Pharmaceuticals and Medical Devices Safety Information

No. 281 July 2011

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

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No. 281 July 2011

Pharmaceutical and Food Safety Bureau,
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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

ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BE	Base excess
BUN	Blood urea nitrogen
CHDF	Continuous haemodiafiltration
CRP	C-reactive protein
CT	Computed tomography
div	Intravenous drip
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HbA_{1c}	Hemoglobin A_{1c}
HCO_3	Bicarbonate
HBs	Hepatitis B surface
IU	International unit
JDS	Japan Diabetes Society
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
Na	Sodium
O_2sat	Oxygen saturation
PCO_2	Arterial carbon dioxide partial pressure
PO_2	Arterial oxygen partial pressure
PEG	Percutaneous endoscopic gastrostomy
pH	Hydrogen ion concentration
PLT	Platelet
PT	Prothrombin Time
RBC	Red blood cell count
RR	Respiratory rate
S2	Segment 2 (Left posterior lateral segment of liver)
SpO_2	Oxygen saturation
SPECT	Single photon emission computed tomography
TACE	Transcatheter arterial chemoembolization
Vp1	Invasion of distal to second order branches of the portal vein
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Revision of Package Inserts of Subcutaneous Port and Catheter

1. Introduction

A subcutaneous port and catheter is a medical device which consists of an injection port with a self-sealing septum connected to a catheter. It has a subcutaneously implanted port and a catheter placed in the subclavian vein, cubital vein or hepatic artery (**Table**) that can be for short-term or long-term use, and it is used for the administration of systemic chemotherapy and nutritional management.

Catheter fracture/breakage, port body breakage, and catheter disconnection from the port have been reported in patients using these devices. In some cases, the fractured catheter migrated into the heart or the pulmonary artery. Based on the above, precautions for use of subcutaneous port and catheter are added to the "Warnings" and the "Precautions" sections of the package insert. The details are described below.

Table List of subcutaneous port and catheter

MAHs	Brand Name
Akita Sumitomo Bakelite Co., Ltd.	• SEPTUM PORT CATHETER • SEPTUM PORT CATHETER (Aero type, Aero mini type)
Cook Japan Inc.	• Vital-Port • Titanium Vital-Port
Create Medic Co., Ltd.	• Cliny Port System (MRI Type) • Cliny Port System (MRI Type, For Intravenous PUR 5Fr / 6Fr Catheter)
Sata Corporation	• SOPH-A-PORT
Terumo Clinical Supply Co., Ltd.	• TherdicaPort
Toray Industries, Inc.	• Anthron ® P-U Catheter • P-U Celsite Port (Kit) • P-U Celsite Port (Discreet kit) • P-U Celsite Port (Kit for intravenous use only) • P-U Celsite Port (Port only)
Nipro Corporation	• Infuser Port • Catheter Access • Catheter Access P (Regular type) • Catheter Access P (Regular type, Separate, for 2.7Fr)
	• Catheter Access AI Kit • Interflex AI Catheter (Catheter coated by heparin)
Nippon Sherwood Medical Industries Ltd.	• Dermaport PP

Piolax Medical Devices, Inc.	• Piolax W Spiral Catheter • Piolax W Spiral Catheter (G Spiral) • Piolax W Spiral Catheter (Coaxial)
	• IV Catheter
Medicon,Inc.	• M.R.I. Plastic Low Profile Port with attachable open-ended silicone 6.6 Fr. Catheter • MRI Implantable port with Groshong catheter • MRI Port with Arterial 6.7 Fr. ChronoFlex catheter • MRI Low Profile Port with TORAY Cathlock • Titanim Low Profile Port with attachable Groshong 8.0 Frech catehter • SlimPort M.R.I. Ultra Low Profile plastic port with attachable open ended ChronoFlex 6.0 Fr. catheter • X-PORT Low Profile Port with TORAY • X-Port isp M.R.I. plastic port with attachable Groshong 8.0 Fr. catheter • X-Port isp M.R.I. plastic port with attachable open ended ChronoFlex 6.0 Fr. catheter
Unitika Ltd.	• UK-Catheter kit (Catheter for Reservoir)

2. Defect reports on port and catheter

A total of 740 cases of port and catheter defects have been reported for 12 products of 6 marketing authorization holders (MAHs) between April 2004 and December 2010.

Of these, 484 cases (65.4%) involved catheter fracture/breakage. These were observed on the port connector in 275 cases, near the port connector in 15 cases, between the first rib and the clavicle in 16 cases, at the elbow in 8 cases, at other sites in 12 cases and at unspecified sites in 158 cases. On the other hand, 392 cases of those were reported that the fractured catheter migrated into the heart or the pulmonary artery. Other than catheter fracture/breakage, 182 cases of port body breakage and 51 cases of catheter disconnection from the port were reported.

Catheter fracture/breakage may be attributed to multiple factors, including the port-catheter connecting procedure and the physical stress on the port connector due to body movement or the cardiac pulsation of patients with long-term use of these devices. Fracture of catheters pinched between the first rib and the clavicle may be due to the surgical technique of catheter placement in the subclavian vein. Catheter fracture at other sites may also be caused by continual physical stress due to bending and extending of the arm of patients with long-term use. Catheter disconnection may be attributed to inadequate port-catheter connection at the time of placement as well as increased pressure in the port due to the use of a syringe less than 10mL in size to inject drugs.

3. Safety measures

In light of the above-mentioned accidents, the MAHs have been improving their products (e.g., modification of port-catheter connection and improvement of connector parts). Meanwhile, to increase caution for the catheter placement procedure and long-term use, MHLW issued a notification on May 25, 2011 and required the MAHs to include the following precautions in the “Warnings” and “Precautions” sections of package inserts.

- There is a risk of catheter fracture or other adverse events associated with long-term use of the device.
- Consider removal from patients for whom the placements of the devices are no longer needed.
- Use an appropriate-sized syringe for flushing.
- There are possible risks associated with the use of a subcutaneous port and catheter.

Specifically, the "Warnings" and the “Precautions” sections have been revised as follows. Take the following precautions and follow-up patients carefully when using a subcutaneous port and catheter.

○ The “Warnings” section should include the following precautions:

(1) When placing a catheter in the subclavian vein, make sure not to be pinched between the first rib and the clavicle. [Catheter fracture or occlusion may occur.]

(2) Catheter fracture or migration into the heart may occur associated with long-term use. Removal of this product is recommended, if continuous use of this product is not medically necessary and it can be removed safely, after considering the patient's risk.

○ In the “Precautions” section, the following precaution (1) should be included in the “Important Precautions”, and the following precaution (2) should be included in the “Defects and Adverse Events”.

(1) Use an XX mL or larger size of syringe (the appropriate size should be designated based on the validation test of individual products by the MAH) when injecting drugs into the port chamber or flushing the catheter. [If a syringe less than XX mL is used, the pressure in the port chamber may increase and cause damage,etc. to the port or catheter.]

(2) The following are possible risks associated with the use of a subcutaneous port and catheter. Caution should be exerted to these risks at the time of follow-up of patients.

- Port migration or reversal
- Port body breakage
- Septum breakage
- Infection around the implanted site
- Hematoma around the implanted site
- Catheter disconnection from the port
- Catheter perforation
- Catheter fracture
- Catheter migration into a blood vessel
- Catheter occlusion
- Catheter-deployed venous occlusion
- Fibrin sheath
- Subcutaneous extravasation of drug
- System-associated infection
- Skin disorder around the puncture site
- Pulmonary thromboembolism

2 Important Safety Information

This section presents the contents of revisions and case summaries that served as the basis for these revisions to important adverse reactions included under the Precautions section of the package inserts of drugs that have been revised in accordance with the Notification dated May 31, 2011.

1 Freeze-dried Live Attenuated Measles Vaccine; Freeze-dried Live Attenuated Measles, Rubella Combined Vaccine

Brand Name (name of company)	**Freeze-dried Live Attenuated Measles Vaccine** DRIED LIVE ATTENUATED MEASLES VACCINE (SCHWARZ FF-8 STRAIN) "Takeda" (Takeda Pharmaceutical Company Limited) Freeze-dried Live Attenuated Measles Virus Vaccine "Kitasatodaiichisankyo" (Kitasato Daiichi Sankyo Vaccine Co., Ltd.) MEASLES VIRUS VACCINE LIVE ATTENUATED "BIKEN CAM" (The Research Foundation for Microbial Diseases of Osaka University) **Freeze-dried Live Attenuated Measles, Rubella Combined Vaccine** FREEZE-DRIED LIVE ATTENUATED MEASLES AND RUBELLA COMBINED VACCINE (SCHWARZ FF-8 STRAIN/TO-336 STRAIN) "Takeda" (Takeda Pharmaceutical Company Limited) Freeze-dried Live Attenuated Measles, Rubella Combined Vaccine "Kitasatodaiichisankyo" (Kitasato Daiichi Sankyo Vaccine Co., Ltd.) MEARUBIK (The Research Foundation for Microbial Diseases of Osaka University)
Therapeutic Category	Vaccines, Mixed biological preparations
Indications	**Freeze-dried Live Attenuated Measles Vaccine** Use for prevention of measles. **Freeze-dried Live Attenuated Measles, Rubella Combined Vaccine** Use for prevention of measles and rubella.

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 generally occur within several days to 2 weeks after vaccination. If ADEM is suspected, the patients should be diagnosed using MRI etc., and appropriate measures should be taken.

Encephalitis/encephalopathy: Encephalitis or encephalopathy may occur. Patients should be carefully monitored. If any abnormalities are observed, the patients should be diagnosed using MRI etc., and appropriate measures should be taken.

Reference Information

Freeze-dried Live Attenuated Measles Vaccine

The number of reported adverse reactions (for which a causality to the vaccine could not be ruled out) for the past 3 years (April 1, 2008 to April 30, 2011)

- Acute disseminated encephalomyelitis: 2 cases (no fatal cases)

The number of patients using this vaccine per year estimated by MAHs: Approximately 76,000 (2010)

Launched in Japan: June 1971

Freeze-dried Live Attenuated Measles, Rubella Combined Vaccine

The number of reported adverse reactions (for which a causality to the vaccine could not be ruled out) for the past 3 years (April 1, 2008 to April 30, 2011)

- Encephalopathies: 6 cases (no fatal cases)

The number of patients using this vaccine per year estimated by MAHs: approximately 4,600,000 (2010)
Launched in Japan: December 2005

Case Summary

<Freeze-dried Live Attenuated Measles Vaccine>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 10s	Measles immunization (none)	0.5 mL Once	**Acute disseminated encephalomyelitis** Day of vaccination: The patient received freeze-dried live attenuated measles vaccine. 18 days after vaccination: During softball club activities, she suddenly experienced glare in both eyes and lost consciousness. Afterwards, she returned to consciousness and went back home. At home, she was found foaming at the mouth on her bed, with a flushed face and ankylosis. She was then transferred to Hospital A by ambulance. Following this, systemic tonic convulsion starting with numbness of the left hand and twitching of the left eyelid was observed 6 times in total. 27 days after vaccination: The patient was transferred to Hospital B. Cerebrospinal fluid cell count and neopterin increased. The single photon emission computed tomography (SPECT) showed an increased cerebral blood flow in the lesion. She was diagnosed with secondary encephalitis (acute disseminated encephalomyelitis). Steroid pulse therapy, human immunoglobulin therapy, and post-steroid therapy (oral) were performed. During the treatment course, continuous administration of midazolam and oral administration of sodium valproate and gabapentin were required to control convulsive seizure. Oral administration of gabapentin was continued. 57 days after vaccination: The symptoms remitted and the patient was discharged from the hospital.
	Concomitant medications: none			

<Freeze-dried Live Attenuated Measles, Rubella Combined Vaccine>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male Under age of 10	Prevention of measles and rubella (none)	0.5 mL Once	**Acute encephalopathy** Day of vaccination: The patient received freeze-dried live attenuated measles, rubella combined vaccine. Day 9 of vaccination: The patient had pyrexia of 39°C and vomited once in the evening.

				Day 10 of vaccination: The patient had pyrexia between 37.7°C to 38.2°C in the morning. He visited the reporting hospital. Cough (-), nasal discharge (-). Only mild redness of pharynx was noted. He had appetite and felt healthy. Blood test results were normal. Since pyrexia was considered to be caused by the vaccine, no medications were given. Convulsive status epilepticus was observed at night and he was admitted to another Hospital A. Unknown date: After admission, convulsion persisted for 4 - 5 days, with disturbed consciousness. The patient was diagnosed with acute encephalopathy based on an MRI scan. Day 26 of vaccination: The consciousness returned, but rigidity of limbs was noted. (Information about the patient's clinical course was obtained from Doctor A at the other hospital by a phone call). Day 77 of vaccination: The patient was discharged from another Hospital A. He started rehabilitation at another Hospital B. Day 189 of vaccination: The patient recovered, but with sequelae (rigidity of limbs and unsteady neck).
	Concomitant medications: none			

2 **Cisplatin** (intra-arterial injection)

Brand Name (name of company)	IA-call for Intra-arterial Injection 50 mg, 100 mg (Nippon Kayaku Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Hepatocellular carcinoma

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Hepatobiliary disorders: Hepatobiliary disorders including cholecystitis, biloma, and liver abscess may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to April 6, 2011)

- Hepatobiliary disorders: 7 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 7,300 (FY 2010)

Launched in Japan: July 2004

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Hepatocellular carcinoma [Stage III: (alcoholic	80 mg for 1 day	**Liver abscess (multiple)** Medical history: Large intestine carcinoma The patient received transcatheter arterial chemoembolization (TACE) with cisplatin 100 mg about 7 months and 3 months

		hepatopathy, lung cancer [Stage II])		before administration. Ethanol 10 mL was injected when the second TACE was performed. Day 1 of administration: Cisplatin 80 mg was administered for multiple hepatocellular carcinoma (TACE was performed). Cefotiam hydrochloride 1 g was administered. 1 day after administration: Cefotiam hydrochloride 2 g (2 ×) was administered (for 3 days). 4 days after administration: Cefotiam hydrochloride 1g and meropenem hydrate 0.5 g were administered. 5 days after administration: Meropenem hydrate 1 g (2 ×) was administered. 6 days after administration: Meropenem hydrate 2.5 g (5 ×) was administered. 7 days after administration: Meropenem hydrate 2 g (4 ×) and vancomycin hydrochloride 1g (2 ×) were administered. 8 days after administration: Vancomycin hydrochloride 1g was administered (for 10 days). After TACE, antibiotics were administered for prevention of infection, but inflammatory reaction occurred and did not remit. 13 days after administration: An abdominal CT showed air density in the liver carcinoma where TACE was performed. Liver abscess (multiple) developed. Administration of antibiotics was continued, but the symptoms did not remit. 17 days after administration: Abscess drainage was performed. 19 days after administration: Vancomycin hydrochloride 1g was administered (for 6 days). 21 days after administration: Clindamycin 600 mg was administered. 22 days after administration: Clindamycin 1800 mg (3 ×) was administered (for 5 days). 25 days after administration: Vancomycin hydrochloride 0.75 g was administered (for 3 days). 26 days after administration: Gentamicin sulfate 20 mg (intravenous drip [div]) and 180 mg (div) was administered. 27 days after administration: Clindamycin 1200 mg (2 ×) and itraconazole 20 mL (for 8 days) were administered. 28 days after administration: Abscess drainage was performed. During the drainage, CRP was elevated up to 17.6 mg/dL. 32 days after administration: Meropenem hydrate 0.5 g and linezolid 600 mg were administered. 33 days after administration: Meropenem hydrate 1.5 g (3 ×) (for 17 days) and linezolid 1200 mg (2 ×) (for 4 days) were administered. 36 days after administration: Gentamicin sulfate 10 mg was infused into abscess (for 3 days).

				38 days after administration: Linezolid 1200 mg (2 ×) was administered (for 12 days). 40 days after administration: Itraconazole 20 mL was administered (for 10 days). 50 days after administration: Meropenem hydrate 1 g (2 ×) (for 2 days) and linezolid 600 mg were administered. 51 days after administration: Linezolid 1200 mg (2 ×) was administered (for 28 days). 52 days after administration: Meropenem hydrate 1.5 g (3 ×) was administered (for 27 days). 62 days after administration: CRP was decreased to 3.6 mg/dL. 71 days after administration: After having returned to hospital following staying out overnight, he developed pneumonia aspiration. 79 days after administration: Respiratory failure progressed, and the patient died.
	Concomitant medications: gelatin, epirubicin hydrochloride, mitomycin C, iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil, ramosetron hydrochloride, pentazocine, alprostadil, iohexol			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Hepatocellular carcinoma [Stage IVA] (hepatitis C, hepatic cirrhosis)	60 mg for 1 day	**Biloma, Liver abscess** The patient developed multiple tumor stains measuring 10 to 20 mm in the right lobe of his liver. The stage of the portal vein invasion was Vp1. A tumor stain measuring 45 mm was showed in S2. Day 1 of administration: Cisplatin 30 mg and the iodine addition product of the ethylesters of the fatty acids obtained from poppyseed oil were administered intra-arterially via left hepatic artery, and embolization was performed with gelatin. Cisplatin 30 mg and the iodine addition product of the ethylesters of the fatty acids obtained from poppyseed oil were injected into the posterior segmental branch of the dominant right hepatic artery. 9 days after administration: CRP was as high as 10.03 mg/dL. A follow-up observation was performed. 14 days after administration: CRP was 5.6 mg/dL. 17 days after administration: The patient was temporally discharged from the hospital. 19 days after administration: Pyrexia developed, and biloma was noted in the right lobe and the caudate lobe on images. CRP was elevated again to 8.37 mg/dL. WBC was 10200/μL. 26 days after administration: Biloma increased in both lobes. Liver abscess developed. 28 days after administration: The patient was treated with oral levofloxacin hydrate 600

				mg/day (for 4 days), but his symptoms could not be controlled. 31 days after administration: The patient was admitted to the hospital. A CT showed an increased liver abscess. Sulbactam sodium and cefoperazone sodium 4 g/day were administered (for 19 days). 51 days after administration: Inflammatory reaction was slightly improved, and the patient was discharged from the hospital. 79 days after administration: CRP was 7.78 mg/dL. Biloma and liver abscess had not resolved. Approximately 7 months after administration: Biloma and liver abscess had not resolved. The patient died of the primary disease.
	Concomitant medications: iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil, gelatin			

3 Sitagliptin Phosphate Hydrate

Brand Name (name of company)	GLACTIV Tablets 25 mg, 50 mg, 100 mg (Ono Pharmaceutical Co., Ltd.) JANUVIA Tablets 25 mg, 50 mg, 100 mg (MSD K.K.)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatment: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies (3) Thiazolidine along with diet and exercise therapies (4) Biguanide along with diet and exercise therapies (5) α-glucosidase inhibitor along with diet and exercise therapies

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur. If pyrexia, cough, dyspnoea or abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids 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 and 5 months (from initial marketing to April 30, 2011)

- Interstitial pneumonia: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 630,000 (May 2010 to April 2010)
Launched in Japan: December 2009

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female	Diabetes	50 mg for	**Interstitial pneumonia**

	60s	mellitus (tobacco user, hypertension)	34 days	Day 1 of administration: The patient started receiving sitagliptin phosphate hydrate. Within several days of administration: The patient became aware of dyspnoea. Day 33 of administration: Dyspnoea gradually progressed. The patient was admitted to the hospital for the purpose of bronchoscopy. Day 34 of administration (day of discontinuation): A CT showed an obvious image of interstitial pneumonia in the lung fields. Steroid pulse therapy (60 mg for 3 days) was started. Administration of sitagliptin phosphate hydrate was discontinued. 6 days after discontinuation: KL-6 2084 U/mL, LDH 394 IU/L, CRP 5.4 mg/dL. 40 days after discontinuation: Interstitial pneumonia remitted. Steroid 30 mg/day being administered. LDH 167 IU/L. 44 days after discontinuation: KL-6 1457 U/mL.
	Concomitant medications: telmisartan, saikanto, goshuyuto			

Laboratory Examination

	1 day after discontinuation	2 days after discontinuation	4 days after discontinuation	6 days after discontinuation	11 days after discontinuation	40 days after discontinuation	44 days after discontinuation
WBC (/μL)	7800	9000	8400	8900	8700	—	—
Hemoglobin (g/dL)	12.3	12.3	12.1	12.4	12.8	—	—
PLT ($\times 10^4$/μL)	47.7	53.2	47.2	42.8	49.8	—	—
CRP (mg/dL)	2.91	3.14	3.48	5.4	0.9	—	—
PT (%)	67.5	—	—	64	—	—	—
KL-6 (U/mL)	—	—	—	2084	—	—	1457
LDH (IU/L)	—	—	—	394	—	167	—

4 Sorafenib Tosilate

Brand Name (name of company)	Nexavar Tablet 200 mg (Bayer Yakuhin, Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Radically unresectable or metastatic renal cell carcinoma, unresectable hepatocellular carcinoma

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Fulminant hepatitis, hepatic dysfunction/jaundice, hepatic failure, hepatic encephalopathy: Fulminant hepatitis, hepatic dysfunction with elevations of AST (GOT) or ALT (GPT), jaundice, hepatic failure, or hepatic encephalopathy may occur. Patients should be carefully monitored. If abnormalities are observed, the dose of this drug should be reduced or administration of this drug should be suspended and discontinued, and appropriate measures should be taken. Hepatic encephalopathy has been reported mainly in patients with hepatocellular carcinoma or hepatic cirrhosis. When administering this drug to such patients, they should be carefully

monitored for changes in their clinical symptoms including disturbed consciousness.
Haemorrhagic enterocolitis and ischaemic enterocolitis: Serious enterocolitis including haemorrhagic enterocolitis and ischaemic enterocolitis may occur. Patients should be carefully monitored, and if symptoms including severe abdominal pain, diarrhoea, or bloody stool 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 (from initial marketing to April 10, 2011)

- Fulminant hepatitis: 2 cases (2 fatal cases)
- Haemorrhagic enterocolitis, ischaemic enterocolitis: 7 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 6,000 (June 2010 to May 2011)
Launched in Japan: April 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Right renal cancer (hyperuricaemia, hypertension, metastases to lymph nodes, metastatic lung cancer)	800 mg for 100 days	**Fulminant hepatitis** Day 1 of administration: The patient started receiving sorafenib tosilate. Day 100 of administration (day of discontinuation): Fulminant hepatitis developed. Administration of sorafenib tosilate was discontinued. Administration of glycyrrhizin/DL-methionine and ursodeoxycholic acid was started. Jaundice and hepatic encephalopathy occurred (Grade 2). 12 days after discontinuation: Jaundice worsened. 14 days after discontinuation: Renal failure occurred. 16 days after discontinuation: Haemodialysis and bilirubin adsorption were performed. 22 days after discontinuation: Decreased level of consciousness was observed early in the morning. Haemodialysis and bilirubin adsorption were scheduled but canceled. Around noon, the patient died of hepatic failure. Abdominal CT test: (Day 94 of administration) Metastasis to liver was not confirmed, Gallbladder: Swelling was noted. Abdominal ultrasonography: (15 days after discontinuation) Liver: Mild uneven surface, Gallbladder: circumferential thickening.
	Concomitant medications: none			

Laboratory Examination

	7 days before administration	Day 14 of administration	Day 42 of administration	Day 72 of administration	Day 100 of administration (day of discontinuation)	5 days after discontinuation	15 days after discontinuation	22 days after discontinuation
Albumin (g/dL)	4.0	4.1	4.4	4.5	3.9	3.2	2.4	2.5
Total bilirubin (mg/dL)	0.5	0.6	0.6	0.5	5.1	8.2	19.0	23.1

AST (GOT) (IU/L)	21	30	132	86	2204	1257	446	59
ALT (GPT) (IU/L)	20	27	240	135	2388	1432	441	111
LDH (IU/L)	205	360	352	295	1085	568	337	608
Al-P (IU/L)	256	260	331	266	769	696	575	407
γ-GTP (IU/L)	19	29	68	60	490	459	192	276
Ammonia (μg/dL)	—	—	—	—	133	—	—	126
PT activity (%)	99	102	103	105	63	73	51	20

5 **Metformin Hydrochloride** (products with "Dosage and Administration" of maximum daily dosage of 2250mg)

Brand Name (name of company)	METGLUCO Tablets 250 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies

PRECAUTIONS (underlined parts are revised)

Important Precautions

Lactic acidosis may occur due to dehydration. If any symptoms of dehydration are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

In patients with renal impairment, the excretion of this drug in the kidneys is decreased, leading to increased blood concentration. Before and after treatment is started, caution in regards to the following points should be exerted:

1) Patients should be carefully monitored for renal impairment and dosing adjustment should be considered.
2) During administration of this drug, the renal function (eGFR, serum creatinine level, etc.) should be checked periodically, or more frequently in patients requiring careful follow-up observation, such as elderly patients. If renal function is aggravated, administration of this drug should be discontinued, or the dose of this drug should be reduced.

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 April 28, 2011)

- Lactic acidosis due to dehydration: 2 cases (1 fetal case)
- Lactic acidosis due to aggravated renal function: 1 case (no fatal case)

The number of patients using this drug per year estimated by MAHs: approximately 190,000 (June 2010 to May 2011)

Launched in Japan: May 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Diabetes mellitus (Chronic cholecystitis)	750 mg for 22 days ↓ 1000 mg	**Lactic acidosis, intestinal obstruction** About two and a half years before administration, the patient was referred and admitted to the hospital because she became bedridden due to sequelae of cerebral infarction (prolonged disturbed consciousness, right hemiplegia, speech loss,

			for 33 days	pseudobulbar palsy), right femoral neck fracture, diabetes mellitus, and because gastrogavage via gastric fistula was necessary for long-term continuous treatment. At an early stage of hospitalization, blood glucose was controlled with insulin. The dose of insulin was gradually decreased, and from about one year and 11 months before administration of METGLUCO Tablet, administration of glimepiride and metformin hydrochloride was started. Administration of glimepiride was discontinued about 11 months before administration of METGLUCO Tablet, and metformin hydrochloride alone was continued. Day 1 of administration: Metformin hydrochloride (750 mg/day) was switched to METGLUCO Tablet 750 mg/day. Day 23 of administration: The dose of METGLUCO Tablet was increased to 1000 mg/day for improving glucose tolerance. Day 49 of administration: There was no finding of ileus when the gastric fistula catheter was exchanged. Day 54 of administration: The patient vomited after enteral nutrition in the evening. Percutaneous endoscopic gastrostomy (PEG) catheter was opened, and there was drainage of 50 mL. Abdominal distension was noted. Body temperature 36.5°C, pulse rate 126, blood pressure 193/117 mmHg, SpO_2 93%. Day 55 of administration (day of discontinuation): The patient vomited again after enteral nutrition in the morning. PEG catheter was opened, and there was drainage of 60 mL in about 3 hours. The patient was fasted in the daytime and drip infusion of glucose-electrolyte solution 1000 mL was started. In the afternoon, abdominal X-ray and other test results were obtained. The patient was diagnosed with ileus and dehydration, drip infusion of physiological saline solution 1000 mL diluted two-fold was added. Placement of bladder balloon catheter, measurement of urine output, and twice-daily measurement of blood glucose were instructed. Abdominal distension was noted. Body temperature 36.3°C, pulse rate 108, blood pressure 193/71 mmHg, SpO_2 96%, respiratory rate (RR) 42. Urine output measured was very small. After 3 hours and 40 minutes, insulin 8 U was subcutaneously administered due to a high level of blood glucose. After 4 hours and 43 minutes, jaw breathing occurred. Inhalation of oxygen 5 L/min was started. After 4 hours and 55 minutes, administration of dopamine hydrochloride was started due to blood pressure 40 mmHg (palpation). After 6 hours and 20 minutes, blood glucose level was 562 mg/dL. After 6 hours and 30 minutes, body temperature 36.4°C, pulse rate 120, blood pressure 80 mmHg (palpation), SpO_2 94%. Urine output was small. After 8 hours and 35 minutes, the patient was in cardio-respiratory arrest. Cardiac massage was performed. After 9 hours and 28 minutes, the patient died. (Cause of death: lactic acidosis)

	Concomitant medications: aspirin, monoammonium glycyrrhizinate/glycine/DL-methionine, famotidine, metoclopramide

Laboratory Examination

	Approx. 2.5 years before administration	Approx. 1 year and 11 months before administration	Approx. 11 months before administration	Approx. 5 months before administration	Day 21 of administration	Day 55 of administration (day of discontinuation)
Blood glucose (mg/dL)	156	95	100	98	140	576
HbA_{1c} (JDS level) (%)	5.0	—	—	6.1	6.3	—
BUN (mg/dL)	21.5	19.8	29.3	21.2	25.0	47.5
Serum creatinine (mg/dL)	0.53	0.71	0.83	0.74	0.80	1.73
Total protein (g/dL)	6.8	6.2	6.8	6.6	6.8	8.6
RBC ($\times 10^4/mm^3$)	496	—	513	540	512	626
Hemoglobin (g/dL)	15.6	—	16.6	16.4	16.5	20.3
Hematocrit (%)	45.4	—	48.4	49.5	49.2	62.1
Na (mEq/L)	139	138	142	143	140	138

	Day 55 of administration (day of discontinuation)
Arterial blood pH	7.415
PCO_2 (mmHg)	16.4
PO_2 (mmHg)	102.8
HCO_3- (mM)	10.4
BE (mM)	-10.4
O_2sat (%)	97.7
Lactic acid (mg/dL)	91.4
Pyruvic acid (mg/dL)	3.77

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 90s	Diabetes mellitus (none)	750 mg for 14 days ↓ 1500 mg for 14 days ↓ 2250 mg for 33 days	**Lactic acidosis** From approximately 17 years before administration: The patient had received oral medications for diabetes mellitus. From approximately 2 months before administration: The patient had received buformin hydrochloride 150 mg/day. Day 1 of administration: Blood glucose 257 mg/dL and HbA_{1c} 6.0%. Buformin hydrochloride was switched to METGLUCO Tablet 750 mg/day. Serum creatinine was 1.3 mg/dL Day 15 of administration: Blood glucose 299 mg/dL. The dose of METGLUCO Tablet was increased to 1500 mg/day. Day 29 of administration: Blood glucose 201 mg/dL. The dose of METGLUCO Tablet was increased to 2250 mg/day. Day 49 of administration: Serum creatinine 1.6 mg/dL, HbA_{1c} 6.9% Day 60 of administration: Dysarthria and perceptual disturbance on the left side of the

				body occurred. An MRI showed no abnormalities. Fluid replacement 500 mL and methylmethionine sulfonium chloride 400 mg were administered. Day 61 of administration (day of discontinuation): The patient was transferred to the hospital by ambulance due to physical deconditioning. Results of tests conducted at the hospital visit showed lactic acid 157.9 mg/dL, pH 6.832, PCO_2 9.0 mmHg, PO_2 254.5 mmHg (reservoir 10L), base excess (BE) -32.5 mmol/L, HCO_3- 1.5 mmol/L. The patient was diagnosed with lactic acidosis, and started inpatient care. Administration of METGLUCO Tablet was discontinued. Continuous haemodiafiltration (CHDF) was performed. Blood concentration of metformin: 39300 ng/mL 2 days after discontinuation: Lactic acid level was almost normal, and acidosis disappeared. 3 days after discontinuation: CHDF was discontinued. 5 days after discontinuation: Oral food intake was started. The patient was moved from the intensive care unit to the general ward. (Lactic acidosis resolved.)
	Concomitant medications: none			

Laboratory Examination

(The hospital where metformin hydrochloride was originally prescribed)

	Day 1 of administration	Day 49 of administration
Fasting blood glucose level (mg/dL)	257	214
HbA_{1c} (JDS level) (%)	6.0	6.9
BUN (mg/dL)	—	26
Serum creatinine (mg/dL)	1.3	1.6
RBC ($\times 10^4/mm^3$)	—	407
Hemoglobin (g/dL)	8.9	12.3
Hematocrit (%)	—	36.6

(Hospital where the patient was transported)

	Day 61 of administration (day of discontinu-ation)	1 day after discontinu-ation	2 days after discontinu-ation	3 days after discontinu-ation	5 days after discontinu-ation
Fasting blood glucose level (mg/dL)	301	29	170	172	252
BUN (mg/dL)	96	68	42	29	32
Serum creatinine (mg/dL)	7.3	4.5	2.6	1.8	1.8
Serum lactic acid (mg/dL)	157.9	120.6	21.1	12.3	13.0
pH	6.832	7.453	7.473	7.527	—
BE (mmol/L)	-32.5	-6.0	4.6	5.1	—
RBC ($\times 10^4/mm^3$)	414	323	332	309	288
Hemoglobin (g/dL)	12.9	9.9	10.4	9.6	9.1
Hematocrit (%)	40.4	29.7	29.9	28.1	26.4
Na (mEq/L)	141	155	142	140	142

3

Revision of Precautions (No. 227)

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 May 31, 2011 (excluding those presented in 2. Important Safety Information of this Bulletin).

1

Adrenal hormone preparations

Cortisone Acetate
Dexamethasone (oral dosage form)
Dexamethasone Metasulfobenzoate Sodium (injectable dosage form)
Dexamethasone Sodium Phosphate (injectable dosage form)
Triamcinolone
Triamcinolone Acetonide (injectable dosage form for intraarticular/intramuscular/intradermal)
Hydrocortisone Sodium Phosphate
Fludrocortisone Acetate
Prednisolone (oral dosage form)
Prednisolone Sodium Succinate
Prednisolone Sodium Phosphate
Betamethasone
Betamethasone Acetate/Betamethasone Sodium Phosphate
Betamethasone Sodium Phosphate (injectable dosage form, enema)

Brand Name

CORTONE Acetate Tablets 25 mg (Nichi-Iko Pharmaceutical Co., Ltd.)
DECADRON Tablets 0.5 mg (Nichi-Iko Pharmaceutical Co., Ltd.), LenaDex Tablets 4 mg (Celgene K.K.)
MESADORON Injection 2 mg, 3 mg (Kobayashi Kako Co., Ltd.)
DECADRON Phosphate Injection 1.65 mg, 3.3 mg (MSD K.K.)
LEDERCORT Tablets 4 mg (Alfresa Pharma Corporation)
KENACORT-A INTRADERMAL INTRAARTICULAR Suspension Liquid Injection 50 mg/5 m L (Bristol-Myers K.K.)
Hydrocortone Injection 100 mg, 500 mg (Aqueous) (Nichi-Iko Pharmaceutical Co., Ltd.)
FLORINEF TABLETS 0.1mg (Bristol-Myers K.K.)
Predonine Tablets 5 mg (Shionogi & Co., Ltd.)
Predonine 10 mg, 20 mg, 50 mg (Aqueous) (Shionogi & Co., Ltd.)
PREDONEMA Enema 20 mg (Kyorin Pharmaceutical Co., Ltd.)
Rinderon Tablets 0.5 mg, Rinderon Powder 0.1%, Rinderon Syrup 0.01%, Rinderon Suppository 0.5 mg, 1.0 mg (Shionogi & Co., Ltd.)

Rinderon Suspensions for Injection (Shionogi & Co., Ltd.)
Rinderon Injection 20 mg, 100 mg (Shionogi & Co., Ltd.),
STERONEMA ENEMA 3 mg, 1.5 mg (Nichi-Iko Pharma Factory Co., Ltd.)

Important Precautions

Hepatitis may occur due to hepatitis B viral growth in hepatitis B virus carriers who were administrated a corticosteroid. Attention for the occurrence of signs or symptoms related to hepatitis B viral growth should be paid by continuously monitoring results of liver function tests or hepatitis viral markers during and after the administration period of this drug. If any abnormalities are observed, dose reduction of this drug should be considered, and appropriate measures including administration of an antiviral drug should be taken. In addition, hepatitis due to hepatitis B virus has been reported in patients who were negative for HBs antigen before the start of administration.

Adverse Reactions (clinically significant adverse reactions)

Induced infection or aggravated infection: Induced infection or aggravated infection may occur. Hepatitis due to hepatitis B viral growth may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

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2 Adrenal hormone preparations

Dexamethasone Palmitate

Brand Name

Limethason INTRAVENOUS INJECTION 2.5 mg
(Mitsubishi Tanabe Pharma Corporation)

Important Precautions

Hepatitis may occur due to hepatitis B viral growth in hepatitis B virus carriers who were administrated a corticosteroid. Attention for the occurrence of signs or symptoms related to hepatitis B viral growth should be paid by continuously monitoring results of liver function tests or hepatitis viral markers during and after the administration period of this drug. If any abnormalities are observed, dose reduction of this drug should be considered, and appropriate measures including administration of an antiviral drug should be taken. In addition, hepatitis due to hepatitis B virus has been reported in patients who were negative for HBs antigen before the start of administration.

Adverse Reactions (clinically significant adverse reactions)

Induced infection or aggravated infection: Induced infection or aggravated infection may occur. Hepatitis due to hepatitis B viral growth may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

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3 Adrenal hormone preparations

Hydrocortisone

Brand Name

Cortril Tablets 10mg (Pfizer Japan Inc.)

Important Precautions

Hepatitis may occur due to hepatitis B viral growth in hepatitis B virus carriers who were administrated a corticosteroid. Attention for the occurrence of signs or symptoms related to hepatitis B viral growth should be paid by continuously monitoring results of liver function tests or hepatitis viral markers during and after the administration period of this drug. If any abnormalities are observed, dose reduction of this drug should be considered, and appropriate measures including administration of an antiviral drug should be taken. In addition, hepatitis due to hepatitis B virus has been reported in patients who were negative for HBs antigen before the start of administration.

Adverse Reactions (clinically significant adverse reactions)

Infection: Induced infection or aggravated infection, etc. may occur. Hepatitis due to hepatitis B viral growth may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

4

Adrenal hormone preparations

Hydrocortisone Sodium Succinate
Methylprednisolone
Methylprednisolone Sodium Succinate
Methylprednisolone Acetate

Brand Name

Solu-Cortef for Intravenous Use 250 mg, 500 mg, 1000 mg,
Solu-Cortef Injection 100 mg (Pfizer Japan Inc.)
Medrol Tablets 2 mg, 4 mg (Pfizer Japan Inc.)
Solu-Medrol for Intravenous Use 40 mg, 125 mg (Pfizer Japan Inc.)
Depo-Medrol Sterile Aqueous Suspension 20 mg, 40 mg (Pfizer Japan Inc.)

Important Precautions

Hepatitis may occur due to hepatitis B viral growth in hepatitis B virus carriers who were administrated a corticosteroid. Attention for the occurrence of signs or symptoms related to hepatitis B viral growth should be paid by continuously monitoring results of liver function tests or hepatitis viral markers during and after the administration period of this drug. If any abnormalities are observed, dose reduction of this drug should be considered, and appropriate measures including administration of an antiviral drug should be taken. In addition, hepatitis due to hepatitis B virus has been reported in patients who were negative for HBs antigen before the start of administration.

Adverse Reactions (clinically significant adverse reactions)

Infection: Induction or masking of signs of infection, worsening of infection, etc., from viruses, bacteria, fungi, protozoa, or parasites may occur. It has been reported that the incidence of these infections was elevated with a dose of corticosteroid. Appropriate measures including antimicrobial drugs should be taken. Hepatitis due to hepatitis B viral growth may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

5

Adrenal hormone preparations

Betamethasone/*d*-Chlorpheniramine Maleate

Brand Name

CELESTAMINE Combination Tablets, CELESTAMINE Combination Syrup (MSD)

Important Precautions

Hepatitis may occur due to hepatitis B viral growth in hepatitis B virus carriers who were administrated a corticosteroid. Attention for the occurrence of signs or symptoms related to hepatitis B viral growth should be paid by continuously monitoring results of liver function tests or hepatitis viral markers during and after the administration period of this drug. If any abnormalities are observed, dose reduction of this drug should be considered, and appropriate measures including administration of an antiviral drug should be taken. In addition, hepatitis due to hepatitis B virus has been reported in patients who were negative for HBs antigen before the start of administration.

Adverse Reactions (clinically significant adverse reactions)

Induced infection or aggravated infection: Induced infection or aggravated infection may occur. Hepatitis due to hepatitis B viral growth may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

6

Hormones-Miscellaneous

Mitotane

Brand Name

Opeprim (Yakult Honsha Co., Ltd.)

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

7 Synthetic antibacterials

Linezolid

Brand Name	ZYVOX Tablets 600 mg, ZYVOX Injection 600 mg (Pfizer Japan Inc.)
Important Precautions	Hyponatraemia may occur in association with administration of this drug. Patients should be monitored by checking serum sodium level periodically. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
Adverse Reactions (clinically significant adverse reactions)	**Hyponatraemia**: Hyponatraemia associated with disturbed consciousness, queasy, vomiting, anorexia, etc. may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

8 Vaccines

Freeze-dried, Cell Culture-derived Japanese Encephalitis Vaccine (Inactivated) (ENCEVAC)

Brand Name	ENCEVAC for Subcutaneous Injection (The Chemo-Sero-Therapeutic Research Institute)
Adverse Reactions (clinically significant adverse reactions)	**Encephalitis/encephalopathy**: Encephalitis/encephalopathy may occur. In such cases, symptoms including pyrexia, quadriplegia, convulsion, and disturbed consciousness may develop after vaccination. If encephalitis/encephalopathy is suspected, diagnosis should be made by MRI etc., and appropriate measures should be taken.

9 Vaccines

Freeze-dried, Cell Culture-derived Japanese Encephalitis Vaccine (Inactivated) (JEBIK V)

Brand Name	JEBIK V (The Research Foundation for Microbial Diseases of Osaka University)
Adverse Reactions (clinically significant adverse reactions)	**Encephalitis/encephalopathy**: Encephalitis/encephalopathy may occur. In such cases, symptoms including pyrexia, quadriplegia, convulsion, and disturbed consciousness may develop after vaccination. If encephalitis/encephalopathy is suspected, diagnosis should be made by MRI etc., and appropriate measures should be taken.

10 Various functional testing reagents

Inulin

Brand Name	INULEAD Inj. (Fujiyakuhin Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylactoid symptoms**: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored, and if abnormalities including dyspnoea or decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of the drug in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of July 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
l-Menthol MINCLEA catapasm for internal use 0.8%	Nippon Pharmaceutical Co., Ltd.	January 11, 2011
Levofloxacin Hydrate CRAVIT INTRAVENOUS DRIP INFUSION BAG 500 mg/100 mL, CRAVIT INTRAVENOUS DRIP INFUSION 500 mg/20 mL	Daiichi Sankyo Company, Limited	January 11, 2011
Paliperidone Invega Tablets 3 mg, 6 mg, 9 mg	Janssen Pharmaceutical K.K.	January 17, 2011
Ciclesonide Alvesco 50 µg Inhaler 112 puffs, Alvesco 100 µg Inhaler 112 puffs, Alvesco 200 µg Inhaler 56 puffs*[1]	Teijin Pharma Limited	January 21, 2011
Roxatidine Acetate Hydrochloride ALTAT CAPSULES 37.5, 75*[1]	ASKA Pharmaceutical Co., Ltd.	January 21, 2011
Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg	Janssen Pharmaceutical K.K.	February 4, 2011
Azacitidine Vidaza for Injection 100 mg	Nippon Shinyaku Co., Ltd.	March 11, 2011
Fondaparinux Sodium Arixtra Injection 5 mg, 7.5 mg	GlaxoSmithKline K.K.	March 11, 2011
Ustekinumab (Genetical Recombination) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	March 14, 2011
Dabigatran Etexilate Methanesulfonate Prazaxa Capsules 75 mg, 110 mg	Nippon Boehringer Ingelheim Co., Ltd.	March 14, 2011
Galantamine Hydrobromide REMINYL Tablets 4 mg, 8 mg, 12 mg, REMINYL OD Tablets 4 mg, 8 mg, 12 mg, REMINYL Oral Solution 4 mg/mL	Janssen Pharmaceutical K.K.	March 22, 2011
Eldecalcitol EDIROL Capsule 0.5 µg, 0.75 µg	Chugai Pharmaceutical Co., Ltd.	April 11, 2011
Freeze-dried, Cell Culture-Derived Japanese Encephalitis Vaccine (Inactivated) ENCEVAC Subcutaneous Injection	The Chemo-Sero-Therapeutic Research Institute	April 11, 2011

Romiplostim (Genetical Recombination) Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Ltd.	April 13, 2011
Anti-human Thymocyte Immunoglobulin, Rabbit Thymoglobuline for Intravenous Infusion 25 mg*2	Genzyme Japan K.K.	April 22, 2011
Doripenem Hydrate FINIBAX for Drip Infusion 0.25 g, FINIBAX Kit for Drip Infusion 0.25 g*3	Shionogi & Co., Ltd.	April 22, 2011
Levobupivacaine Hydrochloride POPSCAINE 0.25% inj. 25 mg/10mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL*4	Maruishi Pharmaceutical Co., Ltd.	April 22, 2011
Repaglinide SUREPOST Tablets 0.25 mg, 0.5 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 16, 2011
Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg	Teijin Pharma Limited	May 17, 2011
Levonorgestrel NORLEVO 0.75 mg Tablet	Sosei Co. Ltd.	May 24, 2011
Pioglitazone Hydrochloride/Glimepiride SONIAS Combination Tablets LD&HD	Takeda Pharmaceutical Company Limited	June 6, 2011
Memantine Hydrochloride MEMARY TABLETS 5 mg, 10 mg, 20 mg	Daiichi Sankyo Company, Limited	June 8, 2011
Adalimumab (Genetical Recombination) HUMIRA for s.c. injection syringe 40 mg/0.8 mL, HUMIRA for s.c. injection syringe 20 mg/0.4 mL*5	Abbott Japan Co., Ltd.	July 1, 2011
Erlotinib Hydrochloride TARCEVA Tablet 25 mg, 100 mg*6	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Gabapentin GABAPEN Tablets 200 mg, 300 mg, 400 mg*1	Pizer Japan Inc.	July 1, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 μg, 180 μg*7	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Lamotrigine Lamictal Tablets 25 mg, 100 mg*8	GlaxoSmithKline K.K.	July 1, 2011
Ribavirin COPEGUS Tablet 200 mg*9	Chugai Pharmaceutical Co., Ltd.	July 1, 2011

*1 An additional administration for “pediatrics”

*2 An additional indication for “treatment of acute rejection after renal transplantation”

*3 An additional dosage and administration for “maximum daily dose, 3 g”

*4 An additional indication for “conduction anesthesia”

*5 An additional indication for “treatment of patients with polyarticular-course juvenile idiopathic arthritis”

*6 An additional indication for “treatment of patients with unresectable pancreatic cancer”

*7 An additional indication for “improvement of viraemia in compensated cirrhosis type C in combination therapy with ribavirin”

*8 An additional indication for “suppression of recurrent/relapsed mood episodes in patients with bipolar disorder”

*9 An additional indication for “improvement of viraemia in compensated cirrhosis type C in combination therapy with peginterferon alfa-2a (genetical recombination)”