Pharmaceuticals and Medical Devices Safety Information

No.267 March 2010

Table of Contents

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).

Published by
Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

Office of Safety I,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

Pharmaceuticals and Medical Devices Safety Information

No. 267 March 2010

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	**Precautions on handling of lancing devices for capillary blood sampling**		Lancing devices are used for puncturing the fingertip, etc. on blood glucose monitoring. There were incidents reported where healthcare providers, who intended to take a blood sample from the patient's earlobe, accidentally punctured their fingers that was placed behind the patient's earlobe for support, with the needle that penetrated the patient's earlobe. When this occurs, there is a risk of blood-borne infection between the patient and the healthcare provider. To prevent similar incidents when handling lancing devices, precautions instructed to medical institutions are explained hereafter.	4
2	**Bortezomib (and 1 other)**	*P* *C*	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 Notification dated February 16, 2010.	7
3	**Warfarin Potassium (and 9 others)**		Revision of PRECAUTIONS (No. 214)	15
4	**Products subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of March 1, 2010.	20

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of PRECAUTIONS *C*: Case Reports

To Pharmaceuticals and Medical Devices Safety Management Supervisor
—Please use our e-mail alert service—

The Pharmaceuticals and Medical Devices Agency is providing a "Pharmaceuticals and Medical Devices Information E-mail Alert Service" (http://www.info.pmda.go.jp/info/idx-push.html, Japanese only), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of PRECAUTIONS is issued. You are encouraged to register for and use the service.

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 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.

1

Precautions on handling of lancing devices for capillary blood sampling

1. Introduction

Lancing devices for capillary blood sampling are used for puncturing the fingertip, etc. to take capillary blood samples for glucose testing etc.. Although a target for puncturing is usually fingertip, they are sometimes other areas by requests from patients, who wish to lessen the pain or do not wish to puncture the finger.

There were incidents reported where healthcare providers who intended to take a blood sample from the patient's earlobe, accidentally punctured their fingers that was placed behind the patient's earlobe for support, with the needle that penetrated the patient's earlobe. When this occurs, there is a risk of blood-borne infection between the patient and the healthcare provider. Thus, precautions to be taken when using the lancing device are explained hereafter.

2. Request to healthcare providers

When handling the lancing device, please take note of the following precautions.[1)]

1) Puncturing where the tissue is thin such as the earlobe, etc. may cause puncturing of your finger with the needle that has penetrated the patient's tissue, leading to a risk of blood-borne infection.
2) Look for other areas for puncturing where the tissue is thicker, if there is a risk of penetration.
3) Do not place your fingers for support behind a target for puncturing where the tissue is thin such as the earlobe etc.
4) Regardless of the target, there is a risk of infection due to needle-stick accident or exposure to blood when sampling blood from patients. Take precautionary measures such as wearing gloves, etc. to prevent exposure to blood.

In addition, MHLW has instructed the manufacturers of the lancing device to ensure that the package inserts is revised and the information is provided to medical institutions, etc.[2)]

These manufacturers should check that the following information is included in the "IMPORTANT PRECAUTIONS" of "PRECAUTIONS" section of package inserts and immediately make the necessary revisions if the information as instructed is not included.

1) For products that do not define the target for puncturing in the "INTENDED USE", "INDICATIONS", section or products that do not inhibit earlobe puncture in the "CONTRAINDICATIONS" section.

   Do not place your fingers for support behind a target for puncturing where the tissue is thin such as the earlobe etc. (Puncturing where the tissue is thin such as the earlobe, etc. may cause puncturing of your finger with the needle that has penetrated the patient's tissue, leading to a risk of blood-borne infection. Look for other areas for puncturing where the tissue is thicker, if there is a risk of penetration.)

2) For products other than those listed in section 1).

   Puncturing where the tissue is thin may cause puncturing of your finger by the needle that has penetrated the patient's tissue, leading to a risk of blood-borne infection. The targets for puncturing

should follow the package insert.

3. Cases where healthcare providers fingers for support the patients earlobes were punctured

<Case 1>

In August 2008, when a healthcare provider was taking capillary blood samples from the patient's earlobe using a lancing device in order to perform blood glucose monitoring, the needle penetrated the patient's earlobe and punctured the finger of the healthcare provider for support behind the patient's earlobe, causing a needle-stick injury. The patient did not have any history of infectious diseases, and the healthcare provider did not suffer any health hazard due to infection.

<Case 2>

In March 2009, when a nurse was taking capillary blood samples from the patient's earlobe using a lancing device, the needle penetrated the earlobe and punctured the nurse's left forefinger that had been supporting the earlobe. The nurse did not suffer any health hazard due to infection.

4. Closing comments

For details of the alert[1)] and instructions, etc.[2)] to manufacturers of the lancing device, please refer to the Pharmaceuticals and Medical Devices Agency website (http://www.info.pmda.go.jp/iryoujiko/iryoujiko_index.html) and (http://www.info.pmda.go.jp/mdevices/md-tenken-2009.html). (Japanese only)

<References>

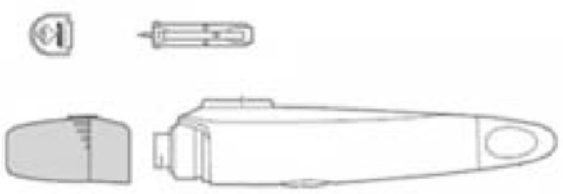
1) Joint HPB/GMSD Notification No. 0301-1 and PFSB/SD No. 0301-7, by the Director of Guidance of Medical Service Division, Health Policy Bureau and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 1, 2010, "Handling of Lancing Devices for Capillary Blood Sampling from Earlobe, etc. (Request for alert and provision of information to users)"
2) Joint PFSB/SD Notification No. 0301-10 and PFSB/ELD/OMDE No. 0301-2, by the Director of Safety Division, Pharmaceutical and Food Safety Bureau and by the Director of Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 1, 2010, "Self-inspections etc. of the Package Inserts of the Lancing Devices for Capillary Blood Sampling"

(Lancing devices for capillary blood sampling)

<Product where the entire device is disposable>

<Product where the needle area is disposable>

<Product where the needle area is not disposable>



2

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 Notification dated February 16, 2010.

1 Bortezomib

Brand Name (name of company)	VELCADE Injection 3 mg (Janssen Pharmaceutical K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Relapsed or refractory multiple myeloma

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (TEN) : Oculomucocutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (TEN) may occur. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

Reversible posterior leukoencephalopathy syndrome: Reversible posterior leukoencephalopathy syndrome may occur (symptoms include convulsions, elevated blood pressure, headaches, disturbances in consciousness, confusion, vision disorders, etc.). If reversible posterior leukoencephalopathy syndrome is suspected, administration 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 denied) for the past 3 years (December 1, 2006 to December 31, 2009):

- Oculomucocutaneous syndrome, toxic epidermal necrolysis: 0 cases (no fatalities)
- Reversible posterior leukoencephalopathy syndrome: 1 case (no fatalities)

The number of patients treated with Bortezomib per year estimated by marketing authorization holder (MAH): approximately 1,470 patients (January to December 2009)

Marketed in Japan in: December 2006

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Multiple myeloma (none)	1.3 mg/m^2 for 11 days	**Leukoencephalopathy** Day 1 of administration: The patient started receiving bortezomib (the first dose of Cycle 1) at a dose of 1.3 mg/m^2 with concomitant use of 8 mg of dexamethasone. Day 4 of administration: The second dose of bortezomib of Cycle 1 was administered. Day 8 of administration: The third dose of bortezomib of Cycle 1 was administered. Day 11 of administration (day of completion): The fourth dose of bortezomib of Cycle 1 was administered. (Completion of Cycle 1) 1 day after completion: The patient had mild disorientation, which rapidly increased. No cerebral haemorrhage was found by head CT. 2 days after completion: Her level of consciousness according to the JCS(Japan Coma Scale) was III-100. She was diagnosed with leukoencephalopathy based on brain MRI findings. 15 days after completion: The patient became lucid and was able to talk, but paralysis of lower limbs on both sides and paresis of the upper limbs on both sides remained. 63 days after completion: Based on the brain MRI findings, the patient was considered to have recovered from leukoencephalopathy.
	Concomitant medications: dexamethasone, oxycodone hydrochloride, etodolac, clotiazepam, sulpiride, sulfamethoxazole/trimethoprim, brotizolam, ranitidine hydrochloride, sennoside, concentrated human red blood cells			

2 Methotrexate

❶ Methotrexate (Tablet 2 mg, Capsule)

Brand Name (name of company)	RHEUMATREX Capsules 2mg (Wyeth) and the others
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous
Indications	Rheumatoid arthritis (only for patients who are not adequately responsive to previous non-steroid anti-inflammatory agents and other antirheumatic drugs) Juvenile idiopathic arthritis associated with arthritic symptoms

《**PRECAUTIONS** (underlined parts are additions)》

[Important Precautions] Serious hepatitis and/or liver disorders, including fatal cases, have been reported after administration of methotrexate to patients who were hepatitis B or C virus carriers. In addition, after the completion of the administration of this drug, hepatitis due to activation of the hepatitis B virus was reported. If this drug is administered to patients who are hepatitis B or C virus carriers, careful attention should be given to the possible onset of signs and symptoms related to hepatitis B

or C viral growth, for example, by testing liver function or monitoring hepatitis viral markers during and after the administration period.

[Adverse Reactions (clinically significant adverse reactions)]

Fulminant hepatitis, hepatic failure: Serious liver disorders (including due to Hepatitis B or C virus) such as fulminant hepatitis, hepatic failure, liver tissue necrosis/fibrosis, or cirrhosis may occur. Patients should be carefully monitored, for example, by testing liver function every 4 weeks. If any abnormalities are observed, appropriate measures including the discontinuation of the administration should be taken.

Encephalopathies (including leukoencephalopathy): Encephalopathies (including leukoencephalopathy) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

❷ Methotrexate (Tablet 2.5 mg)

Brand Name (name of company)	METHOTREXATE TABLETS 2.5mg (Wyeth)
Therapeutic Category	Antimetabolites
Indications	Remission of signs and symptoms of the following diseases Acute leukaemia Chronic lymphocytic leukaemia, chronic myelocytic leukaemia Gestational trophoblastic disease (choriocarcinoma, invasive hydatidiform mole, hydatidiform mole)

《**PRECAUTIONS** (underlined parts are additions)》

[Important Precautions]

Serious hepatitis and/or liver disorders, including fatal cases, have been reported after administration of methotrexate to patients who were hepatitis B or C virus carriers. In addition, after discontinuation of the administration of this drug, hepatitis etc. due to activation of the hepatitis B virus has been reported. . If this drug is administered to patients who are hepatitis B or C virus carriers, careful attention should be given to the possible onset of signs and symptoms related to hepatitis B or C viral growth by testing liver function or monitoring hepatitis viral markers during and after the administration period.

[Adverse Reactions (clinically significant adverse reactions)]

Fulminant hepatitis, Hepatic failure: Serious liver disorders (including due to Hepatitis B or C) such as fulminant hepatitis, hepatic failure, liver tissue necrosis/fibrosis, or cirrhosis may occur. Patients should be carefully monitored, for example, by frequently testing liver function. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

Encephalopathies (including leukoencephalopathy): Encephalopathies (including leukoencephalopathy) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

❸ Methotrexate (Injection)

Brand Name (name of company)	METHOTREXATE INJECTION 200mg, METHOTREXATE PARENTERAL 5mg, 50 mg (Wyeth)
Therapeutic Category	Antimetabolites
Indications	(1) Conventional therapy with Methotrexate Remission of signs and symptoms of the following diseases of the following diseases:

	Acute leukemia Chronic lymphocytic leukaemia, chronic myelocytic leukaemia Gestational trophoblastic disease (choriocarcinoma, invasive hydatidiform mole, hydatidiform mole) (2) Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy Breast cancer (3) Methotrexate and Leucovorin rescue therapy Sarcomas (bone sarcomas, soft part sarcomas, etc.) Remission of leukaemic infiltration of central nervous system or testicles in patients with acute leukaemia Remission of malignant lymphoma infiltration of central nervous system (4) Alternating chemotherapy with methotrexate-fluorouracil Increased fluorouracil antitumor effect against gastric cancer (5) Methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) chemotherapy Urothelial carcinoma (Methotrexate Injection 200 mg is only for (3), Methotrexate Parenteral 5 mg is only for (1), (2), (5))

《**PRECAUTIONS** (underlined parts are additions)》

[Important Precautions]

Serious hepatitis and/or liver disorders, including fatal cases, have been reported after administration of this drug to patients who were hepatitis B or C virus carriers. In addition, after discontinuation of the administration of this drug, hepatitis etc. due to activation of the hepatitis B virus has been reported . If this drug is administered to patients who are hepatitis B or C virus carriers, careful attention should be given to the possible onset of signs and symptoms related to hepatitis B or C viral growth by testing liver function or monitoring hepatitis viral markers during and after the administration period.

[Adverse Reactions (clinically significant adverse reactions)]

Fulminant hepatitis, hepatic failure: Serious liver disorders (including due to Hepatitis B or C virus) such as fulminant hepatitis, hepatic failure, liver tissue necrosis/fibrosis, or cirrhosis (may occur. Patients should be carefully monitored, for example, by frequently testing liver function. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

Encephalopathies (including leukoencephalopathy), other central nervous system disorders, Guillain-Barre syndrome:

Encephalopathies (including leukoencephalopathy), other central nervous system disorders (convulsion, paralysis, aphasia, dementia, coma), or Guillain-Barre syndrome may occur. Patients should be carefully monitored. If any abnormalities are observed, administration 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 denied) for the past 3 years (April 1, 2006 to January 15, 2010)

- Serious liver disorder: 5 cases (including 2 fatalities)
- Encephalopathies: 2 cases (no fatalities)

The number of patients treated with per year estimated by MAH: approximately 790,000 patients (January to December 2009)

Marketed in Japan in: March 1963 (Tablet 2.5 mg)
April 1968 (Injection)
August 1999 (Tablet 2 mg, Capsule)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female (60s)	Rheumatoid arthritis (Hepatitis B virus carrier, diabetes mellitus, hypertension)	6 to 8 mg/week for 996 days	**Fulminant hepatitis** Approx 17 years before administration: The patient developed arthralgia. Approx 16 years before administration: The patient was diagnosed with rheumatoid arthritis and started receiving medical treatment. Salazosulfapyridine, auranofin, bucillamine, actarit were administered, but controlled the disease inadequately. Day 1 of administration: Oral administration of methotrexate (6 mg/week) was started. Day 338 of administration: The dose of methotrexate was increased to 8 mg/week. Day 561 of administration: Concomitant use of prednisolone 5 mg was started. Day 926 of administration: Concomitant use of mizoribine (300 mg/week) was started. Approx 2 years and 9 months after administration: The patient developed general malaise and anorexia. Day 988 of administration: At the time of outpatient visit, elevated liver enzymes were found with AST (GOT) 179IU/L, ALT (GPT) 357IU/L; and mizoribine was discontinued. Day 995 of administration: At the time of a follow-up visit, AST (GOT) and ALT (GPT) were further elevated to 383IU/L and 536IU/L, respectively. The patient was found to be positive for HBs antigen. HBV-PCR ≧ 7.6Log. Day 996 of administration (day of discontinuation): The patient was admitted to a hospital. Administration of entecavir (1 mg) and interferon beta (6 million IU) for acute hepatitis B were started. Oral administration of methotrexate was discontinued. 5 days after discontinuation: AST (GOT) and ALT (GPT) were further elevated to 2825IU/L and 1575IU/L, respectively. Since PT decreased to 52%, steroid pulse therapy (methylprednisolone 1000 mg) and continuous intravenous infusion with ciclosporin were started. 12 days after discontinuation: Since PT decreased to 29% and flapping tremor occurred, the patient was diagnosed with fulminant hepatitis. Starting from the same day, plasma exchange and haemodiafiltration were carried out for 3 days, but liver function did not improve. 18 days after discontinuation: Administration of antibiotics was started because of fever and aggravated respiratory condition. 19 days after discontinuation: Ventilator management was started. 20 days after discontinuation: Blood pressure decreased. Catecholamine was administered, however, no improvement was shown. The patient died of liver failure.

	Concomitant medications: prednisolone, mizoribine, dried ferrous sulfate, pioglitazone hydrochloride, amlodipine besilate, naproxen, rebamipide

Clinical Laboratory Values

	Day 925 of admini straion	Day 988 of admini stration	Day 966 of Adm. (day of discontinuation)	5 days after discontinuation	16 days after discontinuation
WBC (/mm^3)	7,800	3,300	3,400	6,200	27,500
PLT(×10^4/mm^3)	31.9	16.6	13	7	7.1
AST (GOT) (IU/L)	20	179	470	2,825	262
ALT (GPT) (IU/L)	32	357	616	1,575	355
ALP (IU/L)	347	503	731	643	390
LDH (IU/L)	204	308	393	1,071	70
γ-GTP (IU/L)	19	191	542	498	460
Total bilirubin (mg/dL)	0.5	0.7	1.5	8.3	17.2
TP (g/dL)	7.2	6.3	6.7	5.3	5.4
Albumin (g/dL)	3.9	3.3	3.5	2.6	3.0
BUN (mg/dL)	27.9	19.2	21.5	21.9	33.2
Serum creatinine (mg/dL)	0.58	0.46	0.48	0.47	0.84
CRP (mg/dL)	1.05	0.63	0.96	1.24	2.31

WBC: White blood cell count
PLT: Platelet
AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)
ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)
ALP: Alkaline phosphatase
LDH: Lactate dehydrogenase
γ-GTP: gamma-glutamyl transpeptidase
TP: Total protein
BUN: Blood urea nitrogen
CRP: C-reactive protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female Age Unknown	Rheumatoid arthritis (Hepatitis C virus carrier)	4 to 6 mg/week for 610 days	**Liver disorder** 128 days before administration: The patient started various treatments for rheumatoid arthritis. Day 1 of administration: Oral administration of methotrexate (4 to 6 mg/week) was started. Later, the patient occasionally developed liver disorder with AST (GOT) and ALT (GPT) of around 50 to 60 IU/L and 80 IU/L, respectively, which spontaneously returned to normal. Month 4 of administration: The patient visited a hospital with a chief complaint of stiffness of fingers on both hands. Methotrexate (4 mg/week) had been administered to the patient since the initial visit. Day 610 of administration (day of discontinuation): AST (GOT) and ALT (GPT) were 55 IU/L and 73 IU/L, respectively.

				Methotrexate was discontinued due to a liver disorder. 14 days after discontinuation: AST (GOT) and ALT (GPT) were 90 IU/L and 145 IU/L, respectively. 35 days after discontinuation: AST (GOT) and ALT (GPT) were further elevated to 771 IU/L and 1006 IU/L, respectively. 36 days after discontinuation: The patient was admitted to the hospital. All oral medications were discontinued. After admission, AST (GOT) and ALT (GPT) spontaneously decreased to 211 IU/L and 465 IU/L, respectively. 53 days after discontinuation: AST (GOT), ALT (GPT), and A1-P were 489 IU/L, 703 IU/L, and 533 IU/L, respectively. (Continued to decrease until 43 days after discontinuation, but increased again.) 57 days after discontinuation: Administering of glycyrrhizin/glycine/cysteine was started. Liver functions have gradually improved. 64 days after discontinuation: AST (GOT), ALT (GPT), and A1-P were 51 IU/L, 136 IU/L, 367 IU/L, respectively. 76 days after discontinuation: AST (GOT) and ALT (GPT) were 30 IU/L and 34 IU/L, respectively. No findings suggesting development of fulminant hepatic failure were observed. The patient recovered from the liver disorder.
	Concomitant medications: meloxicam, teprenone, salazosulfapyridine, folic acid, alendronate sodium hydrate, benfotiamine, pyridoxine hydrochloride, cyanocobalamin			

Clinical Laboratory Values

	Day 1 of administration	Day 610 of administration (day of discontinuation)	14 days after discontinuation	35 days after discontinuation	43 days after discontinuation	53 days after discontinuation	64 days after discontinuation	67 days after discontinuation	76 days after discontinuation
WBC (/mm^3)	5,210	4,200	—	5,620	5,240	—	—	7,200	—
AST (GOT) (IU/L)	—	55	90	771	—	489	51	—	30
ALT (GPT) (IU/L)	—	73	145	1,006	—	703	136	—	34
ALP (IU/L)	123	232	—	468	379	533	367	112	—
Total bilirubin (mg/dL)	0.3	—	—	0.7	—	—	—	—	—
TP (g/dL)	7.3	6.9	—	7.5	—	—	—	—	—
Albumin (g/dL)	4.0	4.0	—	3.9	—	—	—	—	—

WBC: White blood cell count
AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)
ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)
ALP: Alkaline phosphatase
TP: Total protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 60s	Rheumatoid arthritis (none)	8 mg/week for 1081 days	**Reversible posterior leukoencephalopathy** Day 1 of administration: The patient was started receiving oral methotrexate for rheumatoid arthritis. Day 1,041 of administration: At the time of outpatient treatment, she had no notable complaints and her condition appeared to be favorable. Day 1,073 of administration: The patient complained of flash vision. She was aware of light-headed feeling and visited another medical institution (department of neurosurgery). Brain MRI scan showed no abnormalities. Day 1,081 of administration (Day of discontinuation): Administration of oral methotrexate was discontinued. 5 days after discontinuation: The patient had a convulsive seizure at home, and lost consciousness. She was taken to another medical institution (department of neurosurgery) by ambulance. However, no abnormal neurologic findings were found, and she had no fever or inflammatory response. Based on the brain MRI findings, high signal on FLAIR images was detected in the cortex of the right occipital lobe; and an abnormal area with high signal was observed in the diffusion weighted image. Administration of methylprednisolone was started at a dose of 500 mg for 3 days. Anticonvulsant drug and folic acid were also administered. 11 days after discontinuation: The abnormal findings in the brain MRI had disappeared. The symptoms also nearly disappeared. Abnormalities in eyes such as flash vision still remained. 16 days after discontinuation: The patient was transferred to the reporting physician's hospital. 22 days after discontinuation: Abnormalities in eyes had disappeared and the patient recovered from the event. The DLST was positive for methotrexate.
	Concomitant medications: infliximab (genetical recombination), prednisolone, diclofenac sodium			

3

Revision of PRECAUTIONS

(No. 214)

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 February 16 and March 1, 2010 (excluding those presented in "2. Important Safety Information" of this Bulletin).

---

1 <Anticoagulants>
Warfarin Potassium

[Brand Name] Warfarin Tablets 0.5mg, 1 mg, 5 mg (Eisai Co., Ltd.) and the others

[Precautions of Dosage and Administration]

Dosage should be determined based on blood coagulation tests (prothrombin time and thrombotest), etc., and conduct adequate coagulation management during treatment with this drug

Generally, the International Normalized Ratio (INR) is used as a measure for the prothrombin time and thrombotest assay value, other thanprothrombin activity (%). When using INR, the therapeutic range should be decided based on age, disease, and concomitant medication use, and other factors, with reference to the latest information including guidelines etc. issued by academic societies in Japan or overseas.
Sensitivity to warfarin potassium differs greatly among individuals, and since there are patients who are at high risk for bleeding, the initial dose should be carefully determined based on the risks and benefits. It is advisable that the initial dose should be limited to a small amount, bearing in mind various factors such as, risk of bleeding caused by high dosage, age, disease, and concomitant medication use.

---

2 <Central Nervous System Agents-Miscellaneous>
Nalfurafine Hydrochloride

[Brand Name] REMITCH CAPSULES 2.5μg (Toray)

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder with siginimicant elevations of AST (GOT), ALT (GPT), Al-P and/or γ-GTP or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

---

3 <Autonomic Nervous System Agents >
Bethanechol Chloride

[Brand Name] Besacolin Powder 5%(Sannova Co., Ltd.)

[Important Precautions]

Cholinergic crisis may occur. If nausea, vomiting, abdominal pain, diarrhoea, excessive saliva secretion, sweating, bradycardia, decreased blood pressure, miosisetc. are observed, administration should be discontinued, and 0.5 mg to 1 mg of atropine sulfate hydrate should be administered (The dose should be adjusted depending on the symptoms of the patient). Respiratory failure may also occur. In such cases, open the

airway, and consider artificial respiration, if necessary.

[Adverse reactions (clinically significant adverse reactions)]

Cholinergic crisis: Cholinergic crisis may occur. If nausea, vomiting, abdominal pain, diarrhoea, excessive saliva secretion, sweating, bradycardia, decreased blood pressure, miosis etc. are observed, administration should be discontinued, and 0.5 mg to 1 mg of atropine sulfate hydrate should be administered (The dose should be adjusted depending on the symptoms of the patient). Respiratory failure may also occur. In such cases, open the airway, and considerartificial respiration, if necessary.

4 **<Ophthalmic Agents>**

Dorzolamide Hydrochloride

[Brand Name] Trusopt Ophthalmic Solution 0.5%, 1% (Banyu Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (TEN): Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (TEN) may occur**.** Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

<Antihypertensives>

5 Candesartan Cilexetil/Hydrochlorothiazide Telmisartan/Hydrochlorothiazide Valsartan/Hydrochlorothiazide

[Brand Name] ECARD Combination Tablets LD, ECARD Combination Tablets HD (Takeda Pharmaceutical Company Limited)
Micombi Combination Tablets AP, Micombi Combination Tablets BP (Nippon Boehringer Ingelheim Co., Ltd)
Co-DIO combination tablets MD, Co-DIO combination tablets EX (Novartis Pharma K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Hyponatraemia: Hyponatraemia may occur accompanied by malaise, anorexia, queasy, vomiting, disturbances in consciousness, and other symptoms (especially among the elderly). Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken immediately.

< Allergic agents-Miscellaneous >

6 Montelukast Sodium

[Brand Name] KIPRES Fine Granules 4mg, KIPRES Tablets 5mg, 10mg, KIPRES Chewable Tablets 5mg (Kyorin Pharmaceutical Co.,Ltd.)
SINGULAIR Fine Granules 4mg, SINGULAIR Tablets 5mg, 10mg, SINGULAIR Chewable Tablets 5mg (Banyu Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Fulminant hepatitis, hepatitis, hepatic function disorder, jaundice: Fulminant hepatitis, hepatitis, hepatic function disorder, and jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

<Vaccines>

7 Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cell)

[Brand Name] Cervarix (GlaxoSmithKline.K.K.)

[Important Precautions]

Fainting may occur as vasovagal reactions after vaccination. Therefore, it is advisable that the patient should be monitored for about 30 minutes after vaccination.
The syringe cap and plunger of this drug contains natural rubber (latex). Careful

attention should be made since allergic reactions may appear in patients sensitive to latex.

---

8 <Over-the-counter drugs>
Medical Products Containing Bromhexine Hydrochloride

[Brand Name] Bisolvon Cough Syrup (SSP Co., Ltd), Pabron S Cough Medicine (Taisho Pharmaceutical Co., Ltd.), Histomin Cough Medicine (Kobayashi Pharmaceutical Co., Ltd.) and the others

[When not to use the product] Persons who have experienced an allergic reaction after using this product in the past should not use the product.

[Consultation] If you experience any of the following symptoms after taking the product, immediately discontinue the use of the product, and consult your physician or pharmacist with this leaflet.

The following serious symptoms rarely occur. In such case, immediately receive the medical aid.

Shock (anaphylactic reaction): Immediately after taking the product, urticaria, oedema, chest distress, and other symptoms may occur along with pale face, cold hands and feet, cold sweat and difficulty in breathing.

---

9 <Over-the-counter drugs>
Medical Products Containing Ketoprofen (dermatologic preparation)

[Brand Name] Epasgel (Takaichi Pharmaceutical Industry), Epatec A cream, Epatec A gel, Epatec A lotion (ZERIA Pharmaceutical Co.,Ltd.), Omneed Ketoprofen Poultice (Teikoku Seiyaku Co., Ltd.) and the others

[Consultation] If you experience any of the following symptoms during or after using the product, immediately discontinue the use of the product and show this document to your physician or pharmacist for consultation.

The following serious symptoms rarely occur. In such a case, immediately seek medical aid.

Shock (anaphylactic reaction): Immediately after taking the product, urticaria, oedema, chest distress, and other symptoms may occur along with pale face, cold hands and feet, cold sweat and difficulty in breathing.

---

10 <Autonomic Nervous System Agents>
Distigmine Bromoide preparation

[Brand Name] UBRETID TAB.5mg (Torii Pharmaceutical Co.,Ltd) and the others

[WARNINGS]

WARNINGS

Serious cholinergic crisis associated with disturbances in consciousness, which has led to fatal outcome, have been reported after distigmine bromoide was administered. When administering distigmine bromoide, the following precautions should be taken. Patients must **be carefully monitored under the strict supervision of a physician** (refer to sections on "Careful Administration," "Important Precautions," "Clinically Significant Adverse Reactions," and "Overdose").

If signs of **cholinergic crisis** are observed (Initial symptoms includes nausea/vomiting, abdominal pain, diarrhoea, excessive saliva secretion, excessive airway secretion, sweating, bradycardia, miosis, dyspnoea, etc. A laboratory test shows lowered serum cholinesterase.) during treatment with distigmine bromoide, administration should be discontinued immediately.

If **cholinergic crisis** occurs, 0.5 to 1 mg of atropine sulfate hydrate should be administered intravenously (The dose should be increased according to the symptoms of the patient). Respiratory failure may also occur. In such cases, open

	the airway, and provide artificial respiration, if necessary. Prior to administration of distigmine bromoide, **the patient or suitably qualified person must fully understand** the possible onset of the adverse reaction. If any of the following initial symptoms of **cholinergic crisis** occurs, they must be advised to discontinue the administration of distigmine bromoide and immediately contact the physician and seek medical advice. Nausea/vomiting, abdominal pain, diarrhoea, excessive saliva secretion, excessive airway secretion, sweating, bradycardia, miosis, and dyspnoea
[Indications]	Dysuria after surgery or due to hypotonic urinary bladder including neurogenic bladder. Myasthenia gravis
[Dosage and Administration]	Dysuria after surgery or due to hypotonic urinary bladder including neurogenic bladder. The usual adult dosage of distigmine bromoide for oral use is 5 mg daily. Myasthenia gravis The usual adult dosage of distigmine bromoide for oral use is 5 to 20 mg daily as divided doses for one to four. The dose should be adjusted depending on the symptoms of the patients.
[Precautions of Dosage and Administration]	Under the close supervision of a physician, **patients with myasthenia gravis** should start with the usual adult dose of 5 mg/day of distigmine bromoide and be carefully monitored. Adjust the dose depending on the symptoms of the patients.
[Careful Administration]	Patients with renal disorder [Since distigmine bromoide is excreted from the kidney, blood concentration of distigmine bromoide may increase.] Patients who are taking cholinergic agents or cholinesterase inhibitors [Since distigmine bromoide and cholinergic agents or cholinesterase inhibitors enhance the effects of each other, adverse reactions may occur. (refer to the section on "Drug Interactions")]
[Important Precautions]	**Cholinergic crisis associated with disturbances in consciousness** may occur after administration of distigmine bromoide. The following cautions should be exercised. (Refer to sections on "WARNINGS" and "Clinically Significant Adverse Reactions.") Since many of adverse reactions occurred within the first 2 weeks after administration, precautions should especially be taken for signs of **cholinergic crisis** especially within the first 2 weeks after administration (Initial symptoms includes nausea/vomiting, abdominal pain, diarrhoea, excessive saliva secretion, excessive airway secretion, sweating, bradycardia, miosis, dyspnoea, etc. A laboratory test shows lowered serum cholinesterase). Symptoms have also been reported during continuous administration of distigmine bromoide. Precautions should be taken for any signs of **cholinergic crisis**. If any signs of **cholinergic crisis** appear, discontinue administration immediately and appropriate measures should be taken (refer to the section on "Clinically Significant Adverse Reactions". In patients with myasthenia gravis**, serious worsening of myasthenia symptoms, dyspnea, and dysphagia (crisis)** may occur. In such cases, differentiate crisis based on the clinical symptoms. If it is difficult, intravenously administer 2 mg of edrophonium chloride to the patients, and differentiate crisis, before taking the next measure. Cholinergic Crisis If symptoms such as nausea/vomiting, abdominal pain, diarrhea, excessive saliva secretion, excessive airway secretion, sweating, bradycardia, miosis, dyspnoea, or lowered serum cholinesterase are observed, or if symptoms aggravate or remain unchanged even after administering edrophonium chloride to patients, the administration of distigmine bromoide should be discontinued immediately and appropriate measures should be taken (refer to the section on "Clinically Significant Adverse Reactions").
[Interactions (precautions for concomitant use)]	Cholinesterase inhibitors Donepezil Hydrochloride, Neostigmine Bromide, Pyridostigmine Bromide, Ambenonium Chloride, etc.

[Adverse Reactions (clinically significant adverse reactions)]

Cholinergic crisis

Cholinergic crisis associated with disturbances in consciousness (Initial symptoms includes nausea/vomiting, abdominal pain, diarrhoea, excessive saliva secretion, excessive airway secretion, sweating, bradycardia, miosis, dyspnoea, etc. A laboratory test shows lowered serum cholinesterase) may occur after administration of distigmine bromoide (many cases of cholinergic crisis have been reported to occur within the first 2 weeks after administration). In such cases, immediately discontinue administration and intravenously administer 0.5 to 1 mg of atropine sulfate hydrate (The dose should be increased according to the symptoms of the patients). Respiratory failure may also occur. In such cases, open the airway, and provide artificial respiration, if necessary.

[Adverse Reactions (other adverse reactions)]

Skeletal muscles: Fasciculation

[Use in the Elderly]

Since elderly patients often have poor liver and kidney functions and their body weights are likely to be low, adverse reactions occur more readily. Attention must be given to signs of **cholinergic crisis** (Initial symptoms includes nausea/vomiting, abdominal pain, diarrhoea, excessive saliva secretion, excessive airway secretion, sweating, bradycardia, miosis, dyspnoea, etc. A laboratory test shows lowered serum cholinesterase). Elderly patients must be administered distigmine bromoide carefully. (refer to "WARNINGS", "Clinically Significant Adverse Reactions.")

[Overdose]

Signs and Symptoms

Cholinergic crisis associated with disturbances in consciousness (Initial symptoms includes nausea/vomiting, abdominal pain, diarrhoea, excessive saliva secretion, excessive airway secretion, sweating, bradycardia, miosis, dyspnoea, etc. A laboratory test shows lowered serum cholinesterase) may occur with overdose of distigmine bromoide.

Treatment

Immediately discontinue the administration of distigmine bromoide and intravenously administer 0.5 to 1 mg of atropine sulfate hydrate (The dose should be increased according to the symptoms of the patients). Respiratory failure may also occur. In such cases, open the airway, and provide artificial respiration, if necessary.

[Other Precautions]

Results of animal studies suggest that the diet has an influence on oral absorption of distigmine bromide (refer to "PHARMACOKINETICS").

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 collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of March 1, 2010)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Dutasteride Avolve Capsules 0.5 mg	GlaxoSmithKline K.K.	September 4, 2009
Mirtazapine RFLEX TABLETS 15 mg	Meiji Seika Kaisha, LTD.	September 7, 2009
Mirtazapine Remeron tablets 15 mg	Schering-Plough K.K.	September 7, 2009
Mometasone Furoate Asmanex Twisthaler 100 μg 60 doses	Schering-Plough K.K.	September 14, 2009
Aliskiren Fumarate Rasilez Tablets 150 mg	Novartis Pharma K.K.	October 1, 2009
Bimatoprost LUMIGAN OPHTHALMIC SOLUTION 0.03%	Senju Pharmaceutical Co., Ltd.	October 5, 2009
Paroxetine Hydrochloride Hydrate PAXIL Tablets 10 mg, 20 mg[*1]	GlaxoSmithKline K.K.	October 16, 2009
Interferon Beta FERON Injections 1×10^6 IU, 3×10^6 IU, 6×10^6 IU[*2]	Toray Industries, Inc.	October 16, 2009
Ribavirin REBETOL Capsules 200 mg[*3]	Schering-Plough K.K.	October 16, 2009
Voglibose BASEN Tablets 0.2, BASEN OD Tablets 0.2[*4]	Takeda Pharmaceutical Company Limited	October 19, 2009
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL, 400 mg/16 mL Intravenous Infusion[*5]	Chugai Pharmaceutical Co., Ltd.	November 6, 2009
Amlodipine Besilate/Atorvastatin Calcium Hydrate Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban	Pfizer Japan Inc.	December 2, 2009
Aprepitant EMEND Capsules 80 mg, 125 mg, EMEND Capsule Set	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate GLACTIV Tablets 25 mg, 50 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	December 11, 2009

Sitagliptin Phosphate Hydrate JANUVIA Tablets 25mg, 50 mg, 100 mg	Banyu Pharmaceutical Co., Ltd.	December 11, 2009
Tadalafil Adcirca Tablets 20 mg	Eli Lilly Japan K.K.	December 11, 2009
Dexamethasone Cipecilate Erizas Capsule for Nasal Spray 400 μg	Nippon Shinyaku Co., Ltd.	December 11, 2009
Mesalazine ASACOL Tablets 400 mg	Zeria Pharmaceutical Co., Ltd.	December 16, 2009
Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cells) Cervarix	GlaxoSmithKline K.K.	December 22, 2009
Vancomycin Hydrochloride Vancomycin Ophthalmic Ointment 1%	Toa Pharmaceutical Co., Ltd.	December 28, 2009
Nitric Oxide INOflo for Inhalation 800 ppm	Air Water Inc.	January 1, 2010
Tosufloxacin Tosilate Hydrate OZEX fine granules 15% for pediatric	Toyama Chemical Co., Ltd.	January 12, 2010
Budesonide/Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses	AstraZeneca K.K.	January 13, 2010
Adalimumab (Genetical Recombination) HUMIRA SC Injection 40 mg Syringe 0.8 mL[*6]	Abbott Japan Co., Ltd.	January 20, 2010
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion 100[*7]	Mitsubishi Tanabe Pharma Corp.	January 20, 2010
Nonacog Alfa (Genetical Recombination) BeneFIX Intravenous 500, 1000, 2000	Wyeth K.K.	January 20, 2010
Fentanyl Durotep MT Patch 2.1 mg, 4.2 mg, 8.4 mg, 12.6 mg, 16.8 mg[*8]	Janssen Pharmaceutical K.K.	January 20, 2010
Pramipexole Hydrochloride Hydrate BI•Sifrol Tablets 0.125 mg, 0.5 mg[*9]	Nippon Boehringer Ingelheim Co., Ltd.	January 20, 2010
Miriplatin Hydrate MIRIPLA for Intra-arterial Injection 70 mg	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Meropenem Hydrate Meropen Vial for IV Drip Infusion 0.25 g, 0.5g, Meropen Kit for Intravenous Drip Infusion 0.5 g[*10]	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Peramivir Hydrate RAPIACTA Vial for IV Drip Infusion 150 mg, RAPIACTA Bag for IV Drip Infusion 300 mg	Shionogi & Co., Ltd.	January 27, 2010
Pneumococcal polysaccharide conjugate vaccine (adsorbed) Prevenar Suspension Liquid for S.C. Injection	Wyeth K.K.	February 24, 2010

*1: An additional indication for “treatment of patients with social anxiety disorder”

*2: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with ribavirin in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy”

*3: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with interferon beta in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy”

*4:An additional indication for “inhibition of the development of type II diabetes mellitus in patients with abnormal

glucose tolerance (only when diet and exercise therapies failed to improve the condition)"

*5:An additional indication for "treatment of patients with advanced or recurrent, inoperable non-squamous non-small cell lung cancer except for squamous cell carcinoma"

*6:An additional indication for "treatment of patients with psoriasis vulgaris or psoriasis arthropathica, which is not adequately responsive to conventional therapies"

*7:An additional indication for "treatment of patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis, which is not adequately responsive to conventional therapies"

*8:An additional indication for "analgesia of moderate to severe chronic pain cannot be managed by treatments with non-opioid analgesics and weak opioid analgesics (only in patients who switch from an opioid analgesic)"

*9:An additional indication for "treatment of patients with moderate to severe idiopathic restless leg syndrome"

*10: An additional indication for "treatment of patients with febrile neutropenia"