Pharmaceuticals and Medical Devices Safety Information

No. 301 May 2013

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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. 301 May 2013

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

A/G	Albumin globulin ratio
ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
APTT	Activated partial thromboplastin time
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
CIN	Cervical intraepithelial neoplasia
CK (CPK)	Creatine kinase (Creatine phosphokinase)
CK-MB	Creatine kinase MB
CRP	C-reactive protein
CT	Computed tomography
CYP	Cytochrome
DL	Distal latency
ECG	Electrocardiogram
EMG	Electromyogram
ENG	Electronystagmogram
EPPV	Early Post-marketing Phase Vigilance
GIF	Gastrolntestinal fiberscope
Hb	Hemoglobin
HCV-RNA	Hepatitis C virus-Ribonucleic acid
HPV	Human papilloma virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IU	International unit
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LAP	Leucine aminopeptidase
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MCV	Motor nerve conduction velocity
MLF	Medial longitudinal fasciculus
MRI	Magnetic resonance imaging
PLT	Platelet
PT	Prothrombin Time
PT-INR	Prothrombin time - international normalized ratio
RBC	Red blood cell count
SNAP	Sensory nerve action potential
SSRI	Selective serotonin reuptake inhibitor
T-Bill	Total bilirubin
TEN	Toxic epidermal necrolysis
UGT	Uridine diphosphate glucuronosyltransferase
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

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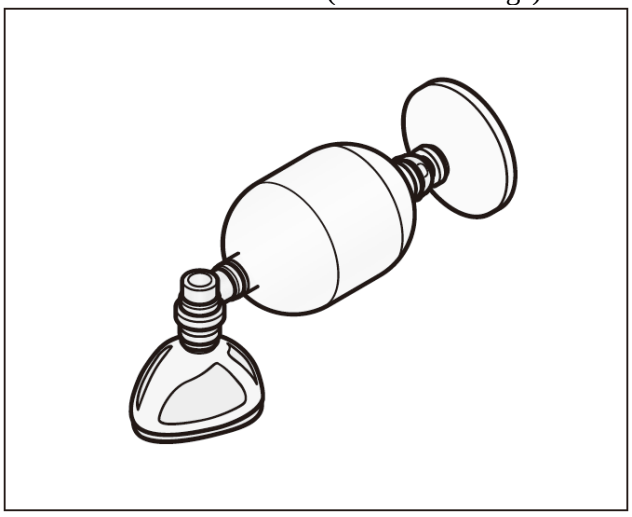
Precautions in Handling of Reusable Resuscitator

1. Introduction

Manual resuscitator (resuscitator bag) is a medical device used for emergency ventilation in patients with apnea or respiratory failure, and there are two types of resuscitator bags, single-use ones and reusable ones, which are reassembled after disassembly, washing, and sterilization,etc.

Medical accidents involving insufficient ventilation in patients treated with reusable resuscitator bags assembled in the wrong way have been reported. This section presents precautions in handling of reusable resuscitator bags.

< Manual resuscitator (resuscitator bags) >



Quoted from PMDA Medical Safety Information No. 38

2. Requests to healthcare professionals

Recently, MHLW instructed marketing authorization holders (MAHs) dealing in reusable resuscitator bags to inspect package inserts and user's manuals and give clear descriptions of how to assemble and check operation of reusable resuscitator bags [1)].

Healthcare professionals are encouraged to confirm whether the latest package inserts and user's manuals of reusable resuscitator bags used in their medical institution are managed properly and to obtain the latest ones from MAHs if needed.

In addition, healthcare professionals are requested to exercise attention to the following points when handling reusable resuscitator bags for proper operation:

While referring to and checking

- procedures for assembling
- procedures for operation check

described in package inserts and the user's manual of the product you assemble, please assemble the parts of the product properly, check operation through proper procedures after assembling, and keep the product after confirming normal ventilation.

3. Conclusion

PMDA Medical Safety Information on handling of reusable resuscitator bags has been released. Please utilize it for safety management activities in your medical institution such as educational activites, etc., on proper handling.

- PMDA Medical Safety Information No. 38 "Improper Assembly of Resuscitator Bags" (only available in Japanese language)
  http://www.info.pmda.go.jp/anzen_pmda/file/iryo_anzen38.pdf

- Website for PMDA Medical Safety Information
  http://www.pmda.go.jp/english/service/medical_info.html

<Reference> (including provisionally translated titles)

1) PFSB/SD Notification No. 0326-2, Director of Safety Division, Pharmaceutical and Food Safety Bureau, the MHLW, dated March 26, 2013, "Self-inspection, etc. of Package Inserts of Reusable Resuscitator" (only available in Japanese language)
http://wwwhourei.mhlw.go.jp/hourei/doc/tsuchi/T130327I0030.pdf

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Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated March 26, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cells)

Brand Name (name of company)	Cervarix (GlaxoSmithKline K.K.)
Therapeutic Category	Vaccines
Indications	Prevention of cervical cancer (squamous-cell carcinoma, adenocarcinoma) and its precursor lesions (cervical intraepithelial neoplasia [CIN] grade 2 and 3) caused by infection with human papillomavirus (HPV) type 16 and 18

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Acute disseminated encephalomyelitis (ADEM): Acute disseminated encephalomyelitis (ADEM) may occur. In such cases, pyrexia, headache, convulsion, movement disorder, and disturbed consciousness, etc., generally occur within several days to 2 weeks after vaccination. If ADEM is suspected, diagnosis should be made by MRI etc., and appropriate measures should be taken.

Guillain-Barre syndrome: Guillain-Barre syndrome may occur. If any symptoms such as flaccid paralysis originating from the distal extremities, decreased or absent tendon reflexes, 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 (from initial marketing to January 31, 2013)

- Acute disseminated encephalomyelitis-related cases: 3 cases (no fatal cases)
- Guillain-Barre syndrome-related cases: 5 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 2.73million (December 2009 to December 2012)

Launched in Japan: December 2009

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 10s	Prevention of cervical cancer (none)	0.5 mL for 1 day 0.5 mL for 1 day	**Acute disseminated encephalomyelitis, diplopia, nystagmus, giddiness, staggering gait, bilateral medial longitudinal fasciculus (MLF) syndrome, increased myelin basic protein in cerebrospinal fluid, demyelinating lesions, vision disorder, balance disorder, vertigo** <Medical history> Asthma, allergic rhinitis • History of thyroid disease: No • History of type 1 diabetes mellitus: No • History of inflammatory bowel disease: No

				• Family history (particularly demyelinating diseases such as multiple sclerosis and chronic inflammatory demyelinating polyneuropathy): Nothing in particular First vaccination: The patient received first vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine. Approximately 1 month after first vaccination: The patient received second vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine. 14 days after second vaccination: Vision disorder occurred from the evening. 15 days after second vaccination: Diplopia, nystagmus, and giddiness occurred from the time of awakening. 17 days after second vaccination: Staggering gait developed. 19 days after second vaccination: The patient visited the neurology department. Bilateral MLF syndrome was noted. 20 days after second vaccination: The patient was admitted to the hospital. Head magnetic resonance imaging (MRI) showed an abnormal intensity area in the pontine tegmentum. With increased myelin basic protein in cerebrospinal fluid, a demyelinating lesion was suspected. 21 days after second vaccination: Administration of intravenous drip infusion of methylprednisolone was started (for 3 days). 31 days after second vaccination: As the symptom improved, the patient was discharged from the hospital. 96 days after second vaccination: As improvement was confirmed on MRI, medical care was terminated. <Test results, findings, etc.> • Status at onset of event and time to onset of event after vaccination: 14 days after second vaccination • Symptoms: Diplopia, nystagmus, dizziness, balance disorder • Whether the patient developed the same symptoms in the past: No • Cerebrospinal fluid test (white blood cell [WBC], differential count, red blood cell [RBC], protein, glucose, oligoclonal band, myelin basic protein): Yes • Other tests (e.g. serum viral test, urine analysis): Yes • Central nervous imaging procedure (MRI or computed tomography [CT] scan): Yes • Nerve conduction studies (e.g. electronystagmogram [ENG], electromyogram [EMG]): Yes
	Concomitant medications: none			

Laboratory Examination

	21 days after second vaccination	23 days after second vaccination	24 days after second vaccination	26 days after second vaccination
WBC (cells/mm^3)	-	242	151	99
Cerebrospinal fluid cell count	<1	-	-	-
Cerebrospinal fluid β2-microglobulin	1,014	-	-	-
Cerebrospinal fluid oligoclonal	-	-	-	-
Cerebrospinal fluid IgG index	0.44	-	-	-
Cerebrospinal fluid Cl	126	-	-	-
Cerebrospinal fluid Na	147	-	-	-
Cerebrospinal fluid IgG	3.5	-	-	-
Cerebrospinal fluid IgA	<0.5	-	-	-
Cerebrospinal fluid IgM	<0.6	-	-	-
Cerebrospinal fluid albumin	164	-	-	-
Cerebrospinal fluid protein (mg/dL)	38	-	-	-
Cerebrospinal fluid glucose	59	-	-	-
CRP	<0.1	<0.1	<0.1	<0.1

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 10s	Prevention of cervical cancer (none)	0.5 mL for 1 day	**Guillain-Barre syndrome, numbness in left hand, face, and legs (extending over both upper limbs and both lower limbs), decreased motion perception of both forearms and lower legs, dysphagia, slightly decreased ulnar nerve conduction velocity, sensorimotor disorder of distal portions of limbs, hypoaesthesia, abasia, disturbance of face muscle movement, absent ankle jerks, absent patellar tendon reflex, absent biceps brachii muscle reflex, suspected peripheral neuritis** <Medical history> Malignant diseases: No Pregnancy or delivery: No Surgery performed recently: No Spinal cord injury: No Whether infection occurred recently: No Other related medical history/risk factors: No First vaccination: The patient received first vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine. Site of vaccination: Deltoid muscle of upper arm (left) 9 days after vaccination: Numbness in left hand, limbs and face was found. The patient visited and was admitted to this department. 10 days after vaccination: Difficult swallowing also occurred. The patient was diagnosed with Guillain-Barre syndrome, and administration of immunoglobulin G was started. Human normal immunoglobulin G 17.5 g (for 5 days) 13 days after vaccination: Swallowing improved. Sensation of limbs recovered. Reflex also tended to recover. 16 days after vaccination: The symptoms nearly disappeared. 19 days after vaccination: Nerve conduction velocity improved.

				20 days after vaccination: The patient was discharged from the hospital. 30 days after vaccination: Numbness in hands and feet relapsed. The patient visited and was admitted to this department. Hypoaesthesia became prominent. 31 days after vaccination: Administration of immunoglobulin G was started. 35 days after vaccination: Numbness in hands and feet tended to improve. Administration of immunoglobulin G was discontinued. 41 days after vaccination: The patient visited the hospital. Numbness in hands and feet was almost disappeared. 65 days after vaccination: With no relapse of symptoms, medical care was terminated. <Test results, findings, etc.> • State when this event occurred for the first time: Numbness in left hand occurred 9 days after the first vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine. Due to numbness in face and feet, the patient visited the emergency outpatient department. Due to sensorimotor disorder of distal portions of limbs, the patient was admitted to the hospital. • Any symptoms/signs (flaccid weakness/paralysis of limbs [bilateral or unilateral, symmetric or asymmetric], ataxia, ophthalmoplegia, paraesthesia, pain, autonomic symptoms, facial weakness, dysphasia, dysarthria): Yes • If "Yes," symptoms, signs, sites/patterns, and degrees of progression: Numbness in both upper limbs and both lower limbs, hypoaesthesia, abasia, right-left paralysis, numbness in face, disturbance of face muscle movement • Whether the patient fell into respiratory failure: No Whether endotracheal intubation or mechanical ventilation was required: No Other symptoms/signs: Difficult swallowing Results of physical/neurological examinations (vital signs, deep tendon reflex of affected limbs, motor function, findings of cerebral nerve examination, and findings of sensory organ examination): Achilles tendon reflex, patella tendon reflex, biceps brachii muscle reflex decreased or almost disappeared. Standing was possible but with abasia. In nerve conduction velocity studies, articular velocity of both hands was 35 m/s. • Clinical course and outcome of this event: Administration of immunoglobulin G was started 10 days after vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine. The symptoms started to improve about 3 days after administration. The symptoms almost disappeared 6 days after administration. The patient was discharged from the hospital 10 days after administration. • Full blood count, differential count, and platelet count: No abnormality • Electrolyte/hepatic enzyme levels: No abnormality • Cerebrospinal fluid analysis: Not performed. • Anti-ganglioside antibody: Anti-GM1 (-), anti-GQ1b (-) • Campylobacter jejuni examination: No • Other test results: No

				• Central nervous imaging procedure: No abnormality • Nerve conduction studies or evoked potential studies: 12 days after vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine, median nerve (motor nerve conduction velocity [MCV]) right 35.3 m/s, left 37.9 m/s 19 days after vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine, right 48.4 m/s, left 50.0 m/s
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 10s	Prevention of cervical cancer (pneumonia)	0.5 mL for 1 day 0.5 mL for 1 day	**Guillain-Barre syndrome, sudden weakness, difficulty in walking, muscular weakness of limbs, sensory disturbance of limbs (numbness in upper/lower limbs), blood antiglycolipid antibody positive, sleepiness, malaise, symmetric paralysis, decreased deep tendon reflex of upper/lower limbs, absent left patellar tendon reflex, increased cerebrospinal fluid cell count, mycoplasma test positive, slightly prolonged distal latency (DL) in left sensory ulnar nerve, and slightly decreased sensory nerve action potential (SNAP) in left Sural nerve** <Medical history> Malignant diseases: No Pregnancy or delivery: No Surgery performed recently: No Spinal cord injury: No Whether infection occurred recently: Yes (The patient was treated for pneumonia at the previous hospital, and received intravenous treatment about 1 month before first vaccination with recombinant Aasorbed bivalent human papillomavirus-like particle vaccine.) her related medical histories/risk factors: No First vaccination: The patient received first vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine and simultaneous vaccination with Japanese encephalitis vaccine. Approximately 1 month after first vaccination: The patient received second vaccination with recombinant absorbed bivalent human papillomavirus-like particle vaccine. (AM) Site of vaccination: Subcutaneous site in the right upper arm multaneous vaccination with Japanese encephalitis vaccine was performed. (PM) Sudden weakness, difficulty in walking, muscular weakness of limbs, and sensory disturbance were observed. Sleepiness and malaise were noted. After an afternoon nap, weakness and numbness of limbs were noted. Other diseases were considered negative based on blood/cerebrospinal fluid tests. Having been blood antiglycolipid antibody positive, the patient was diagnosed with Guillain-Barre syndrome. 1 day after second vaccination: The patient was admitted to the hospital.

				Sequela (gait disturbance) was found. 7 days after second vaccination: Immunoglobulin therapy (400 mg/kg for 5 days) was performed. Approximately 3 months after second vaccination: Having become able to walk with a single cane, the patient was discharged from the hospital. Approximately 6 months after second vaccination: The patient was able to walk and also to ride a bicycle. The patient needed a handrail for going up and down stairs. Other symptoms improved. <Test results, findings, etc.> • State when this event occurred for the first time: Sleepiness, malaise, and weakness occurred, followed by numbness. • Any symptoms/signs (flaccid weakness/paralysis of limbs [bilateral or unilateral, symmetric or asymmetric], ataxia, ophthalmoplegia, paraesthesia, pain, autonomic symptoms, facial weakness, dysphasia, dysarthria): weakness/paralysis of limbs (symmetric) • Whether the patient fell into respiratory failure: No • Whether endotracheal intubation or mechanical ventilation was required: No • Other symptoms/signs: No • Results of physical/neurological examinations (vital signs, deep tendon reflex of affected limbs, motor function, findings of cerebral nerve examination, and findings of sensory organ examination): Vital signs normal, difficulty in walking, decreased deep tendon reflex of upper/lower limbs, absent left patellar tendon reflex were observed; Cerebral nerve at admission: No abnormalities on head/spinal MRI, no nerve conduction studies abnormal • Clinical course and outcome of this event: remission • Full blood count, differential count, and platelet count: Yes • Electrolyte/hepatic enzyme levels: Yes • Cerebrospinal fluid analysis: Yes • 4 days after second vaccination: Protein level 29, cell count 1, mononuclear cell 1 (100%), oligoclonal band (-) • 16 days after second vaccination: Protein level 31, cell count 20, mononuclear cell - (100%) Anti-ganglioside antibody: Yes Campylobacter jejuni examination: Yes • 3 days after second vaccination: Stool culture showed only E. coli (non-pathogenic) Other test results: Yes (mycoplasma pneumonia) Central nervous imaging procedure: Yes • 1 day after second vaccination: No abnormalities on head MRI • 3 days after second vaccination: No abnormalities on cerebrospinal fluid MRI • Nerve conduction studies or evoked potential studies: Yes
	Concomitant medications: Japanese encephalitis vaccine			

Laboratory Examination

	1 day after second vaccination	4 days after second vaccination	16 days after second vaccination
Cerebrospinal fluid protein (mg/dL)	-	29	31
Cerebrospinal fluid glucose	-	58	52
WBC ($\times 10^3$/mm^3)	7.4	-	-
RBC ($\times 10^6$/mm^3)	4.42	-	-
PLT ($\times 10^3$/mm^3)	197	-	-
Na (mEq/L)	142	-	-
K (mEq/L)	3.9	-	-
Cl (mEq/L)	106	-	-
Ca (mg/dL)	9.4	-	-
CRP (mg/dL)	0.05	-	-
Blood glucose (mg/dL)	79	-	-
IgG (mg/dL)	1102	-	-
IgA (mg/dL)	84	-	-
IgM (mg/dL)	106	-	-
AST (GOT) (IU/L)	16	-	-
ALT (GPT) (IU/L)	12	-	-

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) Patients with high blood HCV RNA level who are treatment-naïve (2) Patients who are non-responders or relapsers to interferon monotherapy or combination therapy with ribavirin

PRECAUTIONS (underlined parts are revised)

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 4 weeks after 12 weeks of administration. Susceptibility to infection may also occur and infection or exacerbation of infection may be induced. Differential count of leucocytes and CRP level should also be measured.

Adverse Reactions (clinically significant adverse reactions)

Sepsis: Susceptibility to infection may occur and development or exacerbation of infection may be induced, leading to sepsis. Patients should be carefully monitored for clinical symptoms (including pyrexia) and periodic measurements of differential count of leucocytes and CRP level, etc., and patient's general status should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Interstitial pneumonia: If respiratory symptoms including cough and dyspnoea, pyrexia, or chest X-ray abnormalities, etc. are observed, administration of this drug should be discontinued and appropriate measures such as administration of corticosteroids should be taken. Patients should be advised to contact a physician immediately if cough or dyspnoea, etc. occurs.

Haemorrhage of digestive tract (melaena, bloody stool, etc.), gastrointestinal ulcers: 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 1 year (from initial marketing to February 13, 2013)

- Interstitial pneumonia-related cases: 1 case (no fatal cases)
- Haemorrhage of digestive tract and gastrointestinal ulcer-related cases: 6 cases (no fatal cases)

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year (from initial marketing to January 31, 2013)

- Sepsis-related cases: 5 (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 8,000 (February 2012 to January 2013)

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 60s	Improvement of viraemia in chronic hepatitis C (hypertension) (carotid artery stenosis) (insomnia)	1,500 mg for 10 days	**Decreased neutrophils, sepsis** The patient was previously treated with interferon + ribavirin. Day 1 of administration: The patient started receiving telaprevir (1,500 mg/day), ribavirin (400 mg/day), and peginterferon alfa-2b (1.5 μg/kg/week) (triple combination therapy). Day 6 of administration: Skin eruption occurred. [Severity] Grade 1: 50% or less of body surface area (localized) [Pruritus] Present Day 8 of administration: The patient had a consultation at the dermatology department. Oral fexofenadine hydrochloride (120 mg/day, until 1 day after discontinuation) was given, diflucortolone valerate cream (as needed, until 1 day after discontinuation, topical) was applied. Neutrophils decreased (576/mm^3). Day 10 of administration (day of discontinuation): Septic shock with disturbed consciousness and decreased blood pressure occurred. As Escherichia coli was identified by blood culture, the patient was treated as having sepsis (meropenem [3 g/day, until 6 days after discontinuation, intravenously], administration of sulfonated human normal immunoglobulin G [5 g/day, until 2 days after discontinuation, intravenously], etc.) were started. Triple combination therapy was discontinued. 1 day after discontinuation: Procalcitonin level was 30 (ng/mL). Pyrexia (39.5°C), disturbed orientation, unrest, and decreased blood pressure were observed. 2 days after discontinuation: In the evening procalcitonin level was 15 (ng/mL) and C-reactive protein (CRP) level was 5 (mg/dL). The condition became less severe compared to the preceding day. [Urine analysis] Chyle (urine), 0.0 (no change until 30 days after discontinuation); urine color, yellow; urine specific gravity, 1.008; urine pH, 7.5; urine protein, + - ; urine sugar, - ; urinary urobilinogen (mg/dL), 0.1; urine bilirubin, - ; urinary

				ketones, - ; urinary occult blood, + -; urinary nitrite, - ; urinary leukocyte, - ; urinary sediment (red blood cells), 2; urinary sediment (white blood cells), 1; urinary sediment (squamous epithelium) cells/visual field (400 × magnification), 1 7 days after discontinuation: Skin eruption improved, became less severe, and resolved. [Urine analysis] Chyle (urine), 0.0 (no change until 30 days after discontinuation); urine color, yellow; urine specific gravity, 1.005; urine pH, 5.5; urine protein, - ; urine sugar, - ; urinary urobilinogen (mg/dL), 0.1; urine bilirubin, - ; urinary ketones, - ; urinary blood, -; urinary nitrite, - ; urinary leukocyte, - ; urinary sediment (red blood cells), < 1; urinary sediment (white blood cells), < 1; urinary sediment (squamous epithelium) cells/visual field (400 × magnification), < 1 12 days after discontinuation: Sepsis improved and resolved. Blood test values also became normal. 30 days after discontinuation: Decreased neutrophils (1,914/mm^3) resolved.
	Concomitant medications: ribavirin (the other suspected drug), peginterferon alfa-2b (the other suspected drug), clopidogrel sulfate, amlodipine besilate, candesartan cilexetil, aspirin, ifenprodil tartrate, omeprazole, brotizolam, allopurinol			

Laboratory Examination (1)

	3 days before administration	Day 1 of administration	Day 3 of administration	Day 5 of administration	Day 8 of administration	Day 10 of administration (day of discontinuation)	1 day after discontinuation
Systolic blood pressure (mmHg)	-	107	-	-	-	87	-
Diastolic blood pressure (mmHg)	-	57	-	-	-	54	-
Heart rate (beats/min)	-	68	-	-	-	120	-
Body temperature (°C)	-	36.5	-	-	-	40.3	-
Hematocrit (%)	-	-	-	-	-	-	-
Hemoglobin (g/dL)	13.8	-	-	-	12.7	-	-
WBC (/mm^3)	3,800	-	-	-	1,700	-	-
Neutrophils (%)	53.5	-	-	-	33.9	-	-
PLT (10^4/mm^3)	13.5	-	-	-	9.7	-	-
Uric acid (mg/dL)	4.6	-	7.1	5.7	4.7	4.1	-
CRP (mg/dL)	0.01	-	-	-	-	0.02	3.09
Serum creatinine (mg/dL)	0.52	-	0.77	0.64	0.61	0.59	
Procalcitonin (ng/mL)	-	-	-	-	-	-	30.56

	2 days after discontinuation		3 days after discontinuation	5 days after discontinu-ation	7 days after discontinuation	10 days after discontinu-ation	12 days after discontinuation (sepsis resolved)	14 days after discontinu-ation	30 days after discontinu-ation (neutrophils recovered)
Systolic blood pressure (mmHg)	-	-	-	-	-	-	125	-	-
Diastolic blood pressure (mmHg)	-	-	-	-	-	-	79	-	-
Heart rate (beats/min)	-	-	-	-	-	-	55	-	-
Body temperature (°C)	-	-	-	-	-	-	36.7	-	-
RBC (10^4/mm^3)	353	-	386	371	361	331	336	354	399
Reticulocyte count (10^4/mm^3)	1.8	-	-	-	-	-	-	-	-

Reticulocyte count (‰)	5	-	-	-	-	-	-	-	-
Hematocrit (%)	32.9	-	35.5	33.7	33.1	30.6	31.5	32.8	37.8
Hemoglobin (g/dL)	10.9	-	11.9	11.4	11.1	10.4	10.5	11.1	12.7
WBC (/mm^3)	6,400	3,900	-	2,400	3,000	2,100	2,000	2,300	3,500
Neutrophils (%)	92.3	-	-	-	36.0	-	41.8	57.0	54.7
PLT (10^4/mm^3)	6.3	-	7.7	9.4	12.0	14.8	15.4	15.8	12.3
Uric acid (mg/dL)	2.3	-	2.0	1.9	2.4	4.6	4.4	5.0	4.3
CRP (mg/dL)	5.69	2.05	2.05	0.40	0.16	0.07	0.05	0.03	0.01
Glomerular filtration rate (mL/min)	77.1	-	84.9	117.9	103.6	98.8	106.2	101.2	101.2
Procalcitonin (ng/mL)	16.78	7.82	7.82	2.04	0.57	0.04	<0.02	-	-
PT (%) /PT (ratio) /PT-INR	83/1.08 /1.09	-	99/0.98/ 0.98	101/0.97/ 0.97	104/0.98/ 0.98	-	-	-	-
APTT (sec)	34.7	-	32.9	30.1	28.5	-	-	-	-
Antithrombin III (%)	70.1	-	-	-	-	-	-	-	-
Fibrin degradation products (μg/mL)	8.4	-	2.6	2.2	2.7	-	-	-	-
D-dimer (μg/mL)	3.6	-	1.1	1.1	1.2	-	-	-	-

Laboratory Examination (2)

	2 days after discontinu-ation	3 days after discontinu-ation	5 days after discontinu-ation	7 days after discontinu-ation	10 days after discontinu-ation	12 days after discontinu-ation (sepsis resolved)	14 days after discontinu-ation	30 days after discontinu-ation (neutrophils recovered)
Hepaplastin test (%)	69	-	-	-	-	-	-	0.3
Total protein (g/dL)	5.6	6.6	6.3	7.0	6.4	6.3	6.2	7.0
Albumin (g/dL)	3.2	3.6	3.9	3.9	3.7	3.6	3.6	4.2
A/G ratio	1.3	1.2	1.3	1.3	1.4	1.3	1.4	1.5
Total bilirubin (mg/dL)	0.7	0.8	0.7	0.6	0.5	0.6	0.5	0.5
AST (GOT) (IU/L)	70	49	27	26	17	15	15	19
ALT (GPT) (IU/L)	47	41	30	35	17	13	13	13
LDH (IU/L)	222	222	185	172	148	141	132	175
ALP (IU/L)	183	186	197	220	211	210	211	256
γ-GTP (IU/L)	33	36	49	54	34	30	27	20
LAP (IU/L)	55	-	-	63	-	52	49	51
Cholinesterase (IU/L)	278	296	294	294	254	249	249	259
CK (CPK) (IU/L)	998	452	80	28	20	20	27	50
CK-MB (IU/L)	9.8	-	-	-	-	-	-	-
Amylase (IU/L)	118	123	103	118	100	105	123	103
Lipase (IU/L)	34.8	-	-	27.5	-	17.8	-	-
Ammonium nitrogen (μg/dL)	54	-	-	-	-	-	-	-
Total bile acids (nmol/mL)	7.0	-	-	-	-	-	-	-
BNP (pg/mL)	52.8	-	-	11.2	-	-	-	-
Endotoxin (pg/mL)	<1.9	-	-	-	-	-	-	-
Lactic Acid (mg/mL)	9.3	-	-	-	-	-	-	-
Pancreatic amylase (IU/L)	-	94	77	-	67	-	-	-
Urine urea Nitrogen (mg/dL)	8	6	6	8	11	12	13	17
Blood glucose (serum) (mg/dL)	127	156	125	97	119	89	88	96

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Improvement of viraemia in chronic hepatitis C (diabetes mellitus) (hypertension)	1,500 mg for 77 days	**Suspected sepsis due to acute pyelonephritis** The patient was previously treated with interferon. Day 1 of administration: The patient was previously treated with interferon alone. Administration of telaprevir (1,500 mg/day), ribavirin (400 mg/day), and peginterferon alfa-2b (1.5 μg/kg/week) was started (triple combination therapy). Day 11 of administration: Skin eruption occurred. [Severity] Grade 1: 50% or less of body surface area (localized). [Pruritus] Yes Skin eruption occurred on the abdomen. Oral administration of bepotastine besilate (2T/day, until Day 77 of administration) and topical administration of betamethasone butyrate propionate ointment (appropriate dose/day, until Day 77 of administration) were given. Day 22 of administration: Hemoglobin (9.7 g/dL) decreased. The dose of ribavirin was changed (300 mg/day). Day 66 of administration: The dose of ribavirin was changed (200 mg/day). Day 71 of administration: There was no marked change at the visit. Peginterferon alfa-2b was administered. Day 72 of administration: Pyrexia of 38°C and diarrhea occurred. Day 77 of administration (day of discontinuation): Sepsis due to acute pyelonephritis was suspected. The patient was taken to hospital by ambulance at night. She had body temperature of 39°C, feeling groggy, and state of dehydration (dry tongue). Transfusion, administration of antibiotics and gabexate mesilate were started immediately. Blood culture showed E. coli. Administration of telaprevir and ribavirin was discontinued. 1 day after discontinuation: Scheduled administration of peginterferon alfa-2b was discontinued. 16 days after discontinuation: Symptoms remitted after treatment with transfusion, antibiotics, and gabexate mesilate. Acute pyelonephritis resolved. 99 days after discontinuation: Decreased haemoglobin resolved (12.6 g/dL). 162 days after discontinuation: Suspected sepsis due to acute pyelonephritis resolved. 178 days after discontinuation: Skin eruption resolved.
	Concomitant medications: ribavirin (the other suspected drug), peginterferon alfa-2b (the other suspected drug), glimepiride, amlodipine besilate, loxoprofen sodium hydrate			

Laboratory Examination

	Day before administration	Day 4 of administration	Day 6 of administration	Day 8 of administration	Day 11 of administration	Day 18 of administration	Day 22 of administration	Day 29 of administration	Day 36 of administration	Day 43 of administration	Day 50 of administration
RBC (10^4/mm^3)	-	-	403	388	399	390	367	349	345	351	336
Hemoglobin (g/dL)	12.9	-	12.4	12.0	12.3	12.1	11.4	10.9	10.7	11.0	10.5
Hematocrit (%)	—	-	36.7	35.0	36.1	34.7	33.5	31.9	31.6	32.2	29.9
WBC (/mm^3)	3,500	-	3,200	2,700	2,900	3,800	3,200	3,000	3,100	2,800	4,400
Neutrophils (%)	54.5	-	50.2	44.7	44.7	56.6	52.3	51.2	52.8	53.5	64.8
Neutrophil count (/mm^3)	1,900	-	1,580	1,210	1,290	2,130	1,650	1,510	1,610	1,510	2,830
BUN (mg/dL)	15	15	17	17	13	20	15	16	17	-	-
Serum creatinine (mg/dL)	0.5	0.7	0.7	0.7	0.6	0.7	0.7	0.6	0.6	-	-
Uric acid (mg/dL)	3.7	7.4	-	6.8	6.8	8.8	7.1	6.7	6.0	-	-
Na (mEq/L)	-	-	-	-	-	-	-	137.6	-	-	-
K (mEq/L)	-	-	-	-	-	-	-	3.4	-	-	-
Cl (mEq/L)	-	-	-	-	-	-	-	99	-	-	-
Ca (mg/dL)	-	-	-	-	-	-	-	9.0	-	-	-

	Day 57 of administration	Day 64 of administration (day of onset of decreased Hb)	Day 71 of administration	Day 77 of administration (day of discontinuation) (day of onset of suspected sepsis)	1 day after discontinuation	8 days after discontinuation	36 days after discontinuation	71 days after discontinuation	99 days after discontinuation (day of recovery of Hb)	162 days after discontinuation (day of resolution of suspected sepsis)
RBC (10^4/mm^3)	347	308	298	302	283	-	-	-	-	-
Hemoglobin (g/dL)	11.0	9.7	9.5	9.6	8.9	9.4	-	-	12.6	-
Hematocrit (%)	31.2	28.1	28.4	28.3	26.7	-	-	-	-	-
WBC (/mm^3)	6,700	2,900	4,000	22,700	20,200	6,500	6,500	5,000	-	4,800
Neutrophils (%)	82.3	64.2	65.6	95.8	95.4	54.4	54.4	56	-	-
Neutrophil count (/mm^3)	5,500	1,880	2,620	21,690	19,240	3,550	3,550	2,780	-	-
PT	-	-	-	13.0	14.7	-	-	-	-	-
PT (%)	-	-	-	75.0	61.9	-	-	-	-	-
PT-INR	-	-	-	1.16	1.31	-	-	-	-	-
Fibrinogen (mg/dL)	-	-	-	-	494	-	-	-	-	-
Fibrin degradation products (μg/dL)	-	-	-	-	11.4	-	-	-	-	-
BUN (mg/dL)	16	14	12	72	82	45	-	-	-	-
Serum creatinine (mg/dL)	0.9	0.7	0.7	3.9	4.5	0.9	0.9	1	-	-
CRP (mg/dL)	-	-	-	26.46	26.70	-	-	-	-	-
Uric acid (mg/dL)	6.9	5.7	5.1	13.3	14.5	5.9	5.9	5.9	-	-
Na (mEq/L)	133.7	-	-	137.1	140.8	-	-	-	-	-
K (mEq/L)	3.9	-	-	3.4	1.8	-	-	-	-	-
Cl (mEq/L)	102	-	-	98	101	-	-	-	-	-
Ca (mg/dL)	9.9	-	-	8.2	7.8	-	-	-	-	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 50s	Improvement of viraemia in chronic hepatitis C (hyperuricaemia) (insomnia)	2,250 mg for 27 days ↓ 1,500 mg for 16 days	**Interstitial pneumonia** Day 1 of administration: The patient started receiving telaprevir (2,250 mg/day), peginterferon alfa-2b (1.5 μg/kg/week), ribavirin (800 mg/day) (triple combination therapy). Day 28 of administration: The dose of telaprevir was changed (1,500 mg/day). Day 43 of administration (day of discontinuation): As a periodic outpatient visit day, the 7th dosing of peginterferon alfa-2b was scheduled, but the patient complained that cough started several days before. Chest X-ray and chest CT showed reticular and ground-glass opacities in both lung fields. KL−6 increased to 1,444 (U/mL), the patient was diagnosed with interstitial pneumonia. On the same day, the patient visited the respiratory department. Administration of telaprevir, ribavirin, and peginterferon alfa-2b was discontinued, and the patient underwent a follow-up observation. [Clinical symptoms] Cough, Yes; Sputum, No; Pyrexia, No; Dyspnoea, No; Swollen lymph nodes, - ; Adventitious sound (crepitations, moist rales, etc.), Crepitations; Dehydration, No; Disturbed consciousness, No 14 days after discontinuation: No changes were noted on images (chest X-ray), follow-up observation was continued. 77 days after discontinuation: [Chest X-ray findings] Shadow, Abnormal; Site, Bilateral lower lung fields; Type, ground-glass opacities (diffuse); Spread of opacities, Proportion of the spread of opacities in one lung was up to 1/3. [Clinical symptoms] Cough, Yes; Sputum, No; Pyrexia, No; Dyspnoea, No; Swollen lymph nodes, - ; Adventitious sound (crepitations, moist rales, etc.), Crepitations; Dehydration, No; Disturbed consciousness, No 196 days after discontinuation: [Chest X-ray findings] Mild improvement was found compared to the condition of 77 days after discontinuation. [Clinical symptoms] No 301 days after discontinuation: [Chest X-ray findings] No change from the condition of 196 days after discontinuation. [Clinical symptoms] No Interstitial pneumonia remitted.
	Concomitant medications: peginterferon alfa-2b (the other suspected drug), ribavirin, allopurinol, zolpidem tartrate			

Laboratory Examination

	Day 43 of administration (at onset of adverse reaction)	14 days after discontinuation	77 days after discontinuation
KL-6 (U/mL)	1,444	1,501	1,228

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Female 60s	Improvement of viraemia in chronic hepatitis C (angina pectoris) (hypertension) (insomnia) (intracranial aneurysm) (peripheral arterial occlusive disease) (gastritis) (gastrooesophageal reflux disease)	1,500 mg for 18 days	**Skin eruption, renal failure, decreased platelets, cystitis, haemorrhage of digestive tract, general malaise, decreased haemoglobin** Medical history: Depression. Oral treatment with clopidogrel sulfate 1 tablet/day for peripheral arterial occlusive disease. Day 1 of administration: The patient started receiving telaprevir (1,500 mg/day), ribavirin (400 mg/day), and peginterferon alfa-2b (1.5 μg/kg/week) (triple combination therapy). Day 4 of administration: Skin eruption (Grade 1) appeared. [Severity] Grade 1: 50% or less of body surface area (localized) [Pruritus] No Day 5 of administration: Clobetasol propionate was prescribed. Impaired appetite and diarrhea occurred. Day 7 of administration: Renal failure and decreased platelets occurred. Creatinine mildly increased to 1.18 (mg/dL). Day 9 of administration: Skin eruption tended to increase. Both diarrhoea and impaired appetite improved. Day 12 of administration: Cystitis occurred. Pollakiuria was noted. Cefcapene pivoxil hydrochloride hydrate was prescribed. Day 14 of administration: Cystitis improved and remitted. (The condition was considered to be cystitis) Day 15 of administration: Haemorrhage of digestive tract and general malaise occurred. Creatinine mildly increased to 1.50 (mg/dL). Administration of peginterferon alfa-2b was discontinued. Decreased platelets remitted. Day 16 of administration: Administration of clopidogrel sulfate was discontinued. Day 17 of administration: Clipping was performed for exudation from the duodenum with gastroscope. Creatinine mildly increased to 1.56 (mg/dL). Day 18 of administration (day of discontinuation): Administration of telaprevir was discontinued. 1 day after discontinuation: Administration of ribavirin was discontinued. Decreased haemoglobin occurred. 3 days after discontinuation: Creatinine was 1.29 (mg/dL). 11 days after discontinuation: Skin eruption improved and remitted. Haemorrhage of digestive tract and decreased haemoglobin remitted. 25 days after discontinuation: Creatinine was 1.08 (mg/dL). Renal failure resolved. General malaise remitted.
	Concomitant medications: clopidogrel sulfate (the other suspected drug), ribavirin (the other suspected drug), peginterferon alpha-2b (the other suspected drug), lansoprazole, amlodipine besilate, olmesartan			

	medoxomil, rosuvastatin calcium, teprenone, nicorandil, rebamipide, trazodone hydrochloride, etizolam, zolpidem tartrate, cefcapene pivoxil hydrochloride hydrate

Laboratory Examination

	Day before administration	Day 7 of administration	Day 15 of administration (day of onset of haemorrhage of digestive tract)	1 day after discontinuation	5 days after discontinuation	11 days after discontinuation (day of remission of haemorrhage of digestive tract)
Hemoglobin (g/dL)	11.8	11.8	10.6	-	9.3	9.3
WBC (/mm^3)	6,800	2,800	3,800	-	4,700	5,600
PLT (10^4/mm^3)	14.6	10.7	16.6	-	14.2	16.4
Serum creatinine (mg/dL)	0.79	1.18	1.5	1.54	1.29	1.04
Uric acid (mg/dL)	6.5	-	-	-	9.8	7.3

	27 days after discontinuation	48 days after discontinuation	69 days after discontinuation	97 days after discontinuation	127 days after discontinuation	155 days after discontinuation
Hemoglobin (g/dL)	9.3	9.8	9.6	9.1	11.2	12.1
WBC (/mm^3)	6,400	8,000	6,300	4,900	9,300	4,200
PLT (10^4/mm^3)	16.1	16.2	15.7	13.5	17.9	14.6
Serum creatinine (mg/dL)	1.08	1.05	0.92	1.07	1.14	1.00
BUN (mg/dL)	-	22	15	-	-	-
Uric acid (mg/dL)	6.3	6.5	6.2	5.9	6.7	7.2

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Male 60s	Improvement of viraemia in chronic hepatitis C (hypertension)	2,250 mg for 22 days ↓ 1,500 mg for 14 days	**Increased serum creatinine level, hyperuricaemia, inappetence, queasy, skin eruption, depressive symptoms, decreased white blood cell, anaemia (decreased haemoglobin), duodenal ulcer** The patient was previously treated with interferon + ribavirin. Day 1 of administration: The patient started receiving telaprevir (2,250 mg/day), ribavirin (800 mg/day), and peginterferon alfa-2b (1.5 μg/kg/week) (triple combination therapy). Day 4 of administration: Increased uric acid level, increased serum creatinine level, hyperuricaemia, inappetence, and queasy occurred. Creatinine level increased to 2.94 (mg/dL). Treatment with fluid replacement was performed. Uric acid level was 14.7 (mg/dL). Treatment with allopurinol 100 mg (200 mg/day) was performed. Mosapride citrate hydrate 5 mg (15 mg/day) was orally administered. Day 6 of administration: Sulpiride 50 mg (100 mg/day, until Day 28 of administration) was orally administered. Day 8 of administration: Skin eruption (Grade 1) occurred. [Severity] Grade 1: 50% or less of body surface area

				(localized) [Pruritus] Present Rikkunshito (6 g/day, until Day 27 of administration) was orally administered and clobetasol propionate cream 0.05% (as needed) was topically administered. Day 12 of administration: Inappetence and queasy remitted by oral treatment. Day 14 of administration: Creatinine level was 2.44 (mg/dL). Uric acid level was 9.0 (mg/dL). Day 15 of administration: Skin eruption remitted. Day 23 of administration: Hyperuricaemia remitted. The dose of telaprevir was changed (1,500 mg/day). Zolpidem tartrate (10 mg/day) was orally administered. Day 26 of administration: Depressive symptoms occurred. Etizolam (2 mg/day, until Day 36 of administration) was orally administered. Day 30 of administration: Hemoglobin (Hb) level was 8.1 (g/dL). Creatinine level was 1.52 (mg/dL). The dose of ribavirin was changed (400 mg/day). White blood cell count decreased to 3,500 (/mm^3). After that, white blood cell count remained from 2,500 to a little less than 4,000 (/mm^3). No particular treatment was performed. Day 36 of administration (day of discontinuation): Administration of telaprevir and ribavirin was discontinued. 1 day after discontinuation: Anaemia (decreased haemoglobin) occurred. Anaemia progressed in outpatient settings. As depressive symptoms also increased, administration of telaprevir was discontinued. Treatment with selective serotonin reuptake inhibitor (SSRI) and others were started for depressive symptoms, and the symptoms gradually improved. The patient was admitted to the hospital due to duodenal ulcer. Creatinine level was 1.44 (mg/dL). Hb level was 5.0 (g/dL). Treatment with blood transfusion was performed. 5 days after discontinuation: Paroxetine hydrochloride hydrate (10 mg/day) and alprazolam (1.2 mg/day) were orally administered. 10 days after discontinuation: Increased creatinine level did not resolve. Administration of ribavirin 400 mg was resumed. 11 days after discontinuation: Depressive symptoms relapsed. Administration of ribavirin was discontinued. The dose of paroxetine hydrochloride hydrate was increased (20 mg/day). 12 days after discontinuation: Hb level was 11.1 (g/dL). Strong depressive symptoms occurred, paroxetine hydrochloride hydrate was administered. Creatinine level was 1.25 (mg/dL). 15 days after discontinuation: Creatinine level improved to 1.02 (mg/dL). 17 days after discontinuation: Etizolam (1 mg/day) was orally administered. 20 days after discontinuation: Creatinine level was 1.02 (mg/dL). Duodenal ulcer did not

				resolve. 29 days after discontinuation: Anaemia (decreased haemoglobin) remitted. Hb improved to 9.6 (g/dL). 32 days after discontinuation: Depressive symptoms did not resolve. The dose of paroxetine hydrochloride hydrate was increased (40 mg/day). 34 days after discontinuation: Administration of ribavirin (400 mg/day) was resumed. 47 days after discontinuation: On upper gastrointestinal endoscopy (gastrolntestinal fiberscope [GIF]), duodenal ulcer improved to S1 stage (red scar stage). Duodenal ulcer resolved. (No recurrence after that) 50 days after discontinuation: The dose of ribavirin was changed (200 mg/day). 91 days after discontinuation: The dose of ribavirin was changed (300 mg/day). 98 days after discontinuation: The dose of ribavirin was changed (400 mg/day). Depressive symptoms remitted. 112 days after discontinuation: The dose of ribavirin was changed (600 mg/day). 189 days after discontinuation: Decreased white blood cell count did not resolve. 291 days after discontinuation: White blood cell count was 1,700/mm^3, still not recovered. 357 days after discontinuation: White blood cell count recovered to 4,500/mm^3. (Decreased white blood cell resolved)
	Concomitant medications: ribavirin (suspected concomitant drug), peginterferon alpha-2b (suspected concomitant drug), magnesium oxide, zolpidem tartrate, etizolam, mosapride citrate hydrate, alprazolam, allopurinol, sodium rabeprazole, ecabet sodium hydrate, paroxetine hydrochloride hydrate			

Laboratory Examination

	Day 1 of administration	Day 4 of administration	Day 6 of administration	Day 8 of administration	Day 14 of administration	Day 15 of administration	Day 23 of administration	Day 30 of administration (day of onset of decreased white blood cell)	1 day after discontinuation (day of onset of duodenal ulcer)	3 days after discontinuation	5 days after discontinuation
Hemoglobin (g/dL)	12.9	-	10.5	-	9.4	-	10.3	8.1	5.0	8.4	11.7
WBC (/mm^3)	5,000	-	4,000	-	4,500	-	4,500	3,500	3,800	-	-
Neutrophils (%)	64.9	-	48	-	61.2	-	66.8	68.5	70.2	-	-
PLT (10^4/mm^3)	28.8	-	18.2	-	15.9	-	24.3	21.1	24.5	-	-
Serum creatinine (mg/dL)	0.89	2.94	2.45	2.22	2.44	2.46	1.63	1.52	1.44	1.16	-
BUN (mg/dL)	27.2	52.5	-	26.9	-	23.1	-	16.7	-	18.3	-
Uric acid (mg/dL)	8.8	14.7	13.3	11.5	9.0	8.9	5.1	5.8	5.1	4.3	-

	8 days after discontinuation	15 days after discontinuation	22 days after discontinuation	29 days after discontinuation	36 days after discontinuation	43 days after discontinuation	50 days after discontinuation	77 days after discontinuation	105 days after discontinuation	168 days after discontinuation	357 days after discontinu-ation (day of resolution of decreased white blood cell)
Hemoglobin (g/dL)	11.1	10.2	9.5	9.6	9.2	8.9	8.2	9.0	10.6	11.3	10.5
WBC (/mm^3)	3,400	4,400	2,900	3,400	2,900	3,100	3,400	2,600	2,500	2,600	4,500
Neutrophils (%)	53.1	58.9	55.6	58.8	55.0	57.3	62.3	-	-	-	-
PLT (10^4/mm3)	15.4	16.8	18.0	17.7	15.9	16.0	16.9	16.8	19.1	22.2	27.2
Serum creatinine (mg/dL)	1.25	1.02	0.96	1.00	0.92	1.00	0.94	0.93	0.97	0.78	0.82
Uric acid (mg/dL)	3.9	3.5	3.3	3.7	4.0	4.3	3.9	5.2	6.3	5.1	6.6

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
6	Male 60s	Improvement of viraemia in chronic hepatitis C	1,500 mg for 7 days ↓ (discontinued) ↓ 750 mg for 85 days	**Ascites, gastric ulcer** The patient was previously treated with interferon + ribavirin. Day 1 of administration: The patient started receiving telaprevir (1,500 mg/day), ribavirin (400 mg/day), and peginterferon alfa-2b (1.5 μg/kg/week) (triple combination therapy). Day 7 of administration (day of discontinuation): Administration of telaprevir and ribavirin was discontinued. 1 day after discontinuation: Inappetence occurred and total bilirubin (T-Bill) mildly increased (6.8 mg/dL). Echography showed ascites. Gastroscopy showed gastric ulcer. Spironolactone tablets (25 mg/day, until 3 days after discontinuation), furosemide tablets (40 mg/day, until 3 days after discontinuation), sodium rabeprazole tablets (2 tablets/day, continued) were orally administered. Administration of peginterferon alfa-2b was discontinued. 3 days after discontinuation: Ascites remitted. Appetite somewhat recovered. 20 days after discontinuation: Gastric ulcer remitted. 21 days after discontinuation (day of readministration): Administration of telaprevir (750 mg/day), ribavirin (200 mg/day), peginterferon alpha-2b (1.5 μg/kg/week) was resumed. Day 85 of readministration: Administration of telaprevir was discontinued.
	Concomitant medications: ribavirin, peginterferon alfa-2b			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
7	Female 60s	Improvement of viraemia in chronic hepatitis C	2,250 mg for 45 days ↓ (discontinued) ↓ 750 mg for 21 days ↓ 1000 mg for 7 days ↓ 1,250 mg for 36 days ↓ (discontinued) ↓ 750 mg for 7 days ↓ 1,000 mg for 35 days	**Hyperuricaemia, rash, decreased haemoglobin, gastric ulcer** Day 1 of administration: The patient started receiving telaprevir (2,250 mg/day), ribavirin (600 mg/day), and peginterferon alfa-2b (1.5 μg/kg/week) (triple combination therapy). Day 8 of administration: Hyperuricaemia with uric acid of 9.7 (mg/dL) occurred. Day 12 of administration: Rash appeared on bilateral upper limbs. [Severity] Grade 2: 50% or less of body surface area (multiple/diffuse) [Pruritus] Present Oral administration of fexofenadine hydrochloride 120 mg was started (until Day 42 of re-re administration). Day 15 of administration: Haemoglobin decreased to 11.8 (g/dL). The dose of ribavirin was reduced from 600 mg/day to 200 mg/day. Day 28 of administration: Rash spread over bilateral upper/lower limbs, chest, abdomen, and back. Oral administration of prednisolone (30 mg/day, until Day 16 of readministration) was started. Day 42 of administration: Rash, decreased haemoglobin, and hyperuricaemia did not resolve. Day 45 of administration (day of discontinuation): Administration of telaprevir was discontinued for the treatment of rash. 19 days after discontinuation (Day 1 of readministration): Rash remitted. Administration of telaprevir (750 mg/day) was resumed. Day 8 of readministration: The patient recovered from the rashes. Day 16 of readministration: Oral administration of prednisolone was discontinued. Day 22 of readministration: Hyperuricaemia did not resolve. Haemoglobin was 10.7 (g/dL) and decreased haemoglobin did not resolve. Uric acid was 7.8 (mg/dL) and also did not recover. The doses of telaprevir (1,000 mg/day) and ribavirin (400 mg/day) were changed. Day 29 of readministration: The dose of telaprevir (1,250 mg/day) was changed. Day 64 of readministration (discontinuation of readministration): As haemoglobin level decreased to 7.9 (g/dL), administration of all of the 3 medications were discontinued. 13 days after discontinuation of readministration: Gastroscopy was performed due to anaemia, gastric ulcer was noted, and then oral administration of sodium rabeprazole 20 mg (until Day 42 of re-re administration)

				was started. 22 days after discontinuation of readministration (Day 1 of re-re administration): Haemoglobin level improved to 10.7 (g/dL), administration of 3 agents [telaprevir (750 mg/day), ribavirin (200 mg/day), and peginterferon alfa-2b (1.5 μg/kg/week)] was resumed. Day 8 of re-re administration: The dose of telaprevir was changed (1,000 mg/day). Day 42 of re-re administration (day of completion): Triple combination therapy by 24-week administration was terminated. 1 day after completion: Gastric ulcer remitted. Decreased haemoglobin did not resolve. Uric acid was 5.2 (mg/dL) and hyperuricaemia resolved.
	Concomitant medications: ribavirin (the other suspected drug), peginterferon alpha-2b (the other suspected drug)			

Laboratory Examination

	Day before administration	Day 8 of administration	Day 15 of administration	Day 22 of administration	Day 29 of administration	Day 36 of administration	Day 43 of administration	5 days after discontinuation
Hemoglobin (g/dL)	13.3	13.5	11.8	10.3	9.6	9.8	10.6	10.0
Uric acid (mg/dL)	6.1	9.7	9.0	9.9	11.3	9.9	9.8	-

	12 days after discontinuation	19 days after discontinuation (Day 1 of readministration)	Day 8 of readministration	Day 15 of readministration	Day 22 of readministration	Day 50 of readministration	Day 12 of re-readministration	1 day after completion
Hemoglobin (g/dL)	10.3	10.4	10.4	11.0	10.7	10.9	10.9	9.6
Uric acid (mg/dL)	5.4	-	7.4	7.0	8.2	8.8	7.5	5.2

3

Revision of Precautions (No. 245)

(1) Drugs

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated March 26 and March 29, 2013 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 Antiepileptics

Gabapentin

Brand Name	GABAPEN Tablets 200 mg, 300 mg, 400 mg, GABAPEN Syrup 5% (Pfizer Japan Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Rhabdomyolysis**: Rhabdomyolysis may occur. Patients should be carefully monitored, and if symptoms including myalgia, feeling of weakness, increased CK (CPK), increased blood myoglobin, or 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.

2 Antiepileptics

Carbamazepine

Brand Name	Tegretol Tablet 100 mg, 200 mg, Tegretol Fine granule 50% (Novartis Pharma K.K.), and the others
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, erythroderma (exfoliative dermatitis):** Serious dermatological symptoms may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, ocular hyperaemia, face swelling, erosion of lips/oral mucosa or genital area, blisters on the skin or mucosa, many small pustules, erythema, pharynx pain, itching, general malaise are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. Since most of these symptoms appear within 3 months after the initiation of administration, patients should be carefully monitored, especially during the initial treatment stage.

3 Central Nervous System Agents-Miscellaneous

Gabapentin Enacarbil

Brand Name	Regnite Tablets 300 mg (Astellas Pharma Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Rhabdomyolysis**: Rhabdomyolysis may occur. Patients should be carefully monitored, and if symptoms including myalgia, feeling of weakness, increased CK (CPK), increased blood myoglobin, or 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.

4 **Diuretics, antihypertensives**

Hydrochlorothiazide
Candesartan Cilexetil/Hydrochlorothiazide
Telmisartan/Hydrochlorothiazide
Valsartan/Hydrochlorothiazide
Losartan Potassium/Hydrochlorothiazide

Brand Name

NEWTOLIDE TABLETS 12.5 mg, 25 mg (Towa Pharmaceutical Co., Ltd.)
ECARD Combination Tablets LD, HD
(Takeda Pharmaceutical Company Limited)
Micombi Combination Tablets AP, BP (Nippon Boehringer Ingelheim Co., Ltd)
Co-DIO Combination Tablets MD, EX (Novartis Pharma K.K.)
PREMINENT Tablets (MSD K.K.)

Adverse Reactions (clinically significant adverse reactions)

Acute myopia, angle closure glaucoma: Acute myopia (including blurred vision, reduced visual acuity, etc.) or angle closure glaucoma may occur. Patients should be instructed to discontinue the drug and immediately consult an ophthalmologist if any abnormalities such as rapid reduced visual acuity and eye pain are observed.

5 **Antitussives, antitussives and expectorants**

Dihydrocodeine Phosphate/dl-methylephedrine Hydrochloride/ Chlorpheniramine Maleate
Platycodon Fluidextract/Glycyrrhiza Extract/Plantago Herb Extract/Peony Root Extract/Dihydrocodeine Phosphate
Dihydrocodeine Phosphate/Ephedrine Hydrochloride/ Ammonium Chloride

Brand Name

CHLOPHEDRIN S Combination Syrup, CHLOPHEDRIN S Combination Tablets, CHLOPHEDRIN S Combination Powder (Kyorin Rimedio Co., Ltd.), Huscode Combination Tablets, Huscode Combination Syrup (Abbott Japan Co., Ltd.), Lightgen Combination Syrup (Teijin Pharma Limited), HUSTEN SYRUP (Dojin Iyaku-kako Co., Ltd.), MIZERON Combination Syrup (Isei Co., Inc.) and the others
OPISEZOL CODEINE Solution (Nichi-Iko Pharmaceutical Co., Ltd.)
SEKICODE Combination Syrup (Nichi-iko Pharmaceutical Co., Ltd.)

Interaction

Dihydrocodeine phosphate contained in this drug is mainly metabolized by the hepatic drug-metabolizing enzymes UGT2B7, UGT2B4, and partially by CYP3A4 and CYP2D6.

Use in Pregnant, Parturient And Nursing Women

Nursing mothers should discontinue breast-feeding during treatment with the drug. [It has been reported that a similar compound of dihydrocodeine phosphate (codeine) was excreted in breast milk, which resulted in morphine intoxication (somnolence, feeding difficulty, dyspnoea, etc.) in the infant. In patients found to have excessive activity of CYP2D6 (ultra-rapid metabolizer), the concentration of dihydromorphine in breast milk may increase.]

Other Precautions

In patients found to have excessive activity of CYP2D6 genetically (ultra-rapid metabolizer), the blood concentration of dihydromorphine, which is an active metabolite of dihydrocodeine phosphate contained in this drug, may increase, thereby possibly easily causing adverse reactions.

6 Antitussives

Diprophylline/Dihydrocodeine Phosphate/dl-Methylephedrine Hydrochloride/Diphenhydramine Salicylate/ Acetaminophen/Bromovalerylurea

Brand Name	Coughcode-N Combination Tablets (Pfizer Japan Inc.)
Interaction	Dihydrocodeine phosphate contained in this drug is mainly metabolized by the hepatic drug-metabolizing enzymes UGT2B7, UGT2B4, and partially by CYP3A4 and CYP2D6.
Use in Pregnant, Parturient And Nursing Women	Nursing mothers should discontinue breast-feeding during treatment with the drug. [It has been reported that a similar compound of dihydrocodeine (codeine) was excreted in breast milk, which resulted in morphine intoxication (somnolence, feeding difficulty, dyspnoea, etc.) in the infant. In patients found to have excessive activity of CYP2D6 (ultra-rapid metabolizer), the concentration of dihydromorphine in breast milk may increase. Animal studies in rats have shown that diphenhydramine is excreted in milk.]
Other Precautions	In patients found to have excessive activity of CYP2D6 genetically (ultra-rapid metabolizer), the blood concentration of dihydromorphine, which is an active metabolite of dihydrocodeine phosphate contained in this drug, may increase, thereby possibly easily causing adverse reactions.

7 Antitussives and expectorants

Cherry Bark Extract/Codeine Phosphate Hydrate

Brand Name	BROCIN-CODEINE COMBINATION SYRUP, Conc. (Daiichi Sankyo Company, Limited), and the others
Interaction	Codeine phosphate hydrate contained in this drug is mainly metabolized by the hepatic drug-metabolizing enzymes UGT2B7, UGT2B4, and partially by CYP3A4 and CYP2D6.
Use in Pregnant, Parturient And Nursing Women	Nursing mothers should discontinue breast-feeding during treatment with the drug. [It has been reported that the drug was excreted in breast milk, which resulted in morphine intoxication (somnolence, feeding difficulty, dyspnoea, etc.) in the infant. In patients found to have excessive activity of CYP2D6 (ultra-rapid metabolizer), the concentration of morphine in breast milk may increase.]
Other Precautions	In patients found to have excessive activity of CYP2D6 genetically (ultra-rapid metabolizer), the blood concentration of morphine, which is an active metabolite of codeine phosphate hydrate contained in this drug, may increase, thereby possibly easily causing adverse reactions.

8 Antitussives and expectorants, opium alkaloids

Codeine Phosphate Hydrate

Brand Name	1% CODEINE PHOSPHATE POWDER "Takeda," CODEINE PHOSPHATE TABLETS 20 mg "Takeda," 10% CODEINE PHOSPHATE POWDER "Takeda," CODEINE PHOSPHATE HYDRATE "Takeda" (Takeda Pharmaceutical Company Limited), and the others
Interaction	This drug is mainly metabolized by the hepatic drug-metabolizing enzymes UGT2B7, UGT2B4, and partially by CYP3A4 and CYP2D6.
Use in Pregnant, Parturient And	Nursing mothers should discontinue breast-feeding during treatment with the drug. [It has been reported that the drug was excreted in breast milk, which resulted

Nursing Women	in morphine intoxication (somnolence, feeding difficulty, dyspnoea, etc.) in the infant. In patients found to have excessive activity of CYP2D6 (ultra-rapid metabolizer), the concentration of morphine in breast milk may increase.]
Other Precautions	In patients found to have excessive activity of CYP2D6 genetically (ultra-rapid metabolizer), the blood concentration of morphine, which is an active metabolite of this drug, may increase, thereby possibly easily causing adverse reactions.

9 **Antitussives and expectorants, opium alkaloids**

Dihydrocodeine Phosphate

Brand Name	1% DIHYDROCODEINE PHOSPHATE POWDER "Takeda," DIHYDROCODEINE PHOSPHATE 10% POWDER "Takeda" (Takeda Pharmaceutical Company Limited) and the others
Interaction	This drug is mainly metabolized by the hepatic drug-metabolizing enzymes UGT2B7, UGT2B4, and partially by CYP3A4 and CYP2D6.
Use in Pregnant, Parturient And Nursing Women	Nursing mothers should discontinue breast-feeding during treatment with the drug. [It has been reported that a similar compound (codeine) was excreted in breast milk, which resulted in morphine intoxication (somnolence, feeding difficulty, dyspnoea, etc.) in the infant. In patients found to have excessive activity of CYP2D6 (ultra-rapid metabolizer), the concentration of dihydromorphine in breast milk may increase.]
Other Precautions	In patients found to have excessive activity of CYP2D6 genetically (ultra-rapid metabolizer), the blood concentration of dihydromorphine, which is an active metabolite of this drug, may increase, thereby possibly easily causing adverse reactions.

10 **Miscellaneous metabolism agents-Miscellaneous**

Denosumab (Genetical Recombination)

Brand Name	RANMARK SUBCUTANEOUS INJECTION 120 mg (Daiichi Sankyo Company, Limited)
Important Precautions	It is reported that nontraumatic atypical fracture of subtrochanteric femur and proximal femoral shaft occurred in patients treated with this drug or bisphosphonate long-term. In some of these reports, precursor pain in the femur, inguinal, or other areas starts several weeks to months before a complete fracture. If such symptoms are observed after the start of administration of this drug, X-ray examination, etc. should be performed, and appropriate measures should be taken. In addition, a bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the other femur and performing an X-ray examination. Characteristic findings such as a thickened bone cortex have been noted in X-rays. If such symptoms are observed, appropriate measures should be taken.
Adverse Reactions (clinically significant adverse reactions)	**Anaphylaxis**: Anaphylaxis 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. **Atypical fracture of subtrochanteric femur and proximal femoral shaft**: Atypical fracture of subtrochanteric femur and proximal femoral shaft may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

11 **Antineoplastics-Miscellaneous**

Sorafenib Tosilate

Brand Name

Nexavar Tablet 200 mg (Bayer Yakuhin, Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Nephrotic syndrome, proteinuria: Nephrotic syndrome or proteinuria may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Hyponatraemia: Hyponatraemia with disturbed consciousness, general malaise, vomiting, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

12 **Antineoplastics-Miscellaneous**

Panitumumab (Genetical Recombination)

Brand Name

Vectibix Intravenous Infusion 100 mg, 400 mg
(Takeda Pharmaceutical Company Limited)

Adverse Reactions (clinically significant adverse reactions)

Hypomagnesaemia: Hypomagnesaemia with symptoms including prolonged QT, convulsion, numbness, general malaise, etc. may occur. Patients should be carefully monitored by checking serum electrolyte levels and careful attention should be exercised for the occurrence of symptoms. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. If the condition is associated with any electrolyte abnormalities such as hypocalcaemia and hypokalaemia as caused by hypomagnesaemia, attention should be paid, particularly because symptoms may be aggravated.

13 **Acting mainly on gram-positive and gram-negative bacteria**

Doripenem Hydrate

Brand Name

FINIBAX for Intravenous Infusion 0.25 g, 0.5 g, FINIBAX Kit for Intravenous Infusion 0.25 g (Shionogi & Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Convulsion, disturbed consciousness: Central nervous system symptoms such as convulsion and disturbed consciousness may occur. Patients should be carefully monitored and if these symptoms are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. As these symptoms are likely to occur especially in patients with a renal disorder or central nervous system disorder such as cerebrovascular disorder, attention should be paid if this drug is administered.

14 **Biological preparations-Miscellaneous**

Interferon Beta-1b (Genetical Recombination)

Brand Name

BETAFERON SC inj. 960 (Bayer Yakuhin, Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Autoimmune phenomena: Symptoms/signs which was considered to be autoimmune phenomena [autoimmune hepatitis, systemic lupus erythematosus, aggravation or onset of type 1 diabetes mellitus] 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.

Nephrotic syndrome: Serious proteinuria with decreased serum total protein and/or decreased serum albumin may occur. Urine tests (urine protein) should be periodically performed. If any abnormalities are observed, appropriate measures such as dose reduction or drug suspension should be taken.

15 Psychotropics

Escitalopram Oxalate

Brand Name	LEXAPRO Tab. 10 mg (Mochida Pharmaceutical Co., Ltd.)
Precautions of Indications	In an overseas placebo-controlled clinical study conducted in patients with major depressive disorder aged 6-17 years, it has been reported that the efficacy could not be confirmed in patients aged 6-11 years. When administrating this drug to patients with major depressive disorder aged under 12 years, the indication should be carefully considered.
Pediatric use	In an overseas placebo-controlled clinical study conducted in patients with major depressive disorder (classification in DSM-IV*) aged 6-17 years, it has been reported that the efficacy could not be confirmed in patients aged 6-11 years. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition by the American Psychiatric Association

16 Psychotropics

Sertraline Hydrochloride

Brand Name	J ZOLOFT Tablets 25 mg, 50 mg (Pfizer Japan Inc.)
Precautions of Indications	In an overseas placebo-controlled clinical study conducted in patients with major depressive disorder aged 6-17 years, it has been reported that the efficacy could not be confirmed. When administrating this drug to patients with major depressive disorder aged under 18 years, the indication should be carefully considered.
Pediatric use	In an overseas placebo-controlled, double-blind clinical study conducted in patients with major depressive disorder (classification in DSM-IV*) aged 6-17 years, it has been reported that the efficacy could not be confirmed. In addition, The incidence of suicide attempt observed in the group treated with this drug [1.1% (2/189 patients)] was the same as that in the placebo group [1.1% (2/184 patients)], and suicidal ideation was observed in 1.6% of patients in the group treated with this drug (3/189 patients). The relationship between these events and this drug is not clear. (Overseas, this drug is not indicated for pediatric patients with major depressive disorder.) *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition by the American Psychiatric Association

17 Psychotropics

Duloxetine Hydrochloride

Brand Name	Cymbalta Capsules 20 mg, 30 mg (Shionogi & Co., Ltd.)
Precautions of Indications	In an overseas placebo-controlled clinical study conducted in patients with major depressive disorder aged 7-17 years, it has been reported that the efficacy could not be confirmed. When administrating this drug to patients with major depressive disorder aged under 18 years, the indication should be carefully considered.
Pediatric use	In an overseas placebo-controlled clinical study conducted in patients with major depressive disorder (classification in DSM-IV-TR*) aged 7-17 years, it has been reported that the efficacy could not be confirmed. *DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision by the American Psychiatric Association

18 **Psychotropics**

Fluvoxamine Maleate

Brand Name	DEPROMEL TABLETS 25, 50, 75 (Meiji Seika Pharma Co., Ltd.), Luvox Tablets 25, 50, 75 (Abbott Japan Co., Ltd.)
Precautions of Indications	For similar drugs, in an overseas placebo-controlled clinical study conducted in patients with major depressive disorder aged under 18 years, it has been reported that the efficacy could not be confirmed. When administrating this drug to patients with major depressive disorder aged 18 years and younger, the indication should be carefully considered.
Pediatric use	For similar drugs, in an overseas placebo-controlled clinical study conducted in patients with major depressive disorder (classification in DSM-IV) aged 18 years and younger, it has been reported that the efficacy could not be confirmed.

19 **Psychotropics**

Mirtazapine

Brand Name	REFLEX TABLETS 15 mg (Meiji Seika Pharma Co., Ltd.), REMERON Tablets 15 mg (MSD K.K.)
Precautions of Indications	In an overseas placebo-controlled clinical study conducted in patients with major depressive disorder aged 7-17 years, it has been reported that the efficacy could not be confirmed. When administrating this drug to patients with major depressive disorder aged under 18 years, the indication should be carefully considered.
Pediatric use	In an overseas placebo-controlled clinical study conducted in patients with major depressive disorder (classification in DSM-IV*) aged 7-17 years, it has been reported that the efficacy could not be confirmed. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition by the American Psychiatric Association

20 **Psychotropics**

Milnacipran Hydrochloride

Brand Name	Toledomin Tablets 12.5 mg, 15 mg, 25 mg, 50 mg (Asahi Kasei Pharma Corporation) and the others
Precautions of Indications	For similar drugs, in an overseas placebo-controlled clinical study conducted in patients with major depressive disorder aged less than 18 years, it has been reported that the efficacy could not be confirmed. When administrating this drug to patients with major depressive disorder aged under 18 years, the indication should be carefully considered.
Careful Administration	Patients with hypertension
Important Precautions	Hypertensive crisis or increased blood pressure may occur. Blood pressure, pulse rate, etc. should be measured appropriately, and if any abnormalities are observed, appropriate measures such as dose reduction, drug suspension or discontinuation should be taken. Particularly for patients with hypertension or heart disorder, periodic measurements should be performed.
Adverse Reactions (clinically significant adverse reactions)	**Hypertensive crisis**: Hypertensive crisis may occur. This drug should be carefully administered by monitoring changes in blood pressure, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Pediatric use	For similar drugs, in an overseas placebo-controlled clinical study conducted in patients with major depressive disorder (classification in DSM-IV*) aged 18 years and younger, it has been reported that the efficacy could not be confirmed. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition by the American Psychiatric Association

(2) Medical Devices

This section presents details of revisions to the Precautions section of package inserts and brand names of medical devices that have been revised in accordance with the Notifications dated March 19, 2013.

1 Implantable Cardiac Pacemaker, Biventricular Pacing Pulse Generator without Defibrillator Function

Important Precautions

Battery chargers for electric cars (including plug-in hybrid cars) may temporarily influence the pacing output of this product. Patients should be instructed to pay attention to the following points.

(1) Patients should not use quick chargers for electric cars.
(2) Patients should stay away from places where a quick charger is installed as much as possible.
If patients carelessly get near to such a place, they should leave the place quickly without pausing.
(3) If patients use an ordinary battery charger for electric cars, they should not assume a position where they may get close to the charging station or charging cable during recharging.

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 new drugs. 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 drugs in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of May 1, 2013)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Paromomycin Sulfate AMEPAROMO capsules 250 mg	Pfizer Japan Inc.	April 12, 2013
Botulinum Toxin Type B NerBloc for Intramuscular Injection 2500 Units	Eisai Co., Ltd.	March 27, 2013
Desmopressin Acetate Hydrate*[1] MINIRINMELT OD Tablet 60 μg	Ferring Pharmaceuticals Co., Ltd.	March 25, 2013
Regorafenib Hydrate Stivarga tablets 40 mg	Bayer Yakuhin, Ltd.	March 25, 2013
Methadone Hydrochloride METHAPAIN Tablets 5 mg, 10 mg	Teikoku Seiyaku Co., Ltd.	March 25, 2013
Fesoterodine Fumarate Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	March 15, 2013
Certolizumab Pegol (Genetical Recombination) Cimzia 200 mg Syringe for S.C. Injection	UCB Japan Co. Ltd	March 8, 2013
Insulin Degludec (Genetical Recombination) TRESIBA Injection FlexTouch, TRESIBA Injection Penfill	Novo Nordisk Pharma Ltd.	March 7, 2013
Monobasic sodium phosphate monohydrate/Dibasic sodium phosphate anhydrous*[2] Phosribbon Combination Granules	Zeria Pharmaceutical Co., Ltd.	March 4, 2013
Fexofenadine Hydrochloride/Pseudoephedrine Hydrochloride dellegra Combination Tablets	Sanofi K.K.	February 28, 2013
Sodium Risedronate Hydrate BENET Tablets 75 mg.	Takeda Pharmaceutical Company Limited	February 28, 2013
Sodium Risedronate Hydrate Actonel Tab. 75 mg	Ajinomoto Pharmaceuticals Co., Ltd.	February 28, 2013
Rotigotine Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013
Levocarnitine L-Cartin FF oral solution 10%, L-Cartin FF injection 1000 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013

Apixaban Eliquis tablets 2.5 mg, 5 mg	Bristol-Myers K.K.	February 26, 2013
Atovaquone/Proguanil Hydrochloride Malarone Combination Tablets	GlaxoSmithKline K.K.	February 22, 2013
Tetrabenazine CHOREAZINE Tablets 12.5 mg	Alfresa Pharma Corporation	February 22, 2013
Famciclovir Famvir Tab. 250 mg*[3]	Asahi Kasei Pharma Corporation	February 21, 2013
Sodium Phenylbutyrate Buphenyl Tablets 500 mg, Buphenyl Granules 94%	Orphan Pacific, Inc.	January 17, 2013
Lanreotide Acetate Somatuline 60 mg for s.c. Injection, Somatuline 90 mg for s.c. Injection, Somatuline 120 mg for s.c. Injection	Teijin Pharma Limited.	January 17, 2013
Omega-3-acid ethyl esters LOTRIGA Granular Capsule 2 g	Takeda Pharmaceutical Company Limited	January 10, 2013
Carmustine Gliadel 7.7 mg Implant	Nobelpharma Co., Ltd.	January 9, 2013
Tobramycin TOBI Inhalation solution 300 mg	Novartis Pharma K.K.	January 9, 2013
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg*[4]	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012
Irbesartan/Amlodipine Besilate AIMIX Combination Tablet LD, HD	Dainippon Sumitomo Pharma Co., Ltd.	December 19, 2012
Olanzapine Zyprexa Rapid Acting Intra-Muscular Injection 10 mg	Eli Lilly Japan K.K.	December 3, 2012
Anagliptin SUINY Tab. 100 mg	Sanwa Kagaku Kenkyusho Co., Ltd.	November 30, 2012
Stiripentol DIACOMIT DRYSYRUP 250 mg, 500 mg, DIACOMIT CAPSULES 250 mg	Meiji Seika Pharma Co., Ltd	November 27, 2012
Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL	Bayer Yakuhin, Ltd.	November 27, 2012
Glycopyrronium Bromide seebri inhalation capsules 50 μg	Novartis Pharma K.K.	November 22, 2012
Lubiprostone Amitiza Capsules 24 μg	Sucampo Pharma Ltd.	November 22, 2012
Tigecycline Tygacil Injection 50 mg	Pfizer Japan Inc.	November 22, 2012
Botulinum Toxin Type A BOTOX for injection 50 Unit, 100Unit*[5]	GlaxoSmithKline K.K.	November 21, 2012
Everolimus AFINITOR tablets 5 mg, 2.5 mg*[6], AFINITOR dispersible tablets 2 mg, 3 mg*[7]	Novartis Pharma K.K.	November 21, 2012
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg*[8]	Wakamoto Co., Ltd.	November 21, 2012
Pazopanib Hydrochloride Votrient Tablets 200 mg	GlaxoSmithKline K.K.	September 28, 2012

*1 An additional indication for “treatment of patients with central diabetes insipidus”

*2 An additional indication for “treatment of patients with hypophosphataemia”

*3 An additional indication for “treatment of patients with herpes simplex”

*4 An additional indication for “treatment of patients with central diabetes insipidus”

*5 An additional indication for “treatment of patients with severe primary axillary hyperhidrosis”

*6 An additional indication for “treatment of patients with renal angiomyolipoma associated with tuberous sclerosis, subependymal giant cell astrocytoma associated with tuberous sclerosis”

*7 An additional indication for “treatment of patients with subependymal giant cell astrocytoma associated with tuberous sclerosis”

*8 An additional indication for “treatment of patients with diabetic macular oedema”