Pharmaceuticals and Medical Devices Safety Information

No. 303 July 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. 303 July 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

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)
ASTM	American Society for Testing and Materials
BUN	Blood urea nitrogen
CHDF	Continuous hemodiafiltration
CK(CPK)	Creatine kinase (Creatine phosphokinase)
CRP	C-reactive protein
Crn	Creatinine
CT	Computed tomography
DBP	Diastolic blood pressure
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
EPPV	Early Post-marketing Phase Vigilance
FDP	Fibrin/fibrinogen degradation product
FLAIR	Fluid attenuated inversion recovery
HBe	Hepatitis B envelope
HBs	Hepatitis B surface
HBs-Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus-Deoxyribonucleic acid
HCV	Hepatitis C virus
HCV-RNA	Hepatitis C virus-Ribonucleic acid
ICU	Intensive care unit
IL-28B SNPs	Interleukin-28B single nucleotide polymorphism
ISO	International Organization for Standardization
IU	International unit
JCS	Japan Coma Scale
JIRA	Japan Medical Imaging and Radiological Systems Industries Association
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
PE	Plasma exchange
PLT	Platelet
PRES	Posterior reversible leukoencephalopathy syndrome
PT	Prothrombin Time
PT/INR	Prothrombin time - international normalized ratio
RBC	Red blood cell count
SAH	Subarachnoid haemorrhage
SBP	Systolic blood pressure
SpO_2	Oxygen saturation
T-Bil	Total bilirubin
TC	Paclitaxel plus carboplatin
TTT	Thymol turbidity test
US	Ultrasonography
WBC	White blood cell count
X-P	X-ray photograph
ZTT	Zinc sulfate turbidity test
γ-GTP	gamma-glutamyl transpeptidase

1

Tolvaptan and Hepatic Dysfunction

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Tolvaptan	Samsca tablets 7.5 mg, 15 mg (Otsuka Pharmaceutical Co., Ltd.)
Therapeutic Category	Diuretics	
Indications	Fluid retention in patients with cardiac failure, which is not adequately responsive to other diuretics such as loop diuretics	

1. Introduction

Tolvaptan (Samsca Tablets 7.5 mg, 15 mg) is a nonpeptide vasopressin V_2-receptor antagonist with an action to selectively block the binding of the antidiuretic hormone vasopressin to the V_2-receptors in the collecting duct of the kidney. In Japan, tolvaptan was approved in October 2010 for the indication, "fluid retention in patients with cardiac failure, which is not adequately responsive to diuretics including loop diuretics." The Marketing Authorization Holder (MAH) has estimated that tolvaptan is used in approximately 39,000 patients (2012) each year.

Serious hepatic dysfunction has been reported after treatment with tolvaptan in Japan and overseas. The package insert of tolvaptan has already included an alert on hepatic dysfunction. Nonetheless, in order to provide information on the proper use of tolvaptan, details of a revision of the Precautions concerning hepatic dysfunction and cases of hepatic dysfunction are provided in this section.

2. Tolvaptan-induced Hepatic dysfunction

In the results of Japanese clinical trials submitted for the review of tolvaptan, there was no report on adverse drug reactions related to serious hepatic dysfunction caused by tolvaptan so that no precaution on hepatic dysfunction was provided in the package insert at the time of approval[1)].

In September 2012, however, cases of hepatic dysfunction related to tolvaptan were reported in Japan; thus, "hepatic dysfunction, increased AST (GOT), increased ALT (GPT), increased γ-GTP, increased Al-P, and increased bilirubin" were added in the "Other adverse reactions" section of the Japanese package insert.

Thereafter in January 2013, serious hepatic dysfunction was reported in another case where a causal relationship to tolvaptan cannot be ruled out. Consequently, PMDA started to review the necessity for an additional alert on hepatic dysfunction with tolvaptan use. As a result, 6 cases of hepatic dysfunction-related events, for which a causal relationship to tolvaptan cannot be ruled out, were identified in Japan. In April 2013, MHLW required the MAH to include possible hepatic dysfunction in the "Clinically significant adverse reactions."

Furthermore, the MAH reevaluated the onset period of hepatic dysfunction in the Japanese patients (including those who were reviewed at the time of adding hepatic dysfunction in the "Clinically significant adverse reactions" section). The results revealed that hepatic dysfunction occurred from the beginning of tolvaptan treatment in Japanese post-marketing reports of adverse drug reactions (**See Figure**.); therefore, PMDA instructed the MAH to prepare educational materials for healthcare professionals and present them on PMDA's website. The MAH prepared an information document on the proper use with respect to frequency of monitoring and measures to avoid clinically significant hepatic dysfunction and provided it to medical institutions in May 2013[2)].

In July 2013, in order to identify hepatic dysfunction as soon as possible, MHLW ordered the MAH to state in the "Important Precautions" section of the package insert that liver function tests should be performed before treatment initiation and frequently during at least the first 2 weeks after the start of the treatment. In addition, MHLW required the MAH to add the results of studies in patients with autosomal dominant polycystic kidney disease conducted in 15 countries including Japan in the "Other Precautions" section in consideration of hepatic function risks during long-term treatment being noted although it is an off-label indication in Japan.

3. Occurrence of hepatic dysfunction associated with tolvaptan

During the period from December 2010 when tolvaptan was launched to May 17, 2013, 27 cases of serious hepatic dysfunction including 5 deaths were reported. Of these, out of the eight cases (no fatal cases) where a causal relationship to tolvaptan cannot be ruled out, one case is presented below.

Case of hepatic dysfunction where a causal relationship to tolvaptan cannot be ruled out

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Cognitive cardiac failure (Heart valve incompetence)	7.5 mg 9 days	**Liver disorder** Month of starting administration: The patient was admitted to hospital due to congestive cardiac failure. Treatment with catecholamine, a vasodilator, and diuretic was started, but she showed treatment resistance. Day 1 of administration: Administration of tolvaptan 7.5 mg/day was started. Day 8 of administration: Abdominal ultrasonography (US) showed no organic disease of the hepatobiliary system. Day 9 of administration (day of discontinuation): The patient complained of abdominal pain. Hematological findings revealed increases in hepatobiliary enzymes. Alanine aminotransferase (ALT) 884U/L, aspartate aminotransferase (AST) 2006U/L, total bilirubin (T-Bil) 3.0 mg/dL, and creatinine (Crn) 2.04 mg/ dL. Hepatic disorder and renal impairment developed. Drug-induced liver disorder was suspected so that administration of tolvaptan was discontinued. Chest/abdominal computed tomography (CT) showed no organic disease of the hepatobiliary system. After discontinuation of tolvaptan, the hepatic function tended to improve. The abdominal pain was suspected of being associated with ischemic enterocolitis, but abdominal ultrasonography revealed no suggestive findings. 3 days after discontinuation: Abdominal X-ray photograph (X-P) showed excess gas in the intestinal tract. Subileus occurred. Administration of glycyrrhizin/glycine/L-cysteine 60 mL was started for hepatitis. 10 days after discontinuation: Renal impairment improved. 12 days after discontinuation: Hepatic disorder improved. 24 days after discontinuation: Abdominal contrast-enhanced CT revealed no organic disease of the hepatobiliary system (diagnosis of hepatic embolism

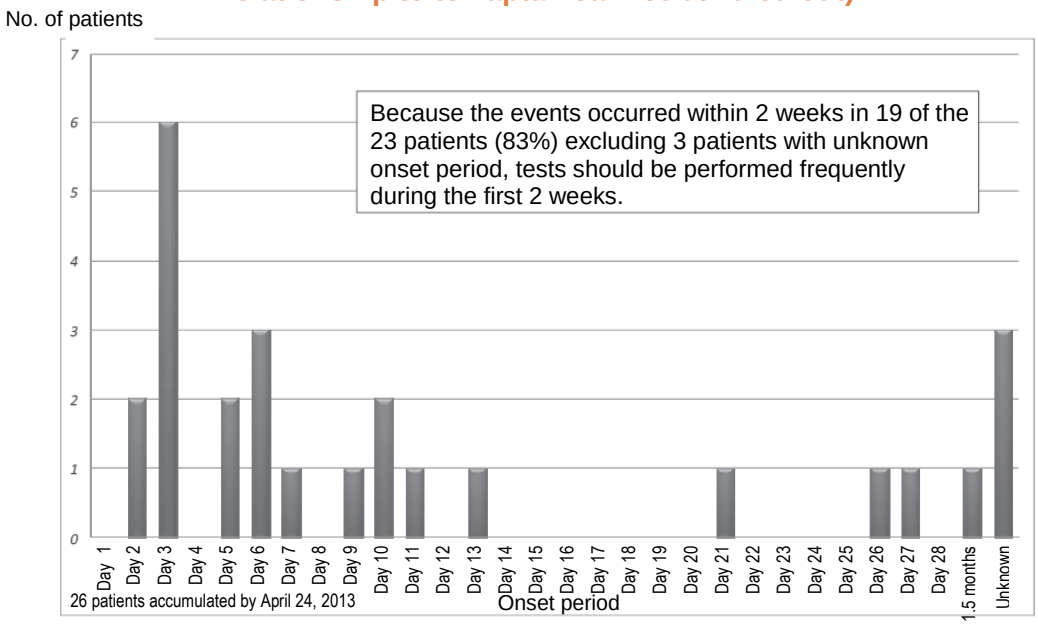
				seems to have been ruled out) and suggested ischemic enterocolitis of the descending colon. 62 days after discontinuation: The patient recovered from subileus. The outcome of abdominal pain was unknown.
	Concomitant medications: spironolactone, warfarin potassium, furosemide, famotidine, folic acid, tocopheryl acetate, sodium ferrous citrate			

Laboratory Examination

	7 days before administration	Day 1 of administration	Day 5 of administration	Day 9 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	5 days after discontinuation	7 days after discontinuation	9 days after discontinuation	10 days after discontinuation	11 days after discontinuation
AST (GOT) (IU/L)	41	35	37	2,006	1,469	815	376	154	89	81	76
ALT (GPT) (IU/L)	12	9	9	884	1,121	796	509	258	150	125	108
γ-GTP (IU/L)	45	37	42	91	103	85	73	62	65	71	84
Al-P (IU/L)	220	220	284	530	522	451	400	337	341	368	413
LDH (IU/L)	667	687	788	3,549	2,135	1,212	972	811	709	744	748
Total bilirubin (mg/dL)	0.8	0.9	1	3	2.1	2.7	2.8	1.7	1.1	2.1	1.6

The onset period of 26 cases of serious hepatic dysfunction obtained by the MAH by April 24, 2013 was as shown in the figure below. The majority of them occurred within 2 weeks after treatment initiation.

Figure 1. Serious hepatic dysfunction reported after marketing in Japan and their onset period (Results of an analysis of cases determined by the MAH that a causal relationship to tolvaptan cannot be ruled out)[2)]



4. Precautions on hepatic dysfunction

When using tolvaptan, measures such as monitoring of thirst, body weight, blood pressure, pulse rate, urine volume, and serum sodium are required. In the light of the above circumstances, healthcare professionals should pay attention to the belowmentioned items concerning hepatic dysfunction and continue collaborating for the proper use of tolvaptan.

(1) Liver function tests should be performed before starting treatment with tolvaptan and frequently during at least the first 2 weeks of the treatment. When the treatment has to be continued thereafter, the tests should be carried out as necessary.

(2) If hepatic dysfunction symptoms (such as fatigue, inappetence, right upper abdominal discomfort, brown urine, and jaundice) are observed, the administration of tolvaptan should be immediately discontinued, and appropriate measures should be taken.

The current package insert includes information and advice on hepatic dysfunction in the [Important Precautions], [Clinically significant adverse reactions], and [Other Precautions] sections as described in the table below; please check them.

Table Information and advice on hepatic disorder in the package insert of tolvaptan (July 2013)

[Important Precautions]	Serious hepatic dysfunction may occur from the beginning of the treatment with Tolvaptan. Liver function tests should be performed before starting treatment with Tolvaptan and frequently during at least the first 2 weeks of the treatment. Subsequent tests should be performed as clinically indicated when the treatment needs to continue.
[Clinically significant adverse reactions]	**Hepatic dysfunction (frequency unknown):** Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), γ-GTP, Al-P, bilirubin, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of the drug should be immediately discontinued, and appropriate measures should be taken.
[Other Precautions]	While it is an off-label indication, in a Phase III, controlled, double-blind study in patients with autosomal dominant polycystic kidney disease receiving tolvaptan 60 to 120 mg/day or placebo for 3 years, increases in total bilirubin by more than 2-fold the upper limit of normal and in serum ALT (GPT) or AST (GOT) by more than 3-fold the upper limit of normal were noted in 2 patients in the tolvaptan group. The incidence of increases in ALT (GPT) by more than 2.5-fold the upper limit of normal was higher in the tolvaptan group than in the placebo group (47 of 960 patients [4.9%] in the tolvaptan group and 6 of 483 patients [1.2%] in the placebo group). The majority of increases in ALT (GPT) by more than 3-fold the upper limit of normal in the tolvaptan group occurred between 3 and 14 months after starting treatment.

<References> (including provisionally translated titles)

1) Documents attached to the application for new drug in October 2010: Module 2 (Document Summaries) 2.7.4 Summary of Clinical Safety (only available in Japanese language)
http://www.info.pmda.go.jp/shinyaku/P201000054/18007800_22200AMX00956000_K100_1.pdf

2) Information on Proper Use of Samsca Tablets
- Request for performing liver function tests to avoid clinically significant hepatic dysfunction - (only available in Japanese language)
(updated on July 10, 2013)
http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201305_1.pdf

2

Revision of Precautions for Magnetic Resonance Imaging System

1. Introduction

Magnetic resonance imaging system (hereinafter referred to as "MR system") is a medical device for imaging organs and blood vessels using nuclear magnetic resonance phenomena.

Magnetic Resonance Imaging (MRI) scans have been contraindicated/prohibited in patients with metal-containing implantable or indwelling medical devices in their body because the effect of a magnetic field generated by an MR system may break medical devices worn by patients, migrate medical devices in the body, or heat up devices causing burn injuries to patients. Also, bringing metal-containing medical devices[Note)] into MRI room has been contraindicated/prohibited because metals are pulled toward an MR system by a magnetic field generated.

Recently, however, implantable or indwelling medical devices have been marketed, which can undergo MRI scans as long as they comply with required conditions and precautions for MRI scans. These devices suit compliance requirements for MRs such as the American Society for Testing and Materials (ASTM) and International Organization for Standardization (ISO). In addition, medical devices have been launched, which are anticipated to be used in an MRI room and can be brought into such a room up to a certain magnetic field intensity.

Note) Including non-medical devices such as hospital drips and wheelchairs.

Example groups of marketed products that can undergo MRI scans or be brought into an MRI room

(Medical devices, for which compliance with requirements for MR system has been confirmed, are limited to some of those in the product groups.)

Implantable or indwelling medical devices	Medical devices anticipated to be used in an MRI room
• Implantable cardiac pacemaker/ lead • Artificial cardiac valve • Stents (for coronary artery, bile duct, iliac artery, etc.) • Coils for cerebrovascular embolization • Annuloplasty ring	• Artificial ventilator • Electrocardiograph electrodes • Multi-parameter monitor • Pulse oximeter probe • Infusion pump

2. Revision of package inserts

Under these circumstances, MHLW has recently instructed the MAHs of an MR system to revise the Contraindications section of the package insert as described below so that patients with implantable or indwelling medical devices, which have been confirmed to be compliant with the requirements for MR systems, can take MRI scans and medical devices, which have been confirmed to be compliant with the requirements for MR systems, can be brought into an MRI room[1)].

[Contraindications] section of the package insert

<Regarding medical devices, etc. that are implanted or placed in the body>

In general, MRI scans should not be performed in patients with metal-containing implantable or indwelling medical devices. [Migration, failure, breakage, malfunction, or burn of implanted or placed medical devices may occur in a patient's body.]

Exceptions are medical devices that have been conditionally demonstrated to be compatible with MR systems. Before performing MRI scans, make sure to confirm imagining conditions, etc. by referring to the package insert, etc. of implantable or indwelling medical devices.

<Regarding medical devices, etc. that are expected to be brought into an MRI room>

Any metal-containing medical devices should not be brought into an MRI room. [These devices may be magnetically attracted to an MR system, broken or damaged, or cause burns, etc.]

Exceptions are medical devices that have been conditionally demonstrated to be compatible with MR systems. Before performing MRI scans, make sure to confirm compatible magnetic field strength by referring to the package inserts of medical devices to be used.

3. Request to healthcare professionals

When MRI scans need to be conducted in patients with metal-containing implantable or indwelling medical devices or when metal-containing medical devices must be brought into an MRI room, please read the package inserts of such medical devices, and be sure to verify that compliance with requirements for MR systems has been confirmed. If that is the case, healthcare professionals are encouraged to carry out MRI scans or bring the devices into an MRI room upon verification and compliance with required conditions and precautions for MRI scans or magnetic field intensity in the MRI room. If compliance has not been confirmed or is unknown, for example, the package insert does not provide information on MRI scans, such medical devices cannot undergo MRI scans or be brought into an MRI room.

4. Closing comments

MRI scans in patients with implantable or indwelling medical devices that are not confirmed to be compliant with MR systems or bringing such medical devices into an MRI room is contraindicated/prohibited. Before performing MRI scans, as usual, please check whether patients or healthcare professionals entering an MRI room are wearing metal-containing products or whether objects, which are brought into an MRI room, contain metals.

PMDA Medical Safety Information on precautions for handling of metallic products at the time of MRI scans has been released. Please utilize it for safety management activities in your medical institutions.

In addition, please utilize a checklist for routine MRI scans in order to use an MR system safely, issued by the Japan Medical Imaging and Radiological Systems Industries Association (JIRA).

- PMDA Medical Safety Information No. 26 "Precautions for Magnetic Resonance Imaging (MRI) Scans (Part 2)"
  http://www.pmda.go.jp/english/service/pdf/safety/No26.pdf

- Checklist before entering an MRI room (only available in Japanese language)
  (Japan Medical Imaging and Radiological Systems Industries Association)
  http://www.info.pmda.go.jp/anzen_gyoukai/file/jira01.pdf

<Reference>

1) Joint PFSB/SD Notification No. 0520-1 and PFSB/ELD/OMDE Notification No. 0520-4 dated May 20, 2013 by the Director of Safety Division, Pharmaceutical and Food Safety Bureau and by the Director of Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW "Revision of Precautions for Magnetic Resonance Imaging System" (only available in Japanese language)
http://www.hourei.mhlw.go.jp/hourei/doc/tsuchi/T130522I0110.pdf

3

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated June 4, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Interferon Beta (products for administration in combination with ribavirin) and Ribavirin (capsules)

[1] Interferon Beta

Brand Name (name of company)	FERON for Injection (1×10^6 IU), (3×10^6 IU), (6×10^6 IU) (Toray Industries Inc.)
Therapeutic Category	Biological preparations-Miscellaneous
Indications	1. Glioblastoma, medulloblastoma, astrocytoma 2. Malignant melanoma of skin 3. Improvement of viraemia in chronic active hepatitis B with positive for HBe-antigen and DNA polymerase 4. Improvement of viraemia in chronic hepatitis C 5. Improvement of viraemia in concomitant use of ribavirin in chronic hepatitis C patients either (1) with high blood HCV-RNA levels or (2) who did not respond to interferon monotherapy or relapsed after interferon monotherapy 6. Improvement of viraemia in compensated cirrhosis type C (excluding patients with high blood level of HCV-RNA of serogroup 1)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions) (administration in combination with ribavirin)

Sepsis: Susceptibility to infection may be increased and sepsis may occur. Patients' general condition should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Retinopathy: Retinopathy may occur. Attention should be paid to retinal haemorrhage, soft exudates, and aggravation of diabetic retinopathy, and patients should be carefully monitored through periodic fundoscopy, etc. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. In addition, patients should be instructed to consult a physician immediately if reduced visual acuity or visual field scotoma is observed.

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, 2010 to March 31, 2013)

- Sepsis: 1 case (1 fatal case)
- Retinopathy-associated cases: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 1,400 (April 2012 to March 2013) (patients with chronic hepatitis C)

Launched in Japan: September 1985

[2] Ribavirin

Brand Name (name of company)	REBETOL Capsules 200 mg (MSD K.K.)
Therapeutic Category	Antivirals
Indications	1. Improvement of viraemia in concomitant use of interferon alfa-2b (genetical recombination), peginterferon alfa-2b (genetical recombination) or interferon beta in chronic hepatitis C patients either(1) with high blood HCV-RNA level or (2) who did not respond to interferon monotherapy or relapsed after interferon monotherapy 2. Improvement of viraemia in compensated cirrhosis C in combination therapy with peginterferon alfa-2b (genetical recombination)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions) (administration in combination with interferon beta)

Sepsis: Susceptibility to infection may be increased and sepsis may occur. Patients' general condition should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Retinopathy: Retinopathy may occur. Attention should be paid to retinal haemorrhage, soft exudates, and aggravation of diabetic retinopathy, and patients should be carefully monitored through periodic fundoscopy, etc. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. In addition, patients should be instructed to consult a physician immediately if reduced visual acuity or visual field scotoma is observed.

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, 2010 to March 31, 2013) (administration in combination with interferon beta)

- Sepsis: 1 case (1 fatal case)
- Retinopathy-associated cases: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 17,000 (April 2012 to March 2013) (as REBETOL Capsules)

Launched in Japan: December 2001

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Chronic hepatitis C (depression) (osteoporosis)	[Interferon beta] 6,000,000 IU (everyday) for 6 days [Ribavirin] 600mg (everyday) for 6 days	**Septic shock, disseminated intravascular coagulation (DIC)** The patient had depression and decreased platelets, antiviral therapy was avoided. However, for reasons such as the combination therapy of interferon beta + ribavirin was approved for insurance and that the genotypes of interleukin-28B single nucleotide polymorphism (IL-28B SNPs) were major homo type, this combination therapy was started after discussion with the patient. Day 1 of administration: The patient was admitted to hospital. The combination therapy with interferon beta 6,000,000 IU/day (everyday) and ribavirin 600 mg/day (morning 200 mg + evening 400 mg) (everyday) was started. Pyrexia occurred. Administration of loxoprofen sodium hydrate was started for pyrexia as needed (for 5 days). As a countermeasure against adverse reactions to loxoprofen sodium hydrate, administration of rebamipide was used as needed (for 5 days). Day 2 of administration:

				Inappetence occurred. Pyrexia was resolved. Day 6 of administration (day of discontinuation): Administration of omeprazole and mosapride citrate was started for inappetence (both medications were terminated on this day). In the evening, the patient had pyrexia at 38°C. Intravenous drip infusion of interferon beta 6,000,000 IU was started after dinner. A nurse visited the hospital room for monitoring of symptoms. The patient was found to have a Japan Coma Scale (JCS) of III-300 and have a large amount of vomiting. After calling the doctor on duty, blood pressure 86/40 mmHg, pulse rate 114 beats/min, and body temperature 41.4°C were confirmed. After starting administration of oxygen and large-volume fluid replacement, a head-chest-abdominal CT (plain) was performed. Oedema across the whole region of the intestinal tract wall and oedema of the gallbladder wall were noted. There was a large amount of watery stool. Administration of catecholamine (dopamine hydrochloride 5 mL/min) was started. With O_2 reservoir mask 12 L, oxygen saturation (SpO_2) level was 99%, and light reaction was found. JCS III-300 remained. The patient was admitted to intensive care unit (ICU). To secure an adequate amount of circulating plasma, human serum albumin 1,750 mL was administered. Endotracheal intubation was performed, and mechanical ventilation was started. To maintain adequate blood pressures, administration of dopamine hydrochloride 10 mL/hr and noradrenaline 8 mL/hr was started. Because of pyrexia at 38°C to 41.4°C, decreased blood pressure, and tachycardia, the patient was diagnosed with septic shock. Due to septic shock, the combination therapy with interferon beta and ribavirin was discontinued. Low platelet count (30,000/mm^3) was considered to be decreased platelets due to DIC caused by sepsis. Procalcitonin 2 to 10 ng/mL was strongly suspected to be a change by infection. Results of blood culture showed gram-negative bacillus (+) (*Enterobacteriaceae*, which is considered to be the causative bacterium for sepsis), and the results of urine culture showed gram-positive cocci (+), gram-positive bacillus (+), and gram-negative bacillus (+) (contamination was not ruled out). 1 day after discontinuation: DIC occurred. Blood fibrin and fibrinogen degradation product (FDP) 528.0 μg/dL; quantitative D-dimer 306.0 ng/mL. Continuous hemodiafiltration (CHDF), plasma exchange (PE), and other treatments were performed, but the patient did not recover and died 3 days after discontinuation. Cause of death was multi-organ failure. In autopsy findings, there was a macroscopic hepatic finding corresponding to F2 to F3 and diffuse gastrointestinal mucosal haemorrhage.
	Concomitant medications: ursodeoxycholic acid, flunitrazepam, sodium valproate, ramelteon, raloxifene hydrochloride, eszopiclone			

Laboratory Examination

	Day 1 of administration (before the start of this combination therapy)	Day 4 of administration	Day 6 of administration		1 day after discontinuation	2 days after discontinuation
Total bilirubin (mg/dL)	0.5	0.7	1.4	-	0.9	0.7
Creatinine (mg/dL)	0.76	0.79	1.32	-	2.39	2.53
Blood glucose (mg/dL)	106	86	144	-	21	175
WBC (/mm^3)	5,000	2,600	4,200	-	5,600	4,100
Neutrophils (%)	43.3	45.9	-	-	48.0	41.0
Eosinophils (%)	1.8	1.2	-	-	0.0	0.0
Basophils (%)	0.2	0.0	-	-	0.5	0.0
Lymphocytes (%)	45.6	37.1	-	-	25.5	40.0
Monocytes (%)	9.1	15.8	-	-	5.0	6.0
PLT (× 10^4/mm^3)	8.7	5.8	3.0	-	1.2	1.4
PT (seconds)	-	-	-	14.2	-	47.0
PT-INR	-	-	-	1.45	-	4.52
PT (%)	-	-	-	57.1	-	12.7
PT (control)	-	-	-	9.6	9.6	9.6
APTT (seconds)	-	-	-	88.8	-	-
APTT (control)	-	-	-	34.0	34.0	-
Procalcitonin (ng/mL)	-	-	-	2 - 10	-	-
Fibrinogen (mg/dL)	-	-	-	129	-	-
Blood FDP (μg/mL)	-	-	-	111.4	528.0	59.2
Quantitative D-dimer (ng/mL)	-	-	-	80.5	306.0	23.1

2 Carboplatin

Brand Name (name of company)	PARAPLATIN INJECTION 50 mg, 150 mg, 450 mg (Bristol-Myers K.K.) and the others
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	○ Head and neck cancer, small cell lung cancer, testicular tumor, ovarian cancer, cervical cancer, malignant lymphoma, non-small cell lung cancer, breast cancer ○ Concomitant therapy with other antineoplastics for the following malignant tumours: Pediatric malignant solid tumor (neuroblastoma, retinoblastoma, hepatoblastoma, central nervous system germ cell tumor, relapsed or refractory Ewing's sarcoma family of tumor, nephroblastoma)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Leukoencephalopathy (including posterior reversible encephalopathy syndrome): Leukoencephalopathy (including posterior reversible encephalopathy syndrome) may occur. If symptoms including staggering gait, lisp, convulsion, headache, confusion, or visual disturbance 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, 2010 to March 31, 2013)

- Leukoencephalopathy-associated cases: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 12,000 (January 2012 to December 2012)

Launched in Japan: May 1990

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Stage III lung squamous cell carcinoma (interstitial lung disease, hypertension, gastrooesophageal reflux disease)	750 mg × 1 3 courses	**Posterior reversible encephalopathy syndrome** The patient was complicated with interstitial pneumonia, and chemotherapy using carboplatin + paclitaxel was performed for 3 courses. Day 1 of administration: The patient received a third course of chemotherapy. 22 days after administration: Headache dull occurred. 25 days after administration: With pyrexia at 37.7°C, the patient visited the hospital. Ptosis of the right corner of the mouth was noted. T2-weighted image and fluid attenuated inversion recovery (FLAIR) image of brain MRI showed high signal intensity in both frontal lobes, the patient was admitted to hospital. Administration of concentrated glycerin/fructose and betamethasone sodium phosphate was started as countermeasures against brain oedema, and intravenous injection of nicardipine was started for the treatment of hypertension. 28 days after administration: A brain MRI (Gd-contrasted) was performed, there was no metastases to brain, and then leukoencephalopathy was suspected. 31 days after administration: Lumbar puncture was performed. The cerebrospinal fluid properties were not markedly changed. 38 days after administration: Ptosis of the right corner of the mouth was alleviated. 39 days after administration: Brain MRI was performed again, and the range of abnormal signals decreased. 44 days after administration: Mild ptosis of the right corner of the mouth remained, but the patient was discharged from hospital. Approximately 6 months after administration: On a brain MRI, abnormal signals almost disappeared. Approximately 14 months after administration: On a brain MRI, abnormal signals almost disappeared. Ptosis of the right corner of the mouth improved.
	The other suspected medications: paclitaxel injection Concomitant medications: loxoprofen sodium tablets, acetaminophen tablets			

Laboratory Examination

Laboratory parameter (unit)		Day 1 of administration	21 days after administration	25 days after administration	30 days after administration	84 days after administration
Body temperature	(°C)	-	37.6	-	-	-
Pulse rate	(/min)	-	89	-	-	-
Blood pressure SBP	(mmHg)	-	150	-	-	-
Blood pressure DBP	(mmHg)	-	94	-	-	-
RBC	($\times 10^4$/mm^3)	448	226	236	249	360
Hemoglobin	(g/dL)	14.3	7.3	7.3	8.1	12.5
WBC	(/mm^3)	9,400	5,000	6,400	7,200	6,100

Differential leukocyte count (%)	Neutrophils	68.8	57.0	75.5	65.0	46.5
	Eosinophils	2.9	0	0.5	0	2.5
	Basophils	0.2	1.0	0	0	0.2
	Monocytes	4.8	10.0	4.4	11.0	6.6
	Lymphocytes	23.3	32.0	19.6	24.0	44.2
PLT	($\times 10^4$/mm^3)	22.9	4.0	9.8	40.7	17.7
AST (GOT)	(IU/L)	21	18	18	16	19
ALT (GPT)	(IU/L)	22	17	16	17	15
Al-P	(IU/L)	368	379	370	303	320
γ-GTP	(IU/L)	75	50	54	58	44
LDH	(IU/L)	236	178	200	184	177
Total bilirubin	(mg/dL)	0.30	0.43	0.53	0.48	0.48
BUN	(mg/dL)	15	18	12	20	19
Serum creatinine	(mg/dL)	0.60	0.88	0.89	0.84	0.78
Blood glucose level	(mg/dL)	118	129	148	86	118
K	(mEq/L)	5.2	4.4	4.0	9.4	9.5
Na	(mEq/L)	139	139	132	135	141
Ca	(mEq/L)	10.8	9.1	9.3	9.4	9.5
Albumin	(g/dL)	4.2	3.9	-	3.7	4.3

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Corpus uteri carcinoma, ovarian cancer (hysterectomy, bilateral adnexectomy)	700 mg × 1 1 course	**Posterior reversible encephalopathy syndrome** Day 1 of administration: The patient received initial dose for paclitaxel plus carboplatin (TC). 10 days after administration: The patient was discharged from hospital. 12 days after administration: In the afternoon, the patient had convulsion at home, and visited the hospital with a family member by ambulance. Vomiting occurred after the visit. About 2 hours after the occurrence of convulsion, blood pressure at the visit was 135/70 mmHg. After head CT was performed, convulsion occurred again. Chloral hydrate rectal suppository (250 mg) was inserted into the rectum, and oxygen was administered. Because of blood pressure 200/100 mmHg, nicardipine hydrochloride 1 mg was intravenously injected, and a head MRI was performed on the same day. A radiologist notified of suspected Posterior reversible encephalopathy syndrome (PRES). For the reduction of blood pressure and prophylaxis for convulsion, or possibility that the condition might shift to subarachnoid haemorrhage (SAH), treatment was provided in consideration of SAH. 13 days after administration: The patient was fully conscious. No vomiting/convulsion occurred. 15 days after administration: Sodium valproate was orally administered. 29 days after administration: Administration of chloral hydrate suppository was discontinued. 46 days after administration:

				While concomitantly using oral sodium valproate and oral antihypertensive drug, the second course of TC therapy was performed. <Head MRI> 12 days after administration: T2-weighted image and FLAIR image showed high signal intensity in the bilateral areas extending from occipital lobes to parietal lobes, bilateral corona radiata, and posterior region of bilateral centrum semiovale, and then PRES was suspected. 19 days after administration: The high signal intensity on T2-weighted image and FLAIR image, which was pointed out on previous head MRI, substantially decreased (With no inconsistency as the course of PRES). A linear lesion was noted in the left occipital lobe, low signal intensity was identified on the T1-weighted image, and therefore there was a possibility that the disease remained.
	The other suspected medications: paclitaxel injection			

Laboratory Examination

Laboratory parameter (unit)		2 days before administration	Day 1 of administration	5 days after administration	12 days after administration	15 days after administration	17 days after administration
Body temperature (°C)		36.5	-	36.6	38.2	-	-
Pulse rate (/min)		77	-	75	110	-	-
Blood pressure SBP (mmHg)		133	-	145	200	-	-
Blood pressure DBP (mmHg)		77	-	91	110	-	-
RBC ($\times 10^4$/mm^3)		3.61	-	3.98	3.93	3.33	3.50
Hemoglobin (g/dL)		11.4	-	12.3	12.2	10.5	10.7
WBC (/mm^3)		4,700	-	3,900	4,800	2,000	7,500
Differential leukocyte count (%)	Neutrophils	66.9	-	78.7	80.6	39.1	82.7
	Eosinophils	2.5	-	2.9	0.1	2.5	0.5
	Basophils	0.3	-	0.1	1.7	0.9	0.2
	Monocytes	10.1	-	0.9	9.0	17.4	5.5
	Lymphocytes	20.2	-	17.4	8.6	40.1	11.1
PLT ($\times 10^4$/mm^3)		16.7	-	14.5	9.1	7.3	10.7
PT (%)		-	-	-	96.1	-	-
FDP (μg/mL)		-	-	-	11.4	-	-
D-dimer (μg/mL)		-	-	-	4.3	-	-
AST (GOT) (IU/L)		17	-	51	20	-	-
ALT (GPT) (IU/L)		12	-	34	19	-	-
Blood glucose level (mg/dL)		-	-	-	136	-	-
BUN (mg/dL)		4.5	-	8.5	6.2	-	-
Serum creatinine (mg/dL)		0.4	-	0.3	0.3	-	-
K (mEq/L)		4.9	-	3.9	3.8	-	-
Na (mEq/L)		140	-	136	137	-	-
Urine output (mL/24hr)		1,600	-	-	-	3,000	1,650

3 Tegafur/Gimeracil/Oteracil Potassium

Brand Name (name of company)	(1) TS-1 combination capsule T20, T25, TS-1 combination granule T20, T25, TS-1 combination OD tablet T20, T25 (Taiho Pharmaceutical Co, Ltd.) (2) ESUEEWAN Combination Capsules T20, T25 (Sawai Pharmaceutical Co., Ltd.), NKS-1 combination capsule T20, T25 (Nippon Kayaku Co., Ltd.)
Therapeutic Category	Antimetabolites
Indications	(1) Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic carcinoma, biliary carcinoma (2) Gastric cancer

PRECAUTIONS (underlined parts are revised)

Important Precautions

Hepatitis due to reactivation of hepatitis B virus may occur in hepatitis B virus carriers or HBs antigen-negative patients with HBc antibody-positive or HBs antibody-positive after administration of this drug. Prior to treatment, patients should be checked for hepatitis virus infection and appropriate measures should be taken before administration of this drug. After the start of administration of this drug, attention to the occurrence of signs or symptoms related to reactivation of hepatitis B virus should be paid by continuously monitoring results of liver function tests or hepatitis virus markers.

Adverse Reactions (clinically significant adverse reactions)

Serious hepatic disorders such as fulminant hepatitis: Serious hepatic disorders such as fulminant hepatitis (including those due to reactivation of hepatitis B virus) may occur. Patients should be carefully monitored through periodic liver function tests, and if any abnormalities 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 3 years (April 1, 2010 to April 10, 2013)

- Cases associated with hepatitis due to reactivation of hepatitis B virus: 5 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: (1) Approximately 134,000 (January 2012 to December 2012)

Launched in Japan: March 1999 (Capsules)
June 2009 (Granules)
June 2013 (OD Tablets)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Lower gum cancer (hepatitis B virus carrier, rheumatoid arthritis, dissecting aortic aneurysm)	80 mg for 40 days ↓ 40 mg for 7 days (2-week treatment by 1-week rest period)	**Hepatic dysfunction** 7 days before administration: The patients started receiving oxycodone hydrochloride hydrate (10 mg × 2/day). 6 days before administration: T-Bil, 0.4; AST, 17; ALT, 13; hepatitis B surface antigen (HBs-Ag), 28.92. Day 1 of administration: Administration of tegafur/gimeracil/oteracil potassium (80 mg/day) was started for lower gum cancer. 41 days after administration: The patient visited an outpatient department. T-Bil, 2.2; AST, 249; ALT, 221. Abnormal hepatic function was found by

				blood sampling, the dose of tegafur/gimeracil/oteracil potassium was reduced (40 mg/day). Administration of a glycyrrhizinate/glycine/L-cysteine hydrochloride combination product (40 mL/day) and ursodeoxycholic acid (900 mg/day) was started. 47 days after administration (day of discontinuation): Hepatic dysfunction and jaundice further progressed. With severe malaise, the patient was immediately admitted to hospital. Administration of tegafur/gimeracil/oteracil potassium and oxycodone hydrochloride hydrate was discontinued. Administration of amino-acid preparation for hepatic failure (500 mL/day) was started. 1 day after discontinuation: There was no particularly marked change in the morning. T-Bil increased to 7.5, AST to 302, ALT to 220, and NH_3 to 152. Hepatitis B virus (HBV) (TaqMan), 8.4 log copy/mL; prothrombin time (PT), 33%. Lactulose (30 mL/day) was administered. Some tendency toward somnolence occurred in the afternoon. Level of consciousness gradually depressed. 2 days after discontinuation: In the morning, JCS was 300. SaO2 decreased to 70 level. Administration of oxygen was started. T-Bil, 8.5; AST, 442; ALT, 243; NH_3, 114. Blood pressure decreased, administration of dopamine hydrochloride was started. Respiratory status was gradually aggravated. In the middle of the night, the patient died (cause of death, hepatic failure; autopsy, none).
	Concomitant medications: oxycodone hydrochloride hydrate, sennoside, magnesium oxide, bucillamine			

Laboratory Examination

		6 days before administration	20 days after administration	41 days after administration	1 day after discontinuation	2 days after discontinuation
HBsAg	(antigen)	28.92	-	-	-	-
HBV−DNA (TaqMan)	(log copy/mL)	-	-	-	8.4	-
Total bilirubin	(mg/dL)	0.4	1	2.2	7.5	8.5
GOT (AST)	(IU/L)	17	31	249	302	442
GPT (ALT)	(IU/L)	13	31	221	220	243
Albumin	(g/dL)	3.2	3.9	3.4	2.5	2.2
Cholinesterase	(IU/L)	190	161	92	55	49
CRP	(mg/dL)	-	0.123	0.432	2.115	2.885
WBC	(/mm^3)	4,140	3,230	3,730	2,160	3,860
Neutrophils	(%)	65.2	76.9	85.8	75.7	69.7
Lymphocytes	(%)	24	14	6.2	14	16.8
Eosinophils	(%)	0.4	0.3	0.5	1.7	0.4
Prothrombin time	(%)	102	-	-	33	-
PT	(INR)	0.99	-	-	2.11	-
APTT	(Sec)	36.1	-	-	86.7	-
Fibrinogen	(mg/dL)	-	-	-	98	-
Antithrombin III	(%)	-	-	-	34	-
TTT	(U)	-	-	-	-	6.7
ZTT	(U)	-	-	-	-	7
NH3	(μmoL/L)	-	-	-	152	114

4 Tolvaptan

Brand Name (name of company)	Samsca tablets 7.5 mg, 15 mg (Otsuka Pharmaceutical Co., Ltd.)
Therapeutic Category	Diuretics
Indications	Fluid retention in patients with cardiac failure which is not adequately responded to other diuretics such as loop diuretics

PRECAUTIONS (underlined parts are revised)

Important Precautions

Decrease in the amount of circulating plasma followed by increase the serum concentration of potassium may occur due to the water diuretic effect of this drug, and ventricular fibrillation or ventricular tachycardia may be induced. Serum concentration of potassium should be measured during administration of this drug.

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis (generalised redness, decreased blood pressure, dyspnoea, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Excessively decreased blood pressure, ventricular fibrillation, ventricular tachycardia: Excessively decreased blood pressure, ventricular fibrillation, or ventricular tachycardia may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years and 4 months (from initial marketing to April 4, 2013)

- Arrhythmia-associated cases: 3 cases (no fatal cases)
- Shock, anaphylaxis-associated cases: 2 cases (no fatal cases)
- Decreased blood pressure-associated cases: 7 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 39,000 (January 1, 2012 to December 31, 2012)

Launched in Japan: December 2010

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Fluid retention (congestive cardiac failure) (cardiac valve disease) (Fallot's tetralogy) (hypokalaemia) (insomnia) (anaemia) (hepatic congestion)	15 mg for 3 days	**Decrease blood pressure, ventricular tachycardia** 1 day before administration: The patient was admitted to hospital. Day 1 of administration: Systolic blood pressure was 85 mmHg. Fluid retention was noted. Administration of tolvaptan 15 mg/day was started (The drug was administered for the first time). Polyuria occurred. Day 2 of administration: Thirst occurred. The patient had urine excretion of about 5000 mL/day. From before oral administration of tolvaptan, oral furosemide, spironolactone, and azosemide were concomitantly used. Due to excessive urine output, decreased blood pressure occurred gradually. Systolic blood pressure temporarily decreased to the 60 mmHg level. Systolic blood pressure was 88 mmHg. Day 3 of administration (day of discontinuation):

				Decreased blood pressure and non-persistent ventricular tachycardia occurred. Mild palpitations were the only symptom of non-persistent ventricular tachycardia. Systolic blood pressure was 79 mmHg. Administration of tolvaptan was discontinued. Administration of the starting solution (2) 1000 mL/day and lidocaine was started. Thirst remitted. Oral administration of other diuretics was also discontinued. Load of infusion solution and administration of dobutamine hydrochloride were started. 1 day after discontinuation: Non-persistent ventricular tachycardia remitted. Administration of lidocaine was terminated. 2 days after discontinuation: Administration of noradrenaline was started. Blood pressure increased gradually. The dose of the starting solution (2) was reduced to 500 mL/day. 3 days after discontinuation: Administration of noradrenaline was discontinued. 4 days after discontinuation: Administration of the starting solution (2) was discontinued. 5 days after discontinuation: Systolic blood pressure increased to the 110 mmHg level. Decreased blood pressure and polyuria remitted.
	Concomitant medications: azosemide, furosemide, spironolactone, potassium chloride, carvedilol, sodium rabeprazole, denopamine, etizolam, brotizolam, torasemide, digoxin, dobutamine hydrochloride, thiamine disulfide phosphate/B6/B12, warfarin potassium, tamsulosin hydrochloride			

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 80s	Chronic cardiac failure (mitral valve replacement) (chronic renal failure) (hyponatraemia) (hypertension) (gastritis) (diabetes mellitus) (iron deficiency anaemia) (constipation)	3.75 mg 1 day	**Anaphylactic shock** Day 1 of administration (day of discontinuation): The patients started receiving tolvaptan 3.75 mg/day. From 8 hours after the start, systemic itching occurred, and subsequently, generalised redness, dyspnoea (SpO_2, 80% level), and decreased systolic blood pressure (SBP, 120 level to 70 level) were found. Decreased blood pressure and preshock state (anaphylaxis) and generalised exanthema occurred. Administration of oxygen and intravenous infusion of methylprednisolone sodium succinate 500 mg were performed immediately (only on the day). The symptoms temporarily improved by administration of steroid but generalised redness relapsed (blood pressure was maintained). Oral administration of 2 tablets of prednisolone 5 mg was started. Administration of tolvaptan was discontinued. Decreased blood pressure and preshock state (anaphylaxis) were resolved. 1 day after discontinuation: Methylprednisolone sodium succinate 250 mg was intravenously infused (only on the day), the symptoms improved. 3 days after discontinuation: Generalised exanthema remitted. 4 days after discontinuation: Oral administration of prednisolone was discontinued.
	Concomitant medications: carperitide (genetical recombination), dobutamine hydrochloride, perindopril			

	erbumine, carvedilol, valsartan, eplerenone, omeprazole sodium, sodium ferrous citrate, sitagliptin phosphate hydrate, sennoside, zopiclone

5 Paroxetine Hydrochloride Hydrate

Brand Name (name of company)	(1) Paxil Tablets 5 mg, 10 mg, 20 mg (GlaxoSmithKline K.K.) (2) Paxil CR Tablets 12.5 mg, 25 mg (GlaxoSmithKline K.K.) (3) PAROXETINE TABLETS 5 mg "TOWA," 10 mg "Towa," 20 mg "Towa," PAROXETINE OD TABLETS 10 mg "Towa," 20 mg "Towa" (Towa Pharmaceutical Co., Ltd.) and the others
Therapeutic Category	Psychotropics
Indications	(1) Depression/depressed state, panic disorder, obsessive-compulsive disorder, social anxiety disorder (2) Depression/depressed state (3) Depression/depressed state, panic disorder, obsessive-compulsive disorder

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

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

Pancytopenia, agranulocytosis, decreased white blood cells, decreased platelets: Pancytopenia, agranulocytosis, decreased white blood cells, and decreased platelets may occur. Patients should be carefully monitored through blood tests, etc., 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 2 years and 10 months (April 1, 2010 to February 11, 2013)

- Rhabdomyolysis-associated cases: 3 cases (no fatal cases)
- Pancytopenia-associated cases: 0 cases (no fatal cases)
- Agranulocytosis, decreased white blood cell-associated cases: 0 cases (no fatal cases)
- Decreased platelets-associated cases: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: (1) (2)
Approximately 970,000 (March 2012 to February 2013)
Launched in Japan: September 2010 (5 mg tablets)
November 2000 (10 mg tablets, 20 mg tablets)
June 2012 (CR tablets)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 20s	Social anxiety disorder Depressive state	20 mg for 30 days 30 mg for 3 days	**Rhabdomyolysis, tonic clonic convulsion** Day 1 of administration: The patient visited the hospital with the chief complaints of hypobulia, nocturnal awakening, and suicidal ideation. Day 15 of administration: The patient visited the hospital again. The symptoms were not improved, quetiapine fumarate was added.

			20 mg for 3 days	Day 30 of administration: With no improvement of the symptoms, the patient had dizziness on standing up and fell. It was considered to be an adverse reaction to quetiapine fumarate, and administration of quetiapine fumarate was discontinued. The dose of paroxetine hydrochloride hydrate was increased from 20 mg to 30 mg. Day 34 of administration: The patient did not feel well, and so he visited the hospital with no appointment. He sometimes fainted suddenly. Myalgia was found. Body temperature was 38.3°C. Neuroleptic malignant syndrome and rhabdomyolysis were suspected, gradual dose reduction and discontinuation of paroxetine hydrochloride hydrate were planned. The dose of paroxetine hydrochloride hydrate was reduced from 30 mg to 20 mg from this day. Day 36 of administration (day of discontinuation): In a blood test, the CK level was as high as 18447, and as such, administration of paroxetine hydrochloride hydrate 20 mg was discontinued. The patient visited another hospital. Administration of all medications were discontinued and blood transfusion was performed. 1 day after discontinuation: Tonic clonic convulsion occurred but resolved on the same day. 3 days after discontinuation: With improvement of symptoms and a tendency toward improvement in blood tests, the patient was discharged from hospital. 6 days after discontinuation: Rhabdomyolysis resolved.
	Concomitant medications: quetiapine fumarate, etizolam, trazodone hydrochloride			

Laboratory Examination

Laboratory parameter		Institutional lower limit of normal	Institutional upper limit of normal	Day 34 of administration	Day 36 of administration (day of discontinuation)
AST	(IU/L)	-	-	102	607
ALT	(IU/L)	-	-	22	96
CK	(IU/L)	-	-	18,447	114,300
WBC	(/μL)	-	-	10,700	5,000
Blood myoglobin	(mg/mL)	-	-	2,551	-

6 Levetiracetam

Brand Name (name of company)	E Keppra Tablets 250 mg, 500 mg (UCB Japan Co., Ltd.)
Therapeutic Category	Antiepileptics
Indications	Concomitant therapy with antiepileptics for partial seizures (including secondary generalized seizures) in epileptic patients who do not sufficiently respond to other antiepileptics

PRECAUTIONS (underlined parts are revised)

Important Precautions

Psychiatric symptoms such as irritability, confusion, irritation, excitement, and aggression may occur, resulting in suicide attempts in some cases. Patients should be carefully monitored for changes in their state and clinical condition during

administration of this drug.
Patients and their families should be sufficiently informed of possible psychiatric symptoms such as aggression and suicide attempt, and should be instructed to keep close contact with a physician.

Adverse Reactions (clinically significant adverse reactions)

Aggression, suicide attempt: Psychiatric symptoms such as irritability, confusion, irritation, excitement, and aggression may occur, resulting in suicide attempts in some cases. Patients should be carefully monitored for their state, and if any of these symptoms are observed, appropriate measures such as discontinuing administration after gradual dose reduction should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years and 10 months (from initial marketing to April 16, 2013)

- Aggression, suicide attempt-associated cases: 10 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: Approximately 51,332 (November 1999 to November 2012)
Launched in Japan: September 2010

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Epilepsy (none)	1,000 mg for 25 days	**Completed suicide** When the patient was in elementary school, symptomatic epilepsy occurred. 1 day before administration: The patient was admitted to hospital due to convulsive seizures. She had epileptic seizures frequently. Day 1 of administration: In addition to zonisamide and clobazam, levetiracetam 1,000 mg was administered. Day 3 of administration: The patient was discharged from hospital. Day 14 of administration: At the visit, the patient complained of a little strong sleepiness. In addition, the patient had one seizure episode on Day 5 of administration of levetiracetam, the dose of zonisamide was reduced. Day 25 of administration: The patient committed suicide. The patient began to get irritated and speak aggressively after oral administration of levetiracetam. Her words were very aggressive and abnormal. No factors for suicide were found.
	Concomitant medications: zonisamide, clobazam			

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 40s	Epilepsy (none)	Unknown dose Unknown duration	**Suicide attempt** The patient had visited for convulsion (epilepsy) from her 10s. Day 1 of administration: Date of starting treatment was unknown. Two months before the occurrence of the event, administration

			500 mg for 5 days	of levetiracetam was discontinued once and switched to gabapentin. About 1 month later, administration of gabapentin was discontinued, and administration of levetiracetam 500 mg was resumed. Then, her mental state was obviously changed and positive symptoms, including excitability, hallucination, and laughing without meaning, appeared outwardly, and her continued excited state started to get out of control; and consequently, the patient was taken by ambulance. At that time, the patient was in a state of strong excitement and was almost in a state of panic. In addition, she often showed affective incontinence, etc. with sudden standing up or shouting. A head CT and electroencephalography showed no specific findings. 4 days after treatment resumption: In the morning, the patient jumped off the balcony of her home. Excitability was almost unchanged from the treatment resumption to suicide attempt. No history of mental change had been found.
	Concomitant medications: zonisamide, carbamazepine			

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Complex partial seizures (dementia)	250 mg for 16 days 500 mg for 29 days	**Suicide attempt** Day 1 of administration: The patients received levetiracetam 250 mg in addition to phenytoin, carbamazepine, and diazepam. Day 17 of administration: The dose of levetiracetam was increased to 500 mg. Around Day 32 of administration: The patient complained that his body is painful. Pain was present from when he began to act restless and strange wholly after 1 month of administration of levetiracetam. Day 32 of administration: The patient was found to be going to hang himself by putting a belt around a beam on the ceiling. He was saved just in time. After that, he still had the behavior of putting a rope around his neck. Day 46 of administration: The patient seemed restless and irritated feeling. He acted in a completely unusual manner, and therefore administration of levetiracetam was discontinued. As a result, he immediately showed improvements in his behaviors and emotions, and returned to the original calm state. 6 days after discontinuation: Suicide attempt, body pain, and irritated feeling were resolved.
	Concomitant medications: phenytoin, carbamazepine, diazepam			

4

Revision of Precautions (No. 247)

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 4 and June 14, 2013 (excluding those presented in "3. Important Safety Information" of this Bulletin).

1 Antipyretics and analgesics, anti-inflammatory agents

Loxoprofen Sodium Hydrate (oral dosage form)

Brand Name	LOXONIN TABLETS 60 mg, LOXONIN FINE GRANULES 10% (Daiichi-Sankyo Company, Limited); Loxoprofen Sodium Oral Solution 60 mg "Nichi-iko" (Nichi-iko Pharmaceutical Co., Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Agranulocytosis, haemolytic anaemia, decreased white blood cell, decreased platelets**: Agranulocytosis, haemolytic anaemia, decreased white blood cell, decreased platelets may occur. Patients should be carefully monitored through blood tests, etc., and if any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. **Rhabdomyolysis**: Rhabdomyolysis may occur. Patients should be carefully monitored, and if signs and symptoms including myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, or increased urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for the development of acute renal failure due to rhabdomyolysis.

2 Antidotes

Sugammadex Sodium

Brand Name	BRIDION Intravenous Injection 200 mg, 500 mg (MSD K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Cardiac arrest, severe bradycardia**: Cardiac arrest or severe bradycardia may occur within several minutes after administration of this drug. Patients should be carefully monitored for hemodynamics, and if any abnormalities are observed, appropriate measures such as administration of anticholinergic agents (e.g. atropine) should be taken.

3 Antimetabolites

Nelarabine

Brand Name	ARRANON G Injection 250 mg (GlaxoSmithKline K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Fulminant hepatitis, hepatic dysfunction, jaundice**: Fulminant hepatitis, hepatic dysfunction and jaundice with elevations of AST (GOT) and ALT (GPT), etc. may occur. Patients should be carefully monitored through periodic liver function tests, etc., and if any abnormalities are observed, appropriate measures, such as extension of the drug suspension duration or discontinuation of administration, should be taken.

4

Over-the-counter drugs

Loxoprofen Sodium Hydrate (oral dosage form)

Brand Name	LOXONIN S (Daiichi-Sankyo Healthcare Co., Ltd.)
Consultation	The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician or a pharmacist for a consultation with this package insert. The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these symptoms.. **Rhabdomyolysis**: Pain in muscles of hands and feet, shoulders, and lower back, etc., numbness of limbs, weakness, stiffness, general malaise, red-brown color urine, etc. may occur.

5

Vaccines

Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cells) and Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (Yeast Origin)

Brand Name	Cervarix (GlaxoSmithKline.K.K.), GARDASIL (MSD K.K.)
Adverse Reactions (clinically significant adverse reactions)	The onset mechanism is unknown, but severe pain not localized in the injection site (myalgia, arthralgia, pain of skin, etc.), numbness, weakness, etc. that persisted for a long period after vaccination are reported. If any abnormalities are observed, measures should be taken such as having patients visit a medical institution that can provide appropriate medical care including neurological and immunological differential diagnosis.

5

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of 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 July 1, 2013)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Oxybutynin Hydrochloride NEOXY TAPE 73.5 mg	Hisamitsu Pharmaceutical Co., Inc.	June 27, 2013
Clofarabine Evoltra 20 mg I.V. Infusion	Genzyme Japan K.K.	June 21, 2013
Lidocaine Penles Tape 18 mg*1	Nitto Denko Corporation	June 14, 2013
Tacrolimus Hydrate Prograf Capsules 0.5 mg, 1 mg*2	Astellas Pharma Inc.	June 14, 2013
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*3	Chugai Pharmaceutical Co., Ltd.	June 14, 2013
Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg*4	Nippon Shinyaku Co., Ltd.	June 14, 2013
Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%	Otsuka Pharmaceutical Co., Ltd.	June 14, 2013
Dexmedetomidine Hydrochloride (1) Precedex Intravenous Solution 200 μg "Hospira" (2) PRECEDEX Intravenous Solution 200 μg "Maruishi"	(1) Hospira Japan Co., Ltd. (2) Maruishi Pharmaceutical Co., Ltd.	June 14, 2013
Denosumab (Genetical Recombination) PRALIA SUBCUTANEOUS INJECTION 60 mg SYRINGE	Daiichi Sankyo Company, Limited	June 11, 2013
Acotiamide Hydrochloride Hydrate Acofide Tablets 100 mg	Zeria Pharmaceutical Co., Ltd.	June 6, 2013
Levetiracetam E Keppra Tablets 250 mg, 500 mg*7	UCB Japan Co. Ltd	May 31, 2013
Istradefylline NOURIAST Tablets 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 30, 2013
Rufinamide Inovelon Tablets 100 mg, 200 mg	Eisai Co., Ltd.	May 29, 2013

Acamprosate Calcium Regtect Tablets 333 mg	Nippon Shinyaku Co., Ltd.	May 27, 2013
Ofatumumab (Genetical Recombination) Arzerra for I.V. infusion 100 mg, 1000 mg	Glaxo SmithKline K.K.	May 24, 2013
Tocilizumab (Genetical Recombination) ACTEMRA 162 mg Syringe for SC Injection, ACTEMRA 162 mg Auto-Injector for SC Injection	Chugai Pharmaceutical Co., Ltd.	May 24, 2013
Exenatide BYDUREON for Subcutaneous Injection 2 mg	Astra Zeneca K.K.	May 16, 2013
Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Stribild Combination Tab.	Japan Tobacco Inc.	May 14, 2013
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 MINIRINMELT OD Tablet 60 μg*[8]	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 Phosribbon Combination Granules*[9]	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*[10]	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*[11]	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012

*1 An additional indication for “relief of pain in laser irradiation treatment of the skin”
*2 An additional indication for “treatment of patients with interstitial pneumonia associated with polymyositis/ dermatomyositis”
*3 An additional indication for “treatment of patients with malignant glioma”
*4 An additional indication for “analgesia of chronic pain cannot be managed by treatments with non-opioid analgesics”
*5 An additional indication for “adjunctive therapy for depression/depressive state”
*6 An additional indication for “sedation in surgery or treatment without intubation under local anesthesia”
*7 An additional administration for “pediatrics”
*8 An additional indication for “treatment of patients with central diabetes insipidus”
*9 An additional indication for “treatment of patients with hypophosphataemia”
*10 An additional indication for “treatment of patients with herpes simplex”
*11 An additional indication for “treatment of patients with central diabetes insipidus”