Pharmaceuticals and Medical Devices Safety Information

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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. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

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This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

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, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

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Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notifications dated December 21, 2006 and January 12, 2007.

1 Rituximab (Genetical recombination)

Brand Name (name of company)	Rituxan Injection 10 mg/mL (Zenyaku Kogyo Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	CD20 positive B-cell non-Hodgkin's lymphoma

<< **PRECAUTIONS** (underlined parts are additions) >>

[Warning]

WARNING

Deaths caused by hepatitis fulminant or exacerbation of hepatitis and hepatic failure have been reported in hepatitis B virus carrier patients during treatment period or after completion of the treatment with this product (See "Important Precautions" and "Clinically significant adverse reactions" sections).

[Important Precautions]

Hepatitis fulminant or exacerbation of hepatitis may occur when hepatitis B virus carrier patients are being treated with this product. Patients should be carefully observed by continuously monitoring liver function tests or hepatitis virus marker during treatment and after completion of the treatment with this product, and appropriate measures, such as discontinuing treatment and immediate administration of antiviral drug, should be taken if any abnormal findings are observed. It has been reported that patients who had been HBS antigen-negative before starting administration developed hepatitis fulminant caused by hepatitis B virus and died (See "Clinically significant adverse reactions" section).
Reduction in peripheral blood lymphocyte may occur during treatment with this drug and may persist after the completion of treatment. Some cases of immunoglobulin reduction following the use of this product have been reported. These immunosuppressive effects may induce emergence or exacerbation of bacteria or virus infections. Patients should be carefully monitored. Appropriate treatments should be conducted if any infectious diseases are observed.

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis fulminant or exacerbation of hepatitis caused by hepatitis B virus: Hepatic failure associated with hepatitis fulminant or exacerbation of hepatitis caused by hepatitis B virus may occur. Patients should be carefully monitored with monitoring of liver function tests or hepatitis virus marker (See "Important Precautions section").
Hepatic function disorder, jaundice: Hepatic function disorder with abnormalities in liver function tests such as AST (GOT), ALT (GPT), Al-P, and total bilirubin and jaundice may occur. Patients should be closely monitored with liver function tests etc. Discontinuation of administration and appropriate treatments should be conducted if any abnormalities are found.
Gastrointestinal perforation: Gastrointestinal tract perforation may occur. Patients should be closely monitored for early symptom of gastrointestinal tract perforation such as abdominal pain, bloated feeling, melaena, vomiting blood or anaemia. If any abnormalities are found, physicians should be encouraged to perform X-ray or, CT examinations, etc to identify the haemorrhage site or the presence/absence of findings of perforations and to take appropriate measures.

<Reference Information>

The number of reported adverse reaction cases in about the last 2 years (November 4, 2004 to December 11, 2006) (events for which a causality to the drug could not be denied)

- Hepatitis fulminant: 6 cases (of which 5 had fatal cases)
- Digestive tract perforation: 3 cases (of which 1 had a fatal case)

The number of patients treated with Rituximab for a year estimated by the marketing authorization holder (MAH): approximately 16000 patients (November 2005 to October 2006)

Marketed in Japan in: September 2001

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 40s	Non-Hodgkin's lymphoma (HBV career, hepatic steatosis)	600 mg 3 times	**Severe hepatitis** Non-Hodgkin's lymphoma (diffuse large B-cell lymphoma), clinical stage: I, past history: At the age of 45, coronary-artery bypass was performed for infarct myocardial, family history: His mother, younger brother, younger sister were HBV career 38 days before administration: The patient was diagnosed with right testicular tumor, and underwent orchiectomy Diagnosis of right testicular malignant lymphoma by pathological result 16 days before administration: HBs antigen (+), HBs antibody (−), HBc antibody (+), HBe antigen (−), HBe antibody (+), HBV-DNA 3.9 LGE/mL. Abdominal ultrasound (US) confirmed hepatic steatosis. 1 day before administration: AST (GOT) 30 IU/L, ALT (GPT) 114 IU/L. On day 1 of administration: (Treatment initiation day) The first course of this product + THP-COP regimen (pirarubicin hydrochloride, vincristine sulfate, cyclophosphamide, prednisolone) was conducted. On day 13 of administration: The second course of this product + THP-COP regimen was conducted. On day 27 of administration: The third course of this product + THP-COP regimen was conducted. AST (GOT) 30 IU/L, ALT (GPT) 81 IU/L. 11 days after completion: Radiation therapy was started to left testicular to prevent recurrence (total 40 Gy). 42 days after completion: Radiation therapy was completed and the patient was discharged. 75 days after completion: AST (GOT) 55 IU/L, ALT (GPT) 136 IU/L at out-patient follow-up examination. 94 days after completion: The patient experienced general malaise and anorexia and visited an emergency room. Marked hepatic function disorder of AST (GOT) 2358 IU/L, ALT (GPT) 3106 IU/L was observed and the patient was hospitalized on the same day.

				The patient was with diagnosed with severe hepatitis due to acute exacerbation of hepatitis B. G-I treatment was conducted, and administration of lamivudine 200 mg/day was started. 98 days after completion: AST (GOT) and ALT (GPT) were elevated to 7073 IU/L and 5151 IU/L, respectively, prothrombin time (PT) fell to 20.5%. Steroid pulse therapy was conducted. 101 days after completion: Although AST (GOT) and ALT (GPT) were improved to 1888 IU/L and 3150 IU/L, respectively, stage II hepatic encephalopathy developed. The patient presented with hepatitis fulminant, plasma exchange and CHDF (continuous hemodiafiltration) were started on the same day. 106 days after completion: The patient died. Cause of death: hepatitis fulminant Autopsy finding: Hepatic atrophy and diffuse necrotic lesions of small yellowish-white spot were observed.
	Concomitant medications: pirarubicin hydrochloride, vincristine sulfate, cyclophosphamide, prednisolone			

Clinical Laboratory Values

	16 days before administration	1 day before administration	On day 27 of administration	11 days after completion	75 days after completion	94 days after completion	95 days after completion	98 days after completion	101 days after completion
Albumin (g/dL)	--	3.8	4.2	3.9	4.6	4.0	--	--	3.6
Total bilirubin (mg/dL)	--	0.42	--	--	--	--	--	--	--
AST (GOT) (IU/L)	--	30	30	14	55	2358	2915	7073	1888
ALT (GPT) (IU/L)	--	114	81	41	136	3106	3343	5151	3150
LDH (IU/L)	--	175	189	154	--	--	--	2072	--
PT (%)	--	--	--	--	--	--	--	20.5	--
HBs antigen	(+)	--	--	--	--	--	--	--	--
HBs antibody	(–)	--	--	--	--	--	--	--	--
HBc antibody	(+)	--	--	--	--	--	--	--	--
HBe antigen	(–)	--	--	--	--	--	(–)	--	--
HBe antibody	(+)	--	--	--	--	--	(+)	--	--
HBV-DNA (LGE/mL)	3.9	--	--	--	--	--	>8.7	--	--

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
PT (%): Prothrombin Activity (%)
HBs: Hepatitis Virus Bs
HBc: Hepatitis Virus Bc
HBe: Hepatitis Virus Be
HBV-DNA: Hepatitis B Virus DNA

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Malignant lymphoma (MALT type) (diabetes mellitus, hypertension)	740 mg 5 times	**Hepatitis B** The patient presented with malignant lymphoma (MALT type). No liver disease was shown in past history and family history. Approx. 4 years before administration: The patient had surgical resection for left lacrimal gland MALT lymphoma. Approx. 1 year before administration: Six courses of COP treatment (cyclophosphamide, vincristine sulfate, prednisolone) were conducted due to recurrence of MALT lymphoma affecting the lymph nodes of the whole body. 28 days before administration: CHO treatment (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate) was started due to recrudescence of lymphoma. 25 days before administration: HBs antigen was (–) On day 1 of administration: (Treatment initiation day) Administration of this product (R-CHO treatment) was initiated. On day 100 of administration: The patient received the 5th administration of this product 1 day after completion: The 6th course of CHO treatment was conducted. 2 months after completion: Malaise, anorexia, and yellowish urine were observed. 65 days after completion: Blood test showed hepatic function disorder. (AST (GOT) 5760 IU/L, ALT (GPT) 4310 IU/L, Al-P432 IU/L, total bilirubin 8.7 mg/dL). Obvious recurrence of MALT lymphoma was not confirmed by CT. Although the patient had been a HBs antigen negative carrier, the patient developed hepatitis B. The clinical test data showed HBs antigen (+), HBs antibody (–), HBc antibody (+), HBe antigen (–), HBe antibody (+), HBV-DNA 8.6 LGE/mL. Treatment with lamivudine and steroid pulse were started. 75 days after completion: Hepatic function disorder was gradually progressed and plasma exchange was started. 76 days after completion:: HBV-DNA 5.2 LGE/mL, AST (GOT) 412 IU/L, ALT (GPT) 482 IU/L, total bilirubin 20.1 mg/dL, PT 35.0%, ammonia 76 μg/dL. 79 days after completion Consciousness disturbed was noted. 80 days after completion: Although continuous hemodialysis was started, no improvement was seen. 85 days after completion: The patient died. Cause of death: fulminant hepatitis B Autopsy finding: Hepatic atrophy and cholestasis were found and bleeding symptoms were scattered.

	Concomitant medications: cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, sulfamethoxazole/trimethoprim, candesartan cilexetil, voglibose, mecobalamin

Clinical Laboratory Values

	25 days before admin.	On day 1 of admin.	On day 31 of admin.	On day 78 of admin.	20 days after completion	65 days after completion	71 days after completion	76 days after completion	80 days after completion	85 days after completion
Albumin (g/dL)	4.7	4.2	4.3	3.7	--	--	3.2	3.0	--	--
Total bilirubin (mg/dL)	0.6	0.3	0.6	0.7	0.3	8.7	13.8	20.1	15.0	23.0
AST (GOT) (IU/L)	19	14	19	21	25	5760	596	412	118	81
ALT (GPT) (IU/L)	25	19	25	19	34	4310	1267	482	114	63
Al-P (IU/L)	132	137	132	178	211	432	576	298	246	216
LDH (IU/L)	161	119	161	141	155	1505	359	368	341	705
APPT (%)	30.4	--	--	--	--	37.9	--	--	--	42.8
PT (%)	101.8	--	--	--	--	46.7	--	35.0	34.7	22.0
Ammonia (μg/dL)	--	--	--	--	--	36	--	76	88	73
HBs antigen	(–)	--	(–)	--	--	(+)	--	--	--	--
HBs antibody	--	--	--	--	--	(–)	--	--	--	--
HBc antibody	--	--	--	--	--	(+)	--	--	--	--
HBe antigen	--	--	--	--	--	(–)	--	--	--	--
HBe antibody	--	--	--	--	--	(+)	--	--	--	--
HBV-DNA (LGE/mL)	--	--	--	--	--	8.6	--	5.2	--	--

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
APPT: Activated Partial Thromboplastin Time
PT (%): Prothrombin Activity (%)
HBs: Hepatitis Virus Bs
HBc: Hepatitis Virus Bc
HBe: Hepatitis Virus Be
HBV-DNA: Hepatitis B Virus DNA

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 60s	Non-Hodgkin's lymphoma (none)	500 mg 2 times	**Gastrointestinal perforation** Non-Hodgkin's lymphoma (diffuse large B-cell lymphoma) Clinical stage: ⅣA, Performance Status: 3, LDH before administration: normal value × 1<, past history: none, complications: none, allergy history: none 7 months before administration: Non-Hodgkin's lymphoma occurred, and pathological lesion was found in gastric region. The patient received 6 courses of CHOP treatment (until 2 months prior to administration of this product). 1 month before administration: The patient received 1 course of MEDOCH therapy. The pathological lesion was not in remission but aggravated and relapsed at the central nerve. 9 days before administration: Administration of prednisolone sodium succinate (20 mg/day) was started for the treatment of non-Hodgkin's lymphoma On day 1 of administration: (Treatment initiation day) The patient received the 1st administration of this product On day 8 of administration: The patient received the 2nd administration of this product 4 days after completion: The patient had uncomfortable feeling in the abdomen and abdominal pain. Abdominal X-ray revealed free air (–). Abdominal pain was temporary alleviated by pentazocine administration. Administration of prednisolone sodium succinate was completed. 5 days after completion: The abdominal CT confirmed the signs of gastrointestinal perforation following the suspicious perforation in the ileum revealed by the abdominal echo. The patient did not complain much of abdominal pain. The patient was transferred to the department of surgery, and underwent an emergency operation. Lymphoma was found in surgical specimen of perforation site. 22 days after completion: Since the postoperative course was good, the patient was transferred to the internal department.
	Concomitant medications: prednisolone sodium succinate, cimetidine, sulfamethoxazole/trimethoprim, diastase, sucralfate, mecobalamin, brotizolam, flunitrazepam			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 70s	Non-Hodgkin's lymphoma (none)	560 mg 3 times	**Small intestine perforation** Non-Hodgkin's lymphoma (diffuse large B-cell lymphoma), past history: none, complications: none 2 months before administration: The patient received consultation with nearby physician with chief complaint of fever. Anemia was also noted. Ulcerative lesion on the upper posterior wall of stomach by upper gastrointestinal endoscopy (GS) was confirmed. The patient was diagnosed with MALT lymphoma by biopsy. Although *H. pylori* eradication therapy was performed, fever and anemia did not improve. The patient was referred and hospitalized for treatment Abdominal CT confirmed 10-cm-sized phyma on the small intestine. Diaphanoscopy of small intestine confirmed an encircling filling defect in the jejunum. Abdominal ultrasonography confirmed wall thickening of the small intestine presenting marked low echo. Blood IL-2 receptor antibody was elevated to 4040 U/mL. Pathological lesions were also found in duodenum. Biopsy of the lesions provided the diagnosis of diffuse large B-cell lymphoma. The patient was diagnosed with malignant lymphoma in the gastrointestinal tract based on these findings. As PET confirmed accumulation in thoracolumbar spine, the disease was considered as stage Ⅳ. 27 days before administration: The first course of THP-COP was conducted. (pirarubicin hydrochloride, cyclophosphamide, vincristine sulfate, prednisolone). On day 1 of administration: (Treatment initiation day) This product was administered for the 1st time and 2nd course of THP-COP was conducted. Thereafter, GS, abdominal CT, and abdominal echo confirmed marked reduction of small intestine tumor. On day 23 of administration: This product was administered for the 2nd time and 3rd course of THP-COP was conducted. On day 33 of administration: Weakness generalized, queasy, and abdominal distension were noted. Symptoms were aggravated. On the same day, the patient was taken to hospital by ambulance. Abdominal CT confirmed free intraperitoneal air and the patient was diagnosed with small intestine perforation. On day 34 of administration: The patient had an emergency operation. Since perforation was observed in the region where phyma was thought to be existed, the perforated region was excised including surrounding adhesion region. Although pathology of the excised region confirmed ulcer in the perforation site, there was no tumor tissue. On day 87 of administration: The patient had restored in symptoms, and was discharged from the hospital. On day 120 of administration: This product was administered for the 3rd time and the 4th course of THP-COP was conducted. No recurrence.
	Concomitant medications: pirarubicin hydrochloride, cyclophosphamide, vincristine sulfate, prednisolone			

2 Cefcapene Pivoxil Hydrochloride

Brand Name (name of company)	Flomox Fine Granules 100 mg for Children, Flomox Tablets 75 mg and 100 mg (Shionogi & Co., Ltd.)
Therapeutic Category	Antibiotics acting mainly on gram-positive and gram-negative bacteria
Indications	(Granules) <Susceptible strains> Cefcapene susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *Pneumococcus* sp., Moraxella (*Branhamella*) *catarrhalis*, *Escherichia coli*, *Citrobacter* sp., *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Morganella morganii*, *Providencia* sp., *Haemophilus influenzae*, *Peptostreptococcus* sp., *Bacteroides* sp., *Prevotella* sp. (excluding *Prevotella bivia*), and *Propionibacterium* acnes. <Indications> ○ Superficial skin infection, deep skin infection, lymphangitis/lymphadenitis, chronic pyoderma ○ Pharyngolaryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia ○ Cystitis, pyelonephritis ○ Otitis media, sinusitis ○ Scarlet fever (Tablets) <Susceptible strains> Cefcapene susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *Pneumococcus* sp., Neisseria gonorrhoeae, Moraxella (*Branhamella*) *catarrhalis*, *Escherichia coli*, *Citrobacter* sp., *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Morganella morganii*, *Providencia* sp., *Haemophilus influenzae*, *Peptostreptococcus* sp., *Bacteroides* sp., *Prevotella* sp. (excluding *Prevotella bivia*), and *Propionibacterium* acnes. <Indications> ○ Superficial skin infection, deep skin infection, lymphangitis/lymphadenitis, chronic pyoderma ○ Secondary infection following trauma, burns, surgical wounds, etc., mastitis, perirectal abscess ○ Pharyngolaryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, secondary infections following chronic respiratory diseases ○ Cystitis, pyelonephritis ○ Urethritis, cervicitis ○ Cholecystitis, cholangitis ○ Bartholinitis, intrauterine infection, uterine adnexitis ○ Dacryocystitis, hordeolum, tarsadenitis ○ Otitis externa, otitis media, sinusitis ○ Periodontal tissue inflammation, pericoronitis, gnathitis

<< **PRECAUTIONS** (underlined parts are additions) >>

[Adverse Reactions (clinically significant adverse reactions)

Hepatitis fulminant, hepatic function disorder, jaundice: Severe hepatitis such as hepatitis fulminant, hepatic function disorder with increase in AST (GOT), ALT (GPT) and Al-P etc., jaundice may occur. Patients should be closely observed by periodically conducting laboratory tests. If any abnormality is observed, the treatment should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to December 5, 2006) (events for which a causality to the drug could not be denied)

- Hepatitis fulminant: 3 cases (of which 1 had a fatal case)

The number of patients treated with Cefcapene Pivoxil Hydrochloride for a year estimated by MAH: approximately 20000000 (January 2006 to December 2006)
Marketed in Japan in: June 1997

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male Under the age of 10	Upper respiratory inflammation (epilepsy)	50 mg 1 day	**Hepatitis fulminant** Past history: None Approx. 3 years and 6 months before administration: The patient developed epilepsy, and administration of carbamazepine was started (the patient had been received administration of 300 mg/day when referred to this department). Approx. 2 years and 8 months before administration: Administration of phenytoin was started for epilepsy (the patient had been received administration of 110 mg/day when referred to this department). On day 1 of administration: The patient received a checkup at his hospital for fever in the morning. WBC 16000/mm^3, CRP 2.1 mg/dL, AST (GOT) 49 IU/L, ALT (GPT) 29 IU/L. The patient was prescribed with this product and a liquid medicine (unspecified) and sent home. Both drugs were taken only once. The patient had started dozing off on the same day night. 1 day after discontinuation: As the patient fell into a doze for a long time, the medicines could not be taken. 2 days after discontinuation: The patient was diagnosed with hepatic failure at the follow-up visit of his hospital based on blood tests and was referred and transferred to this department. At the hospitalization of this department, his clinical laboratories were AST (GOT) of 7070 IU/L, ALT (GPT) of 4100 IU/L, PT of 8%. Stage IV hepatic coma was confirmed, and the patient was diagnosed with hepatitis fulminant. After accessing central vein (CV) , drip infusion of nafamostat mesilate, steroid pulse, cefotiam hydrochloride, glycyrrhizin/glycine/cysteine, transnasal infusion of lactulose and kanamycin sulfate, drip infusion of D-sorbitol/D-mannitol were conducted. The 1st plasma exchange + hemodialysis were conducted. Administration of carbamazepine and phenytoin was discontinued. 3 days after discontinuation: AST (GOT) 2985 IU/L, ALT (GPT) 1886 IU/L, PT 31% The 2nd plasma exchange + hemodialysis were conducted. The level of consciousness in JCS (Japan Coma Scale) improved to one digit. 4 days after discontinuation: AST (GOT) 569 IU/L, ALT (GPT) 769 IU/L, PT 34% The 3rd plasma exchange + hemodialysis were conducted. 5 days after discontinuation: AST (GOT) 171 IU/L, ALT (GPT) 381 IU/L, PT 82% A follow-up was conducted without conducting artificial liver support. Electroencephalogram finding was improved. Transnasal infusion of elemental diet for hepatic failure was started.

				7 days after discontinuation: CV was removed. 8 days after discontinuation: The patients started oral ingestion. 11 days after discontinuation: DLST was conducted: this product (positive), phenytoin (positive), carbamazepine (positive) 14 days after discontinuation: Symptoms were alleviated (AST (GOT) 43 IU/L, ALT (GPT) 62 IU/L, PT 96%). Since the general condition was good, the patient transferred to another hospital. Viral test result (at the hospitalization): IgM-HA antibody (–), IgM-HBc antibody (–), HBs antigen (–), HCV antibody (–), EBV-VCA IgG: 80 times, EBV-VCA IgM: <10 times, EBV-EBNA: 40 times, CMV IgG: 14.3, CMV IgM: 0.21, echovirus type 11 antibody: <8 times, adenovirus antibody (CF): <4 times, coxsackie virus antibody, group A, type 9: 16 times, coxsackie virus antibody, group B, type 3: 16 times
	Concomitant medications: phenytoin, carbamazepine			

Clinical Laboratory Values

	On Day 1 of administration (before administration)	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	5 days after discontinuation	14 days after discontinuation
AST (GOT) (IU/L)	49	7070	2985	569	171	43
ALT (GPT) (IU/L)	29	4100	1886	769	381	62
Al-P (IU/L)	926	1328	--	--	--	--
LDH (IU/L)	267	6460	558	340	194	226
γ-GPT (IU/L)	--	203	--	--	--	--
Total bilirubin (mg/dL)	0.21	2.6	2.1	2.4	1.4	0.6
Ammonia (μg/dL)	--	79	111	86	97	37
PT (%)	--	8	31	34	82	96

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GPT: γ-Glutamyltranspeptidase
PT (%):Prothrombin Activity (%)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Prevention of infectious disease after tooth extraction (none)	300 mg 3 days	**Hepatitis fulminant** Past history: none On day 1 of administration: The patient was prescribed with this product for prevention of infectious diseases after tooth extraction at a dentist. The patient was also prescribed with lysozyme hydrochloride and biodiastase 1000. On day 3 of administration: (Last day of administration): Administration of this product, lysozyme hydrochloride and biodiastase 1000 was completed. Approx. 2 weeks after completion: The patient noted jaundice and general malaise. 18 days after completion: The nearby physician suggested liver disorder (AST (GOT) 908 IU/L, ALT (GPT) 1211 IU/L, total bilirubin 10.6 mg/dL, direct bilirubin 7.0 mg/dL). 20 days after completion: The patients was hospitalized in Hospital A. Transfusion of 100 mL/day of glycyrrhizin/glycine/cysteine and FFP (fresh frozen human plasma) were started,. 26 days after completion: AST (GOT) 815 IU/L, ALT (GPT) 1176 IU/L, total bilirubin 25.1 mg/dL, direct bilirubin 16.1 mg/dL, albumin 2.3 g/dL, ammonia 165 μg/dL, PT 28%, hepaplastin test 17% and his symptoms did not improve well. 27 days after completion: The patient was transferred to this hospital. Consciousness level was stage Ⅱ hepatic encephalopathy, AST (GOT) 667 IU/L, ALT (GPT) 915 IU/L, total bilirubin 27.2mg/dL, direct bilirubin 17.3 mg/dL, ammonia 121 μg/dL, PT 30%, hepaplastin test 22%. Plasma exchange was immediately conducted. 28 days after completion: Since the blood test value showed the signs of improvement, only FFP transfusion was conducted without plasma exchange. 29 days after completion: AST (GOT), ALT (GPT), total bilirubin, direct bilirubin, ammonia, PT, and hepaplastin test were deteriorated to 438 IU/L, 690 IU/L, 31.0 mg/dL,17.4 mg/dL, 221 μg/dL, 31%, and 21%, respectively. Consciousness level was also worsened to stage Ⅳ hepatic encephalopathy. Steroid pulse therapy (methylprednisolone sodium succinate 1 g × 3 days, gradual decrease thereafter), daily plasma exchange (4 days), and continuous daily dialysis filtration were conducted. 33 days after completion: Consciousness levels of stages Ⅳ to Ⅴ hepatic encephalopathy were unchanged. Plasma exchange was temporarily discontinued and FFP transfusion was conducted. 34 days after completion: Subcutaneously injected somatropin (genetical recombination) 3.9 mg was performed for liver regeneration (3 days). 36 days after completion: The level of consciousness was improved to about stage Ⅱ hepatic encephalopathy. Blood test values also showed a tendency towards improvement.

				38 days after completion: Hyperthermia occurred in the afternoon. Slight depression in level of consciousness was noted. Administration of imipenem/cilastatin 0.5 g/day, human normal immunoglobulin 2.5 g/day as well as endotoxin removal therapy were conducted. 39 days after completion: MRSA was detected by catheter culture and blood culture, teicoplanin 800 mg/day was added. 41 days after completion: Although fever tended to resolve, consciousness level decreased to stages Ⅲ to Ⅳ and urine output was tended to decrease. Renal function was gradually aggravated, BUN 47 mg/dL, creatinine 3.2 mg/dL. 42 days after completion: Although dopamine hydrochloride, dobutamine hydrochloride, norepinephrine were used for blood pressure decreased, the blood pressure gradually decreased and the patient died. Cause of death: hepatitis fulminant, sepsis Autopsy finding: obtained IgM-HA (−), HBs antigen (−), HBs antibody (+), HBV-DNA: <3.7 LEG/mL, HCV antibody (−), HCV-PCR (−), CMV-IgM (−), CMV-IgG (+), EBV-VCA IgG: 160 times, EBV-VCA IgA: <10 times, EBV-VCA IgM: <10 times, EBV-EA IgA: <10 times, EBV-EA IgG: <10 times, anti EBNA: 40 times, PV-19 IgM (−), antinuclear antibody: 18.9 times
	Concomitant medications: lysozyme hydrochloride, biodiastase 1000			

Clinical Laboratory Values

	18 days after completion	26 days after completion	27 days after completion	29 days after completion	37 days after completion	41 days after completion
AST (GOT) (IU/L)	908	815	667	438	62	77
ALT (GPT) (IU/L)	1211	1176	915	690	82	71
Al-P (IU/L)	409	--	391	--	315	410
LDH (IU/L)	855	--	395	--	343	668
γ-GPT (IU/L)	229				33	36
Total bilirubin (mg/dL)	10.6	25.1	27.2	31.0	26.8	31.5
Direct bilirubin (mg/dL)	7.0	16.1	17.3	17.4	15.7	18.1
Albumin (g/dL)	--	2.3	--	--	3.3	3.2
Ammonia (μg/dL)	--	165	121	221	74	132
PT (%)	--	28	30	31	--	--
Hepaplastin test (%)	--	17	22	21	--	--

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GPT: γ-Glutamyltranspeptidase
PT (%):Prothrombin Activity (%)

3 Nyoshinsan

Brand Name (name of company)	TSUMURA Nyoshinsan Extract Granules for Ethical Use
Therapeutic Category	Kampo medicines
Indications	Following symptoms with hot flash and vertigo Postpartum neurosis, menstrual irregularity, a set of nervous symptoms associated with aging in women

<< **PRECAUTIONS** (underlined parts are additions) >>

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder with significant increase in AST (GOT), ALT (GPT), Al-P and γ-GTP levels etc. and jaundice may occur. Patients should be carefully monitored, and if abnormalities are found, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 2003 to November 2006) (events for which a causality to the drug could not be denied)

- Hepatic function disorder, jaundice: 3 cases (no fatal case)

The number of patients treated with Nyoshinsan for a year estimated by MAH: Approximately 6500 (FY2005)
Marketed in Japan in: 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Premenstrual tension (chronic thyroiditis)	7.5 g 113 days	**Hepatic function disorder** On day 1 of administration: Administration of this product for premenstrual tension was started. On day 70 of administration: The patient developed general malaise. Although the patient experienced persisting general malaise, she did not receive treatment for the symptom. On day 105 of administration: The patient received medical checkup at nearby hospital. AST (GOT) 205 IU/L, ALT (GPT) 337 IU/L, γ-GTP 164IU/L. On day 113 of administration: (day of discontinuation) Administration of this product was discontinued. 2 days after discontinuation: The patient was referred to this hospital and had a consultation as outpatient. The patient had persistent general malaise. Since AST (GOT), ALT (GPT), and γ-GTP increased to 239 IU/L, 337 IU/L and 180 IU/L, respectively, reservation for hospitalization was made. 6 days after discontinuation: The patient was hospitalized in our hospital. Treatment was given while the patient rested. Intravenous infusions of 500 mL fluid replacement of 5% glucose and glycyrrhizin/glycine/cysteine, etc. was started. 7 days after discontinuation: The patient had no problem with oral ingestion. 9 days after discontinuation: Tendency to improve in general malaise was found. 13 days after discontinuation: General malaise almost disappeared. 18 days after discontinuation: The patient was given a permission to go out. No marked change after return to the hospital was noted. 21 days after discontinuation: A permission was given to stay out overnight. No marked change after return to the hospital was noted. 24 days after discontinuation: The patient was discharged. 30 days after discontinuation: The patient made an outpatient visit to the hospital for examination. No signs of symptom were found.
	Concomitant medications: ibuprofen, scopolamine butylbromide			

Clinical Laboratory Values

	On day 18 of administration	On day 105 of administration	2 days after discontinuation	6 days after discontinuation	30 days after discontinuation
AST (GOT) (IU/L)	32	205	239	364	35
ALT (GPT) (IU/L)	14	337	337	531	43
Al-P (IU/L)	159	--	342	436	336
γ-GPT (IU/L)	11	164	180	233	111
LDH (IU/L)	418	--	203	260	160
Total bilirubin (mg/dL)	0.6	--	0.8	0.9	0.6

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GPT: γ-Glutamyltranspeptidase

Virus marker

	2 days after discontinuation
IgM-HA antibody	Negative (≤0.1)
HBs antigen	Negative (0.1)
HCV antibody	Negative (0.3)

IgM-HA: IGM Hepatitis A Virus
HBs: Hepatitis Virus Bs
HCV: Hepatitis C Virus

Immune serum test

	6 days after discontinuation
Antinuclear antibody	<40 times
Antimitochondrial antibody	<20 times

2

Revision of PRECAUTIONS (No. 184)

This section presents details of revisions of PRECAUTIONS in package inserts and brand names of drugs that have been revised according to the Notifications after January 12, 2007 (excluding those presented in "1 Important Safety Information" of this Bulletin.)

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1 <Peptic ulcer agent>

Sodium Rabeprazole

[Brand Name] Pariet Tablets 10 mg and 20 mg (Eisai Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Acute renal failure, interstitial pneumonia: Acute renal failure and interstitial pneumonia may occur. Patients should be carefully monitoredby renal function tests (BUN, creatinine, etc.). If any abnormalities are found, treatment should be discontinued and appropriate measures taken.
Hyponatremia: Hyponatremia may occur. If any abnormalities are found, treatment should be discontinued and appropriate measures should be taken.
Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, weakness, increased CK (CPK) and increased myoglobin in blood or urine may occur. If symptoms occur, treatment should be discontinued and appropriate measures taken.

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2 Over the counter drugs

Neo Cedar

[Brand Name] Neo Cedar (Antarc Co.)

[Inhibited patients]

Do not take this product if you:
are not a habitual smoker.
are at the age under 20.
Do not take following medicines while taking this product:
Stop smoking aid

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3 Over the counter drugs

Nyoshinsan

[Brand Name] Nyoshinsan Extract Granules KM (Kahya)

[Consultation]

In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.
The following symptoms are observed after taking this drug
In rare instances, the following serious symptoms may occur. Visit a physician immediately in such cases.
Hepatic function disorder: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

3

List of products subject to Early Post-marketing Phase Vigilance

(As of February 1, 2007)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Inulin / Inulead Inj.	FUJIYAKUHIN Co., Ltd.	August 22, 2006
Alendronate Sodium Hydrate / Fosamac Tablets 35 mg	Banyu Pharmaceutical Co., Ltd.	September 15, 2006
Alendronate Sodium Hydrate / Bonalon Tablet 35 mg	Teijin Pharma Limited	September 15, 2006
Itraconazole / Itrizole Oral Solution 1%	Janssen Pharmaceutical K.K.	September 15, 2006
Temozolomide / Temodal Capsules 20 mg and 100 mg	Schering-Plough K.K.	September 15, 2006
Budesonide / Pulmicort Respules 0.25 mg and 0.5 mg	AstraZeneca K.K.	September 15, 2006
Entecavir Hydrate / Baraclude Tablets 0.5 mg	Bristol Pharmaceuticals Y.K.	September 21, 2006
Cetrorelix Acetate / Cetrotide for Injection 0.25 mg and 3 mg	Nippon Kayaku Co., Ltd.	September 21, 2006
Manganese Chloride Tetrahydrate / Bothdel Oral Solution 10	Meiji Dairies Corporation	September 25, 2006
Gabapentin / Gabapen Tablets 200 mg, 300 mg, and 400 mg	Pfizer Japan Inc.	September 25, 2006
Olopatadine Hydrochloride / Patanol Ophthalmic Solution 0.1%	Alcon Japan Ltd.	October 5, 2006
Busulfan / Busulfex Injection 60 mg	Kirin Brewery Company, Limited	October 10, 2006[*1] / October 20, 2006[*2]
Fexofenadine Hydrochloride / Allegra Tablets 60 mg[*3]	Sanofi-Aventis K.K.	October 20, 2006
Landiolol Hydrochloride / Onoact 50 for Injection	Ono Pharmaceutical Co., Ltd.	October 20, 2006
Mozavaptan Hydrochloride / Physuline Tablets 30 mg	Otsuka Pharmaceutical, Co., Ltd.	October 24, 2006
Interferon Beta-1a (Genetical recombination) / Avonex IM Injection Syringe 30 μg	Biogen Idec Japan Ltd.	November 6, 2006
Moxifloxacin Hydrochloride / Vegamox Ophthalmic Solution 0.5%	Alcon Japan Ltd.	November 6, 2006
Pneumococcal Vaccine / Pneumovax NP	Banyu Pharmaceutical Co., Ltd.	November 29, 2006

Bortezomib Velcade Injection 3 mg	Janssen Pharmaceutical K.K.	December 1, 2006
Itraconazole Itrizole Injection 1%	Janssen Pharmaceutical K.K.	December 6, 2006
Ropinirole Hydrochloride ReQuip Tablets 0.25 mg, 1 mg, and 2 mg	GlaxoSmithKline K.K.	December 6, 2006
Lansoprazole Takepron Intravenous 30 mg	Takeda Pharmaceutical Company Limited	December 7, 2006
Losartan Potassium/Hydrochlorothiazide Preminent Tablets	Banyu Pharmaceutical Co., Ltd.	December 8, 2006
Polidocanol Polidocasklerol 0.5% Inj. 2 mL, 1% Inj. 2 mL, and 3% Inj. 2 mL	Sakai Chemical Industry Co., Ltd.	December 14, 2006
Fexofenadine Hydrochloride Allegra Tablets 30 mg	Sanofi-Aventis K.K.	January 9, 2007
Perflubutane Sonazoid for Injection	Daiichi Pharmaceutical Co., Ltd.	January 10, 2007
Pemetrexed Sodium Hydrate Alimta Injection 500 mg	Eli Lilly Japan K.K.	January 22, 2007
Remifentanil Hydrochloride Ultiva Intravenous 2 mg and 5 mg	Janssen Pharmaceutical K.K.	January 22, 2007
Infliximab (Genetical recombination)*4 Remicade for I.V. Infusion 100	Tanabe Seiyaku Co., Ltd.	January 26, 2007
Zanamivir Hydrate*5 Relenza	GlaxoSmithKline K.K.	January 26, 2007
Tacrolimus Hydrate*6 Prograf Capsules 0.5 mg and 1 mg	Astellas Pharma Inc.	January 26, 2007
Baclofen*7 Intrathecal Gabalon 0.005%, 0.05%, and 0.2%	Daiichi Pharmaceutical Co., Ltd.	January 26, 2007
Micafungin Sodium*8 Funguard 25 mg, 50 mg, and 75 mg for Infusion	Astellas Pharma Inc.	January 26, 2007

*1: For the adult dose initially approved
*2: An additional administration for “pediatrics”
*3: An additional administration for “pediatrics (aged 7 and older)”
*4: An additional indication for “the treatment of refractory uveitis in patients with Behcet’s disease (only in cases which are not adequately responsive to conventional therapies)”
*5: An additional indication for “prophylaxis of influenza A or B virus infection”
*6: An additional indication for “Lupus nephritis (in a case where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions)”
*7: An additional administration for “pediatrics”
*8: An additional indication for “Prophylaxis of Aspergillus and Candida infections in patients undergoing hematopoietic stem cell transplantation”