onset)	Day 6 of administra tion	Day 7 of administra tion	Day 8 of administra tion	Day 15 of administra tion	Day 22 of administra tion	Day 29 of administra tion	Day 36 of administra tion
Serum creatinine (mg/dL)	1.16	1.71	2.04	1.71	1.51	1.67	1.55	1.55	1.37
BUN (mg/dL)	18.1	28.1	41.6	38.4	29.5	-	-	-	17.2
Uric acid (mg/dL)	5.2	8.5	12.9	11.2	9.0	10.1	9.9	7.7	7.5

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 60s	Viraemia in chronic hepatitis C (diabetes mellitus, constipation, liver carcinoma)	2,250 mg for 6 days	**Hepatic disorder** The patient developed diabetes mellitus 13 years ago. Nephropathy and retinopathy were not noted. Liver biopsy showed F2-3 and A2-3 (8 years ago). Liver carcinoma developed 7 years ago (disease stage I) and was treated with radiofrequency. Liver carcinoma relapsed 4 years ago (disease stage I) and was treated with radiofrequency. Child-Pugh score was A before treatment. The patient had been drinking alcohol. The patient was previously treated with ribavirin + peginterferon alfa-2b (genetical recombination). 1 day before administration: Laboratory examination: Hb 11.9 g/dL, platelet count 98000/mm^3, aspartate aminotransferase (AST) 32 IU/L, alanine aminotransferase (ALT) 15 IU/L, total bilirubin 0.82 mg/dL, albumin 3.3 g/dL, ammonia 79 μg/dL, prothrombin time (PT) 11.4 seconds, PT activity 81.3%, blood sugar level 412 mg/dL, Hemoglobin A1c (HbA1C) 8.4%. Day 1 of administration: The patient started receiving telaprevir 2,250 mg/day, ribavirin 800 mg/day, and peginterferon alfa-2b (genetical recombination) 1.5 μg/kg/week. Day 3 of administration: The patient ate about 80% of ordinary meals. Day 5 of administration: The patient developed anorexia and became unable to eat meals. AST 45 IU/L, ALT 22 IU/L, ammonia 139 μg/dL. Day 6 of administration (day of completion): His state of consciousness became slightly restless on this day. His blood sugar level increased to 600 mg/dL or higher. Three-drug combination therapy was discontinued. 1 day after completion (day of onset): The patient began to look sick. Periodic examinations were performed. Coma scale in hepatic encephalopathy was II - III. (II until around the day before death) AST and ALT rapidly increased to 1,602 IU/L and 635 IU/L, respectively. Ammonia 125 μg/dL and platelet count 80000/mm^3. The patient underwent re-examination at night: AST 7,350 IU/L, ALT 2,490 IU/L, total bilirubin 3.59 mg/dL, direct bilirubin 1.96 mg/dL. PT decreased to 59.9%. Emergency computed tomography (CT) was performed. A map sign (geographic hyperechoic area) appeared in the posterior segment of the right liver. Morihepamin was administered. BUN, creatinine, and uric acid increased to 75.0 mg/dL, 2.21 mg/dL, and 13.1mg/dL,

				respectively. Emergency dialysis was performed. 2 days after completion: AST 6,477 IU/L, ALT 2,040 IU/L, total bilirubin 4.81 mg/dL, direct bilirubin 2.49 mg/dL. Plasma exchange using dialysis + fresh frozen plasma (FFP) 40 U was started. 3 days after completion: AST 5,430 IU/L, ALT1, 670 IU/L, total bilirubin 6.15 mg/dL, direct bilirubin 3.64 mg/dL. Plasma exchange using dialysis + fresh frozen plasma (FFP) 40 U was continued. Plasma exchange was continuously performed, but the coagulation system did not improve and hepatocellular necrosis spread. Treatment was performed with transfusion, methylprednisolone sodium succinate for injection 500 × 2 V, and 50 mL of Kenketsu albumin 25% × 2 V. 4 days after completion: AST 2,850 IU/L, ALT 995 IU/L, total bilirubin 6.39 mg/dL, direct bilirubin 3.81mg/dL. PT level further worsened to 34.8%. Hemodynamics could not be maintained with fresh frozen plasma (FFP) 40 U alone, and dialysis could not be performed. 5 days after completion: The patient died. Macroscopic pathology: Hemorrhagic necrosis was in the posterior segment of the right liver. Formal findings of autopsy will be obtained 3 months later. The result of drug lymphocyte stimulation test (DLST) was negative.
	Concomitant medications: ursodeoxycholic acid, polaprezinc orally disintegrating tablets, magnesium oxide preparation, portolac, lactitol hydrate preparation, pioglitazone hydrochloride, glimepiride, ribavirin, peginterferon alfa-2b (genetical recombination), esomeprazole magnesium hydrate, bepotastine besilate orally disintegrating tablets			

Laboratory Examination

	1820 days before administration (approx. 5 years ago)	1453 days before administration (approx. 4 years ago)	1145 days before administration (approx. 3 years and 2 months ago)	1093 days before administration (approx. 3 years ago)	718 days before administration (approx. 2 years ago)	694 days before administration (approx. 1 year and 11 months ago)	442 days before administration (approx. 1 year and 3 months ago)	400 days before administration (approx. 1 year and 1 month ago)	365 days before administration (approx. 1 year ago)	337 days before administration (approx. 11 months ago)	85 days before administration (approx. 3 months ago)
RBC (10^4/mm^3)	423	331	-	275	403	425	285	295	346	305	-
HB (g/dL)	14.0	10.8	-	9.1	13.2	13.9	9.9	10.2	11.7	10.3	-
Hematocrit (%)	40.8	33.0	-	28.2	38.8	41.2	31.0	31.6	35.2	31.1	-
PLT (10^4/mm^3)	3.9	3.1	-	5.8	6.0	8.7	6.5	4.7	9.8	5.0	-
WBC (/mm^3)	2,200	1,400	-	1,100	4,100	3,200	1,200	1,200	2,100	1,000	-
Neutrophils (%)	44.4	64.5	-	55.2	81.7	68.0	62.2	64.5	64.5	47.9	-
Eosinophils (%)	1.9	0.0	-	4.8	0.7	1.3	1.6	1.6	2.9	2.1	-
Basophils (%)	0.5	0.0	-	0.0	0.0	0.6	0.0	0.8	0.5	1.0	-
Monocytes (%)	8.8	7.1	-	7.6	5.9	6.0	5.6	8.9	7.2	14.6	-
Lymphocytes (%)	44.4	28.4	-	32.4	11.7	24.1	30.6	24.2	24.9	34.4	-
Total protein (g/dL)	6.0	7.2	-	6.8	6.2	7.3	6.5	6.0	7.0	6.6	-
Albumin (g/dL)	3.0	3.5	-	3.5	3.3	3.5	3.2	3.2	3.7	3.3	-
Total bilirubin (mg/dL)	1.01	0.48	-	0.72	1.16	0.62	1.16	0.99	0.59	1.02	-

Direct bilirubin (mg/dL)	-	-	-	-	-	-	-	-	-	-	-
AST (GOT) (IU/L)	57	25	-	33	75	34	74	62	45	56	-
ALT (GPT) (IU/L)	54	19	-	23	71	17	48	45	29	34	-
ALP (IU/L)	632	371	-	491	406	673	549	814	514	688	-
LDH (IU/L)	145	183	-	229	227	187	279	275	198	253	-
γ-GTP (IU/L)	149	-	-	38	135	98	165	282	148	139	-
Cholinesterase (IU/L)	122	157	-	201	163	175	153	132	133	160	-
CK (CPK) (IU/L)	38	30	-	32	66	48	38	27	32	44	-
Amylase (IU/L)	100	-	-	128	103	117	106	121	115	115	-
Total cholesterol (mg/dL)	-	-	-	113	-	133	107	107	106	115	-
Glomerular filtration rate (mL/min)	-	-	-	-	91.97	76.80	113.61	94.64	101.45	101.45	-
BUN (mg/dL)	13.8	15.7	-	14.6	17.9	16.0	16.2	15.6	13.9	13.6	-
Serum creatinine (mg/dL)	0.62	0.84	-	0.67	0.67	0.79	0.55	0.65	0.61	0.61	-
Uric acid (mg/dL)	-	4.8	-	5.5	3.3	4.9	4.6	4.3	4.3	4.3	-
Ammonium nitrogen (μg/dL)	-	-	-	-	84	-	27	31	57	32	-
Na (mEq/L)	135	140	-	140	132	141	141	135	136	137	-
K (mEq/L)	3.85	4.17	-	4.67	4.32	4.60	4.90	4.72	4.57	5.10	-
Cl (mEq/L)	102	106	-	108	100	101	106	101	101	103	-
Ca (mg/dL)	-	-	-	8.3	8.2	8.9	8.6	8.9	8.7	8.7	-
P (mg/dL)	-	-	-	3.0	2.1	3.2	2.7	3.3	3.1	2.6	-
CRP (mg/dL)	<0.28	-	-	<0.02	0.49	0.12	<0.02	0.03	0.07	<0.02	-
Casual blood glucose (mg/dL)	182	263	243	-	-	324	-	332	-	366	468
Hemoglobin HbA1C (%)	8.2	5.4	6.6	-	-	7.0	-	5.9	-	6.5	8.1
PT-INR	1.33	1.36	-	-	-	-	-	-	-	-	-
IgG (mg/dL)	-	-	-	1,138.0	-	1,370.0	1,293.0	1,260.0	1,254.0	1,419.0	-
IgA (mg/dL)	-	-	-	324.0	-	530.0	412.0	405.0	471.0	428.0	-
IgM (mg/dL)	-	-	-	62.0	-	81.0	59.0	76.0	85.0	88.0	-
Hyaluronic acid (ng/mL)	-	-	-	-	-	-	-	-	-	-	-
AFP (ng/mL)	34.5	14.8	-	10.7	-	8.3	9.4	10.4	10.7	9.0	-
HBc antibody	-	-	-	-	-	-	-	-	-	-	-
PIVKA-II (mAU/ml)	-	-	-	42	-	25	158	162	27	19	-

Laboratory Examination

	71 days before administration	29 days before administration	1 day before administration	Day 5 of administration	Day 6 of administration	1 day after completion (day of onset)		2 days after completion	3 days after completion	4 days after completion
						(periodic)	(night)			
RBC (10^4/mm^3)	410	432	421	396	-	391	401	360	335	341
HB (g/dL)	11.8	12.3	11.9	11.3	-	11.2	11.5	10.3	9.4	9.7
Hematocrit (%)	36.1	37.3	36.0	32.6	-	32.3	33.3	31.2	29.0	29.9
PLT (10^4/mm^3)	7.6	8.4	9.8	8.2	-	8.0	7.4	7.9	6.3	5.5
WBC (/mm^3)	1,900	2,400	2,600	4,200	-	6,100	7,300	12,300	13,900	10,500
Neutrophils (%)	55.7	62.0	56.1	71.7	-	77.2	78.2	89.1	86.7	87.2
Eosinophils (%)	1.6	2.9	5.1	0.0	-	0.0	0.0	0.0	0.0	0.0
Basophils (%)	0.5	0.4	0.8	0.0	-	0.0	0.0	0.0	0.1	0.0
Monocytes (%)	8.0	8.8	8.6	11.8	-	13.0	14.4	6.1	9.2	7.2
Lymphocytes (%)	34.2	25.9	29.4	16.5	-	9.8	7.4	4.8	4.0	5.6
Total protein (g/dL)	6.6	6.9	6.8	7.3	-	7.1	-	7.4	5.3	5.5
Albumin (g/dL)	3.3	3.4	3.3	3.6	-	3.4	-	3.6	2.8	3.2
Total bilirubin (mg/dL)	0.75	0.87	0.82	1.04	-	2.51	3.59	4.81	6.15	6.39
Direct bilirubin (mg/dL)	0.33	0.39	-	-	-	1.39	1.96	2.49	3.64	3.81

AST (GOT) (IU/L)	35	31	32	45	-	1,602	7,350	6,477	5,430	2,850
ALT (GPT) (IU/L)	18	16	15	22	-	635	2,490	2,040	1,670	995
ALP (IU/L)	459	716	509	451	-	788	1,967	2,041	1,076	708
LDH (IU/L)	201	197	200	258	-	1,674	7,740	7,769	5,430	3,100
γ-GTP (IU/L)	62	62	60	58	-	66	73	82	77	90
Cholinesterase (IU/L)	166	179	182	-	-	180	-	231	203	-
CK (CPK) (IU/L)	60	50	68	210	-	340	393	500	2,209	3,267
Amylase (IU/L)	123	113	122	70	-	58	56	55	488	495
Total cholesterol (mg/dL)	126	145	147	-	-	-	-	-	-	-
Glomerular filtration rate (mL/min)	104.74	88.25	92.65	29.48	-	26.39	24.70	37.20	20.25	17.81
BUN (mg/dL)	12.9	17.2	15.9	53.2	-	63.9	75.0	36.3	30.3	22.0
Serum creatinine (mg/dL)	0.59	0.69	0.66	1.88	-	2.08	2.21	1.52	2.65	2.98
Uric acid (mg/dL)	3.6	4.3	4.0	9.9	-	12.0	13.1	8.5	8.2	6.3
Ammonium nitrogen (μg/dL)	51	71	79	139	-	125	107	87	62	95
Na (mEq/L)	137	137	134	129	-	127	125	133	133	136
K (mEq/L)	4.70	4.75	4.56	5.30	-	6.41	6.50	4.84	5.00	4.83
Cl (mEq/L)	104	102	100	95	-	92	94	90	93	92
Ca (mg/dL)	8.5	9.0	8.9	8.5	-	8.5	7.8	8.7	7.3	8.2
P (mg/dL)	2.9	3.1	3.1	4.1	-	5.3	5.5	5.9	4.5	5.8
CRP (mg/dL)	<0.02	0.02	0.02	0.73	-	0.85	1.46	2.59	1.71	1.22
Casual blood glucose (mg/dL)	-	-	412	-	>600	-	-	-	-	-
Hemoglobin HbA1C (%)	-	-	8.4	-	-	-	-	-	-	-
PT-INR	-	-	1.10	-	-	-	1.27	1.26	1.71	1.65
IgG (mg/dL)	1,535.0	1,441.0	1,448.0	-	-	-	-	-	-	-
IgA (mg/dL)	578.0	590.0	576.0	-	-	-	-	-	-	-
IgM (mg/dL)	96.0	90.0	85.0	-	-	-	-	-	-	-
Hyaluronic acid (ng/mL)	-	-	202	-	-	-	-	-	-	-
AFP (ng/mL)	6.4	7.3	7.2	-	-	-	-	-	-	-
HBc antibody	-	-	(+)	-	-	-	-	-	-	-
PIVKA-II (mAU/ml)	15	21	21	-	-	-	-	-	-	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Female 50s	Viraemia in chronic hepatitis C (hypertension)	2,250 mg for 11 days	**Pyrexia, nausea, vomiting, toxic skin eruption, abdominal pain, hepatic disorder** The patient was not previously treated with peginterferon alfa-2b (genetical recombination) and ribavirin. Day 1 of administration: The patient started receiving telaprevir (2,250 mg/day), ribavirin (800 mg/day), peginterferon alfa-2b (genetical recombination) (1.5 μg/kg/week). Laboratory examination: Hb 15.4 g/dL, platelet count 243000/mm^3, AST 53 IU/L, ALT 66 IU/L, creatinine 0.74 mg/dL. Day 2 of administration: The patient had pyrexia of 38°C. CMCP (Cipher prescription chlordiazepoxide + loxoprofen sodium hydrate + methocarbamol, 1 g per time/day as needed) was used for the condition. Day 3 of administration:

				Queasy and vomiting occurred. Abdominal pain developed. Mosapride citrate (15 mg/day), sodium rabeprazole (20 mg/day), and domperidone (30 mg/day) were orally administered, but no improvement was achieved. Redness and a rash appeared on the left knee. Toxicoderma occurred. [Severity] Grade 1: 50% or less of body surface area (localised) [Pruritus] Present Topical administration of bepotastine besilate (20 mg/day), combination cream containing crotamiton/hydrocortisone (appropriate dose, until Day 9 of administration) was started. Day 4 of administration: Drip infusion of metoclopramide 500 mL was performed for 4 days. The condition remitted, and the regimen was changed to oral administration alone. Day 8 of administration (day of onset): After the second dose of peginterferon alfa-2b (genetical recombination) for injection, the patient still was feeling queasy and was vomiting. Domperidone suppository (60 mg) was used as needed at appropriate timings. Hepatic disorder (aggravated) was observed. Day 9 of administration: Rashes spread to both lower limbs and left buttock. Topical betamethasone butyrate propionate ointment (appropriate dose/day) was applied externally, and then the condition improved gradually. Day 11 of administration (day of discontinuation): Re-examination of hepatic function was performed. AST and ALT increased to 585 IU/L and 379 IU/L, respectively. After having obtained informed consent from the patient and her family, administration of telaprevir and ribavirin were discontinued. Treatment (3-drug combination) was discontinued. The patient started receiving monoammonium glycyrrhizinate 100 mL twice this day. The rashes improved gradually. 2 days after discontinuation: Hepatic function tended to improve. The dose of monoammonium glycyrrhizinate was gradually reduced (60 mL/day, until 4 days after discontinuation). 4 days after discontinuation: The patient recovered from feeling queasy and vomiting. Disappearance of rashes was confirmed. The patient was discharged from the hospital. 7 days after discontinuation: Hepatic disorder remitted.
	Concomitant medications: telmisartan/hydrochlorothiazide, ethyl loflazepate, ribavirin (suspected concomitant drug), peginterferon alfa-2b (genetical recombination) (suspected concomitant drug)			

Laboratory Examination

	Day of administration	Day 8 of administration (day of onset)	Day 11 of administration (day of discontinuation)	1 day after discontinuation	4 days after discontinuation	7 days after discontinuation
AST (GOT) (IU/L)	53	150	585	387	88	40
ALT (GPT) (IU/L)	66	95	379	281	125	65
γ-GTP (IU/L)	58	52	81	82	82	79
Total bilirubin (mg/dL)	0.84	-	1.46	1.01	1.12	1.21

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Female 60s	Viraemia in chronic hepatitis C (hyperthy-roidism)	2,250 mg for 3 days ↓ 1,150 mg for 8 days ↓ 750 mg for 4 days	**Renal disorder, musculoskeletal stiffness, rhabdomyolysis** The patient had been treated with levothyroxine sodium (50 μg/day) for hyperthyroidism. 1 day before administration: Laboratory examination: Hb14.4 g/dL, platelet count 178000/mm^3, AST 31 IU/L, ALT 29 IU/L, creatinine 0.49 mg/dL, BUN 12 mg/dL, uric acid 4.7 mg/dL, lactate dehydrogenase (LDH) 191 IU/L, Creatine kinase (creatine phosphokinase) (CK [CPK]) 68 IU/L. Day 1 of administration: The patient started receiving telaprevir 2,250 mg/day, ribavirin 600 mg/day, and peginterferon alfa-2b (genetical recombination) 1.6 μg/kg/week. Day 3 of administration (day of discontinuation): Decreased urine output, increased blood creatinine (1.9 mg/dL), increased urea nitrogen and uric acid were observed. Intravenous drip infusion of glucose-electrolyte solution (starting solution) (500 mL/day, until 10 days after discontinuation) was started. Administration of telaprevir and ribavirin capsules was discontinued. 1 day after discontinuation: Urine output began to recover. 6 days after discontinuation: Creatinine improved to 1.09 mg/dL, BUN to 20 mg/dL, and uric acid to 6.2 mg/dL. 11 days after discontinuation: Administration of ribavirin capsules (400 mg/day) was started. 17 days after discontinuation (Day 1 of readministration): The patient recovered from acute renal disorder. Creatinine improved to 0.59 mg/dL, BUN to 15 mg/dL, and uric acid to 5.3 mg/dL. Administration of telaprevir (1,500 mg/day) was started. Day 8 of readministration: The dose of telaprevir was changed (750 mg/day). Day 11 of readministration (day of discontinuation of readministration): Administration of telaprevir and ribavirin capsules was discontinued. 1 day after discontinuation of readministration (day of onset): The patient was transported by ambulance due to muscle stiffness of upper and lower limbs. Blood test showed LDH of 326 IU/L. Rhabdomyolysis occurred.

				Intravenous administration of diazepam (5 mg as needed), acetate Ringer's solution containing glucose (1,000 mL/day, until 5 days after discontinuation of readministration), and multiple electrolyte transfusion (1,000 mL/day, until 5 days after discontinuation of readministration) was started. 4 days after discontinuation of readministration: Although physical symptoms improved, a blood test showed LDH of 333 IU/L, CK (CPK) of 2,505 IU/L, and AST of 82 IU/L. Drip infusion therapy has been continued from the day of hospital admission. 11 days after discontinuation of readministration: Blood test showed improvements of muscle stiffness and rhabdomyolysis. 13 days after discontinuation of readministration: Administration of ribavirin capsules (400 mg/day) was started.
	Concomitant medications: levothyroxine sodium, nifedipine extended-release tablets, ribavirin (suspected concomitant drug), peginterferon alfa-2b (genetical recombination) (suspected concomitant drug)			

Laboratory Examination

	1 day before administration	Day 3 of administra-tion	6 days after discontinua tion	12 days after discontinua tion	17 days after discontinua tion (Day 1 of readministr ation)	1 day after discontinua-tion of readmin-istration (day of onset)	4 days after discontinua tion of readmin-istration	11 days after discontinua tion of readmin-istration
HB (g/dL)	14.4	-	14.5	13.8	13.5	-	10.9	10.9
Creatinine (mg/dL)	0.49	1.90	1.09	0.77	0.59	1.31	0.65	0.47
BUN (mg/dL)	12	27	-	-	15	25	7	10
LDH (IU/L)	191	191	-	-	211	326	333	252
CK (CPK) (IU/L)	68	34	-	-	57	-	2,505	73

3 Garenoxacin Mesilate Hydrate

Brand Name (name of company)	Geninax Tablets 200 mg (Toyama Chemical Co., Ltd.)
Therapeutic Category	Synthetic antibacterials
Indications	<Applicable microorganisms> Garenoxacin-susceptible strains of *Staphylococcus*, *Streptococcus*, *Pneumococcus* (including penicillin-resistant *Streptococcus pneumoniae*), *Moraxella* (*Branhamella*) *catarrhalis*, *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Haemophilus influenzae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* <Applicable conditions> Pharyngitis/laryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, secondary infection of chronic respiratory lesions, otitis media, sinusitis • *Pneumococcus* includes multiple-drug resistant *Pneumococcus*. • For details of applicable microorganisms including resistant bacteria, refer to the "Clinical Studies" and "Pharmacology" sections.

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Prolonged QT, ventricular tachycardia, (including torsades de pointes), ventricular fibrillation: Prolonged QT, ventricular tachycardia (including torsades de pointes), or ventricular fibrillation 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.

Acute renal failure: Serious renal disorders such as acute renal failure 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.

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 March 31, 2012)

- Ventricular arrhythmia-associated cases: 7 cases (no fatal cases)
- Acute renal failure-associated cases: 6 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: approximately 4,200,000 (May 1, 2011 to April 30, 2012)

Launched in Japan: October 2007

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Nasopharyn-gitis (atrial fibrillation, congestive cardiac failure, abnormal hepatic function)	400 mg for 5 days	**Torsades de pointes** The patient had periodically visited Hospital A due to atrial fibrillation and congestive cardiac failure. Day 1 of administration: The patient visited Hospital A for influenza vaccination. Cough, sputum, and common cold symptoms were observed. Garenoxacin mesilate hydrate, serrapeptase, carbocisteine, and benproperine phosphate were prescribed. Day 4 of administration (day of onset): While resting at home in the afternoon, the patient became unconscious and fell. He was inarticulate for a while. The consciousness returned several minutes later. The patient visited the hospital by walking on his own. Symptoms were not found. He visited Hospital B (neurosurgery department) and magnetic resonance imaging (MRI) and electroencephalography showed no particular abnormality. Holter monitoring was started in the evening. Day 5 of administration (day of discontinuation): Consciousness decreased at home. Holter monitoring showed ventricular tachycardia (VT). Holter monitoring analysis showed torsades de pointes-like VT at the onset of symptoms. The 12-lead electrocardiography at rest also showed prolonged QT, and then the patient was admitted to Hospital C. On admission, prolonged QT (QT ≈ 500 msec) was noted, but VT was not detected. Considering the possibility of drug-induced long QT syndrome, administration of possibly related drugs (garenoxacin mesilate hydrate, serrapeptase, carbocisteine, and benproperine phosphate) were discontinued, and the patient underwent a follow-up observation. Electrocardiography showed gradually-shortened QT. Atrial fibrillation (AF) was noted with pulse rate 40 - 50 beats/min and QT ≈ 300 - 350 msec.

				In an organic heart disorder search by cardiac catheterization, significant coronary artery stenosis could not be pointed out. 1 day after discontinuation: The patient recovered. 12 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: digoxin, aspirin, spironolactone, warfarin potassium, torasemide, allopurinol, cetirizine hydrochloride, bisoprolol fumarate, zopiclone, serrapeptase, carbocisteine, benproperine phosphate			

Laboratory Examination

	96 days before administration	Day 1 of administration	Day 5 of administration (day of discontinuation)	1 day after discontinuation	12 days after discontinuation (at hospital discharge)
Blood pressure (mmHg)	-	112/60	-	-	94/66
Pulse rate (/min)	-	-	40~50	-	62
LDH (IU/L)	-	218	-	210	-
Na (mEq/L)	142	141	-	142	-
K (mEq/L)	4.0	4.0	-	4.0	-
Cl (mEq/L)	103	103	-	105	-
Arteriosclerotic index	1.6	1.8	-	-	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 90s	Nasopharyn-gitis (chronic cardiac failure, dementia, abnormal hepatic function, renal impairment)	400 mg for 4 days	**Ventricular fibrillation** Day 1 of administration: The patient was prescribed with garenoxacin mesilate hydrate, carbocisteine, combination drug containing diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride for common cold at Hospital A. Day 2 of administration: The patient was admitted to Hospital B due to acute aggravation of hepatic dysfunction and chronic cardiac failure, and started receiving intravenous injection and tolvaptan. As inflammatory findings were still noted, administration of garenoxacin mesilate hydrate was continued. Day 3 of administration: As hepatic dysfunction worsened further, intravenous injection of liver extract/flavin adenine dinucleotide sodium was started. In monitoring during day shift hours, single ventricular premature contraction (VPC) was detected, but with no finding of prolonged QT. Prolonged QT-like findings were observed on the monitor at night. About one hour and half later, a bigeminal pulse (originated from the right ventricular outflow tract) was observed on the monitor. Day 4 of administration (day of onset) (day of discontinuation): Ventricular fibrillation occurred in the afternoon. The patient had respiratory arrest. Cardiac massage was started, and the dose of oxygen was increased. Electrical cardioversion (360 J) was performed twice. Ten minutes after (onset of ventricular fibrillation), the

				symptom returned to atrial fibrillation. The restoration of spontaneous breathing was shown. Sinus rhythm and VPC were observed. Administration of garenoxacin mesilate hydrate, dobutamine hydrochloride, and tolvaptan were discontinued. Although her consciousness level was unfavorable, the patient gradually recovered after that. 1 day after discontinuation: The patient had torsades de pointes in the morning. The level of bag valve mask was increased to 10 L, and cardiac massage was started. Two minutes later, the status recovered to sinus rhythm. Drip infusion of lidocaine hydrochloride was started. After that, VPC did not occur. 7 days after discontinuation: Administration of lidocaine hydrochloride was discontinued, but there was no recurrence.
	Concomitant medications: carbocisteine, diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride, monoammonium glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate, dobutamine hydrochloride, heparin sodium, liver extract/flavin adenine dinucleotide sodium, carperitide (genetical recombination), tolvaptan			

Laboratory Examination

	Day 2 of administration	Day 3 of administration	Day 4 of administration (day of onset) (day of discontinuation)	1 day after discontinuation	3 days after discontinuation
Blood pressure (mmHg)	118/68	142/90	132/72	124/68	142/70
Pulse rate (/min)	128	88	118	92	100
LDH (IU/L)	-	-	1061	706	7296
Na (mEq/L)	147	144	145	145	154
K (mEq/L)	3.2	3.2	3.2	3.6	3.7
Cl (mEq/L)	112	108	109	111	119

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Upper respiratory tract infection (renal impairment, diabetes mellitus, autoimmune thyroiditis, myelodysplastic syndrome, hypertension, hyperlipidaemia, osteoporosis, back pain)	200 mg for 4 days	**Renal impairment, hepatic dysfunction** Day 1 of administration: The patient was admitted to the hospital due to suspected upper respiratory inflammation. Administration of garenoxacin mesilate hydrate was started. Day 2 of administration: Pyrexia resolved. Day 4 of administration (day of onset) (day of discontinuation): Blood test showed AST of 750 IU/L, ALT of 1380 IU/L, LDH of 531 IU/L, serum creatinine of 6.76mg/dL, and hepatorenal dysfunction. The patient was transferred to the intensive care unit. Administration of garenoxacin mesilate hydrate was discontinued. 1 day after discontinuation: Continuous hemodiafiltration (CHDF) was performed (a total of 4 times until 4 days after discontinuation).

				7 days after discontinuation: Hemodiafiltration (HDF) was performed (a total of 4 times until 19 days after discontinuation). 23 days after discontinuation: Hemodialysis (HD) was performed (a total of 5 times until 34 days after discontinuation). The patient recovered from hepatic dysfunction. 34 days after discontinuation: The patient did not recover from renal impairment. Maintenance dialysis will be needed hereafter.
	Concomitant medications: losartan potassium, amlodipine besilate, fluvastatin sodium, insulin human (genetical recombination), alfacalcidol, levothyroxine sodium, furosemide, acetaminophen, loxoprofen sodium hydrate, combination poultice containing methyl salicylate			

Laboratory Examination

	Day 1 of administration	Day 4 of administration (day of onset) (day of discontinuation)	1 day after discontinuation	4 days after discontinuation	7 days after discontinuation	14 days after discontinuation	23 days after discontinuation	34 days after discontinuation
BUN (mg/dL)	49.5	105.4	112.7	48.8	73.7	35.2	69.6	75.2
Creatinine (mg/dL)	1.99	6.76	7.78	5.17	8.48	5.62	7.94	7.91
AST (GOT) (IU/L)	20	750	309	75	63	19	17	-
ALT (GPT) (IU/L)	18	1380	943	424	218	52	23	-
Al-P (IU/L)	200	363	328	367	313	262	235	-
LDH (IU/L)	171	531	265	219	184	172	184	-
γ-GTP (IU/L)	26	70	61	90	83	59	44	-
Total bilirubin (mg/dL)	0.6	0.9	0.9	0.8	0.6	0.6	0.5	-
K (mEq/L)	4.6	5.2	5.5	4.3	3.5	3.2	3.9	3.5

3

Revision of Precautions (No. 237)

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 June 5, 2012 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 Psychotropics

Escitalopram Oxalate

Brand Name	LEXAPRO Tab. 10 mg (Mochida Pharmaceutical Co., Ltd.)
Contraindications	Patients with prolonged QT (e.g., congenital long QT syndrome)
Careful Administration	Patients with past or present arrhythmia such as marked bradycardia, patients treated with drugs that are known to cause prolonged QT, patients with congestive cardiac failure, patients with hypokalaemia
Important Precautions	Prolonged QT was reported in association with administration of this drug. Caution should be paid to the cardiovascular condition of patients before this drug is administered to patients with cardiovascular disorders.
Adverse Reactions (clinically significant adverse reactions)	**Prolonged QT, ventricular tachycardia (including torsades de pointes)**: Prolonged QT or ventricular tachycardia (including torsades de pointes) 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 Antihypertensives

Aliskiren Fumarate

Brand Name	Rasilez Tablets 150 mg (Novartis Pharma K.K.)
Contraindications	Patients with diabetes mellitus on treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (except patients whose blood pressure control was still markedly poor despite treatment with other antihypertensive therapies including angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists)
Important Precautions	Serum potassium and serum creatinine levels may increase in patients with renal impairment. This drug should be carefully administered by monitoring the patient's condition. Concomitant use with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists in patients with renal impairment whose eGFR level is less than 60 mL/ min/1.73 m^2 should be avoided except in cases where such use is considered absolutely necessary for the treatment.

3 Antiparkinsonian agents

Ropinirole Hydrochloride

Brand Name	ReQuip Tablets 0.25 mg, 1 mg, 2 mg (GlaxoSmithKline K.K.)
Important Precautions	If dose reduction or discontinuation of this drug is required, the dose of this drug should be tapered. [Neuroleptic malignant syndrome such as hyperthermia, disturbed consciousness, severe muscle stiffness, involuntary movements, shock symptom may occur following rapid dose reduction or discontinuation].
Adverse Reactions (clinically significant adverse reactions)	**Neuroleptic malignant syndrome**: Hyperthermia, disturbed consciousness, severe muscle stiffness, involuntary movements, shock symptom, etc. may occur after administration, dose reduction or discontinuation of this drug. If such symptoms occur in an initial phase of treatment, administration of this drug should be discontinued. If such symptoms occur during dose change or discontinuation, the dose should be carefully tapered after returning the dose to the previous level., And then, appropriate measures such as cooling the body and fluid replacement should be taken. Such symptoms may also occur during the treatment without dose change or discontinuation..

4 Psychotropics

Trazodone Hydrochloride

Brand Name	Desyrel Tablets 25, 50 (Pfizer Japan Inc.), RESLIN Tablets 25, 50 (MSD K.K.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Prolonged QT, ventricular tachycardia (including torsades de pointes), ventricular fibrillation, ventricular extrasystoles**: Prolonged QT, ventricular tachycardia (including torsades de pointes), ventricular fibrillation, or ventricular extrasystoles may occur. Patients should be carefully monitored through periodic electrocardiography, etc. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

5 Diuretics

Azosemide

Brand Name	DIART Tab. 30 mg, 60 mg (Sanwa Kagaku Kenkyusho Co., Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Electrolyte abnormalities**: Electrolyte abnormalities such as hypokalaemia and hyponatraemia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

6 Antihypertensives

Hydralazine Hydrochloride

Brand Name	Apresoline Tablet 10 mg, 25 mg, 50 mg, Apresoline 10% Powder “Ciba”, Apresoline for Injection 20 mg (Novartis Pharma K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Fulminant hepatitis, hepatitis, hepatic dysfunction, jaundice**: Fulminant hepatitis, hepatitis, hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), Al-P, γ-GTP, LDH, bilirubin, etc. or jaundice may occur. Patients should be carefully monitored through periodic tests, etc., and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

7 **Antivirals**

Darunavir Ethanolate

Brand Name	PREZISTA Tablets 300 mg, PREZISTANAIVE Tablets 400 mg (Janssen Pharmaceutical K.K.)
Important Precautions	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, and acute generalised exanthematous pustulosis 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 occurred in less than 0.1% of patients. Most of the rash cases were mild to moderate, occurred within 4 weeks of treatment and achieved remission during the treatment. If severe rash occur, 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 cases were mild to moderate in severity and did not result in treatment restriction or discontinuation.
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, and acute generalised exanthematous pustulosis**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, and acute generalised exanthematous pustulosis have been reported. If any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for 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 July 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Bixalomer Kiklin Capsules 250 mg	Astellas Pharma. Inc.	June 26, 2012
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg ZITHROMAC 250 mg*[1]	Pfizer Japan Inc.	June 22, 2012
Aprepitant EMEND Capsules 125 mg, 80 mg, EMEND Capsules Set*[2]	Ono Pharmaceutical Co., Ltd.	June 22, 2012
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg*[3]	AstraZeneca K.K.	June 22, 2012
Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg*[4]	Pfizer Japan Inc.	June 22, 2012
Lidocaine Penles Tape 18 mg*[5]	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*[6]	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*[7, 8]	Shionogi & Co., Ltd.	May 25, 2012

Thyrotropin Human Alfa (Genetical Recombination) THYROGEN for Intramuscular Injection 0.9 mg*9	Sato Pharmaceutical Co., Ltd.	May 25, 2012
Mometasone Furoate Hydrate NASONEX Nasal 50 μg 56 sprays, NASONEX Nasal 50 μg 112 sprays*8	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
Duloxetine Hydrochloride Cymbalta Capsules 20 mg, 30 mg*10	Shionogi & Co., Ltd.	February 22, 2012
Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, 24 mg*11	Otsuka Pharmaceutical Co., Ltd.	January 18, 2012
Human Fibrinogen/Thrombin Fraction TachoSil Tissue Sealing sheet	CSL Behring K.K.	January 17, 2012
Fosphenytoin Sodium Hydrate Fostoin 750 mg for Injection	Nobelpharma Co., Ltd.	January 17, 2012
Rebamipide Mucosta ophthalmic suspension UD 2%	Otsuka Pharmaceutical Co., Ltd.	January 5, 2012

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

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

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

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

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

*6 An additional indication for “erythema nodosum leprosum”

*7 An additional indication for “pyogenic meningitis”

*8 An additional administration for “pediatrics”

*9 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”

*10 An additional indication for “treatment of pain in patients with diabetic neuropathy”

*11 An additional indication for “improvement of manic symptoms in patients with bipolar disorder”