Pharmaceuticals and Medical Devices Safety Information

No. 270 June 2010

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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.

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No. 270 June 2010

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

[Outline of Information]

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1	**Association between the use of TNF blockers and malignancies**		It was concluded that the association between the use of anti-human tumor necrosis factor alfa monoclonal antibodies (TNF blockers) and malignancies was unclear based on the data submitted at the time of marketing approval. Therefore, TNF blockers' manufacturers were required to conduct post-marketing surveillance to investigate this possible association, and malignancies associated with the use of TNF blockers are described in the "Warnings", "Important Precautions", and "Clinical Studies" sections in the prescribing information to alert healthcare professionals. In August 2009, however, FDA stated that FDA completed its analysis of TNF blockers and concluded that there was an increased risk of lymphoma and other cancers associated with the use of these drugs in children and adolescents, and that FDA will require marketing authorization holder (MAH) of these products to revise the prescribing information. The prescribing information for TNF blockers was revised in December 2009. Based on the above, PMDA reviewed possible association between the use of TNF blockers and the development of malignancies to assess whether safety measures should be taken. As a result, PMDA concluded that providing an alert about possible risk of malignancies in children and adolescents would also be appropriate in Japan. Details are provided in this section.	4
2	**Deferasirox (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 June 1, 2010.	9
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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, 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. 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

Association between the use of TNF Blockers and Malignancies

1. Introduction

In Japan, anti-human tumor necrosis factor alfa monoclonal antibodies (TNF blockers) have been approved for the treatment of rheumatoid arthritis (RA).

Although overseas clinical trials showed the incidence of malignant lymphoma was higher in patients treated with TNF blockers than the general population, it was concluded that association between the use of TNF blockers and malignancies was unclear at the time of marketing approval because malignant lymphoma was known to occur frequently in RA patients. Therefore, TNF blockers' manufacturers were required to conduct post-marketing surveillance to investigate possible association between the use of TNF blockers and malignancies, and it is described in the "Warnings", "Important Precautions", and "Clinical Studies" sections in the prescribing information to alert healthcare professionals.

In August 2009, however, FDA issued an Early Communication describing that FDA completed its analysis of TNF blockers and concluded that there was an increased risk of lymphoma and other cancers associated with the use of these drugs in children and adolescents, and that FDA will require marketing authorization holder (MAH) of these products to revise the prescribing information. The prescribing information for TNF blockers was revised in December 2009.

On the basis above, Pharmaceuticals and Medical Devices Agency (PMDA) reviewed on possible association between the use of TNF blockers and the development of malignancies to assess whether safety measures should be taken. Details are described below.

2. Results of review on malignancies

(1) Adverse reactions reported in Japan

PMDA reviewed adverse reactions of malignancies in association with each TNF blockers reported from the marketing approval in Japan to September 30, 2009. Review results are shown below.

1) Adalimumab

Five adverse reactions associated with adalimumab were reported in 5 cases. These included a report of gastric cancer, malignant tongue cancer, salivary gland neoplasm, lung cancer, and breast cancer. No malignant lymphoma or leukaemia was reported. Adalimumab had been used for treatment of RA in all cases. One case was in the 50 to 59 age range, 2 cases in the 60 to 69 age range, 1 case in the 70 to 79 age range, and 1 case in the 80 to 89 age range. No adverse reaction was reported in children or adolescents. A TNF blocker other than adalimumab had been used as pretreatment in 2 cases. Methotrexate had been concurrently used in 2 cases and steroid preparation in 2 cases (including patients who used both). Time to onset of malignancies had been less than 3 months in 3 cases, 3 to 6 months in 1 case, and 6 months to 1 year in 1 case.

2) Infliximab

A total of 117 reports of adverse reactions associated with infliximab were included in 110 cases. Fifty-one reports of malignant lymphoma, 3 reports of leukaemia, 10 reports of breast cancer, 7 reports of large intestine carcinoma, and 7 reports of lung cancer were included. Infliximab had been used for treatment of RA in 92 cases, for treatment of Crohn's disease in 17 cases and for treatment of other disease in 1 case. Two cases were in the 10 to 19 age range, 2 cases in the 20 to 29 age range, 3 cases in the 30 to 39 age range, 15 cases in the 40 to 49 age range, 25 cases in the 50 to 59 age range, 36 cases in the 60 to 69 age range, 23 cases in the 70 to 79 age range, and 4 cases in the 80 to 89 age range, cases aged 50 or above accounted for 80.0%. No malignant lymphoma was reported in cases under 40. No patients had received pretreatment with a TNF blocker other than infliximab. Methotrexate had been concurrently used in 86 cases and steroid in 68 cases (including patients who used both). Concurrent methotrexate had been used for treatment of RA in all cases. Time to onset of malignancies was less than 3 months in 9 cases, 3 to 6 months in 10 cases, 6 months to 1 year in 11 cases, 1 to 3 years in 29 cases, 3 to 5 years in 10 cases, and unknown in 41 cases.

3) Etanercept

A total of 100 reports of adverse reactions associated with etanercept were included in 94 patients. Thirty-one reports of malignant lymphoma, 1 reports of leukaemia, 10 reports of breast cancer, 9 reports of lung cancer, and 9 reports of gastric cancer were included. Etanercept was used for treatment of RA in all cases. Two cases were in the 30 to 39 age range, 5 cases in the 40 to 49 age range, 17 cases in the 50 to 59 age range, 34 cases in the 60 to 69 age range, 30 cases in the 70 to 79 age range, and 1 case in the 80 to 89 age range. The age of 5 cases was unknown. Patients aged 50 or above accounted for 87.2%. No malignant lymphoma was reported in patients aged under 50. A TNF blocker other than etanercept had been used as pretreatment in 9 cases. Methotrexate was concurrently used in 49 cases and steroid in 57 cases (including patients who used both). Time to onset of malignancies was less than 3 months in 16 cases, 3 to 6 months in 19 cases, 6 months to 1 year in 20 cases, 1 to 3 years in 17 cases, 3 to 5 years in 3 cases, and unknown in 19 cases.

(2) Post-marketing surveillance in Japan

PMDA reviewed incidence of malignancies associated with each type of TNF blockers reported in post-marketing surveillance and that of malignancies in RA patients.

1) Adalimumab

An all cases surveillance in RA patients (patient registration started in June 2008; 6-month follow-up; ongoing) showed incidence of malignancies was 0.40/100 person years (9 cases/2238 person years). According to overseas clinical trial data submitted for regulatory approval, incidence of malignant lymphoma was 0.12/100 person years and that of non-melanoma skin cancer was 0.80/100 person years.[1)]

2) Infliximab

An all cases surveillance in patients with Crohn's disease (patient registration between January 2002 and August 2005; 3-year follow-up; ongoing) showed incidence of malignancies was 0.15/100 person years (11 cases/7149 person years). According to overseas clinical trial data submitted for regulatory approval, incidence of malignancies was 0.79/100 person years.

An all cases surveillance in RA patients (patient registration between July 2005 and December 2006; 6-month follow-up; completed) showed incidence of malignancies was 0.16/100 person years (5 cases/3095.8 person years). A separate long-term use surveillance (patient registration in November 2005; data of 1000 patients to be analyzed; 3-year malignancies evaluation period; ongoing) showed incidence of malignant lymphoma was 0.075/100 person years (2 cases/2654.4 person years) and that of all malignancies including malignant lymphoma was 0.49/100 person years (13 cases/2654.4 person years). According to overseas clinical trial data submitted for regulatory approval, incidence of malignant lymphoma was 0.23/100 person years and that of all malignancies including malignant lymphoma was 1.2/100 person years.[2)]

3) Etanercept

An all cases surveillance in RA patients (patient registration between March 2005 and April 2007; 6-month follow-up; completed) showed incidence of malignancies was 0.70/100 person years (42 cases/6422.6 person years). According to overseas clinical trial data submitted for regulatory approval, incidence of malignant lymphoma was 0.18/100 person years and that of non-melanoma skin cancer was 0.57/100 person years.[3)]

An all cases surveillance in patients with polyarticular-course juvenile idiopathic arthritis (patient registration started in July 2009; 6-month follow-up; ongoing) has reported no malignancies.

4) Others

According to literatures, incidence of malignancies in RA patients ranges between 0.40/100 to 5.88/100 person years.[4-11)]

(3) Overseas situation

PMDA overviewed risk communication about TNF blockers and associated malignancies issued by US and European regulatory authorities.

1) USA

Until December 2009, the "Warnings and Precautions" section in the US prescribing information stated the association between the use of TNF blockers and malignancies was unclear despite a higher incidence of malignant lymphoma and malignancies having been reported in patients treated with TNF blockers compared with control patients in a clinical study because incidence of malignant lymphoma was especially high in RA patients. The "Adverse reactions" section also listed types of malignancies that occurred in the clinical study.

In December 2009, however, the US prescribing information was revised to include an alert in the "Boxed Warnings" and "Warnings" sections about possible risk of malignant lymphoma and malignancies in children and adolescents treated with TNF blockers for the following reasons.[12)]

- Incidence of lymphoma in children and adolescents treated with infliximab or etanercept is statistically significantly higher than the estimated incidence of malignancies in general populations of the same age bracket. For all malignancies, statistically significant difference was not always observed, but incidence tended to be higher in patients treated with TNF blockers.
- Rare malignancies, e.g., leiomyosarcoma, malignant hepatic tumor and renal cell carcinoma, were reported in children and adolescents.
- About one half of reported malignancies in children and adolescents were malignant lymphoma.

2) Europe

In the European Summaries of Product Characteristics (SmPC), the "Special warnings and precautions for use" and "Undesirable Effects" sections include alerts similar to those included in the US prescribing information.

So far no measures have been taken in Europe in association with Early Communication issued by FDA in August 2009.

3. Results of the review regarding necessity of safety measures

Based on the results by the survey and taking into account the expert discussion, PMDA reviewed possible association between the use of TNF blockers and malignancies. The results of the review are presented below.

Although direct comparison may be infeasible, PMDA concluded that the association between the use of TNF blockers and malignancies remains unclear for the time being because the post-market incidence of malignancies in patients treated with TNF blockers were comparable to the overseas incidence reported at the time of marketing approval and the incidence in the general population.

No specific trend has been seen in adverse reactions so far reported in Japan. Information about malignancies in children and adolescents is limited.

Overseas, however, malignancies have been more frequently reported in children and adolescents treated with TNF blockers compared with the general population of the same age bracket and rare malignancies were also reported in this patient population. Therefore, it is concluded that the addition of warnings for possible risk of malignancies in children and adolescents in the Japanese package insert would be appropriate.

4. Safety measures hereafter

PMDA considered association between the use of TNF blockers and malignancies was unclear at the moment.

However, based on the overseas situation, PMDA concluded it is appropriate that the Japanese package insert should also include warnings for possible risk of malignancies in children and adolescents. (Example is shown in Table 2)

Information concerning this issue still needs to be collected and carefully reviewed in cooperation with overseas regulatory authorities and relevant medical associations.

<References>

1) Japanese package insert of adalimumab
2) Japanese package insert of infliximab
3) Japanese package insert of etanercept
4) Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis. 2005；64：1421-1426.
5) Risk of Malignancy among Patients with Rheumatic Conditions. Int J Cancer. 2000；88：497-502.
6) Elevated Incidence of Hematologic Malignancies in Patients with Sjogren's Syndrome Compared with Patients with Rheumatoid Arthritis (Finland). Cancer Causes Control. 1997；8：201-204.
7) Rheumatoid Arthritis and the Risk of Malignancy. Arthritis Rheum. 1997；40(9)：1580-1586.
8) The Risk of Cancer in Rheumatoid Patients in Japan. Scand J Rheumatol. 1995；24：157-159.
9) Risk of Malignant Lymphomas in patients with Rheumatoid Arthritis and in Their First-Degree Relatives. Arthritis Rheum. 2003；48(4)：963-970.
10) Study of Eight Cases of Cancer in 426 Rheumatoid Arthritis Patients Treated with Methotrexate. Ann Rheum Dis. 1997；56：97-102.
11) Tumour Necrosis Factor Blockers Do Not Increase Overall Tumour Risk in Patients with Rheumatoid Arthritis, But May Be Associated with an Increased Risk of Lymphomas. Ann Rheum Dis. 2005；64：699-703.
12) Information for Healthcare Professionals: Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi)
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174474.htm

Table 1

Nonproprietary name	Brand name	Marketing authorization holder
Adalimumab (Genetical Recombination)	HUMIRA SC Injection 40 mg Syringe 0.8 mL	Abbott Japan Co., Ltd.
Infliximab (Genetical Recombination)	REMICADE for I.V. Infusion 100	Mitsubishi Tanabe Pharma Corporation
Etanercept (Genetical Recombination)	ENBREL 10 mg for S.C. Injection, ENBREL 25 mg for S.C. Injection, ENBREL 25 mg Syringe 0.5 mL for S.C.Injection, ENBREL 50 mg Syringe 1.0 mL for S.C.Injection	Pfizer Japan Inc.

Table 2

Before revision	After revision (added sentences underlined)
Important Precautions It has been reported that incidence of malignancies such as malignant lymphoma was higher in patients treated with TNF blockers including this drug compared with controls. Long-term immunosuppressant therapy may increase risks of infection and malignant lymphoma in patients with chronic inflammation such as rheumatoid arthritis. A possible association between the use of TNF blockers and malignancies is unclear; however, patients should be carefully monitored for occurrence of malignancies. (See "Clinical Studies.") All patients (especially patients who have been on long-term immunosuppressant therapy, or patients with psoriasis who have received PUVA therapy) should be checked for non-melanoma skin cancer in advance and continuously monitored during treatment with this drug.	Important Precautions It has been reported that incidence of malignancies such as malignant lymphoma was higher in patients treated with TNF blockers including this drug compared with controls. Long-term immunosuppressant therapy may increase risk of infection and malignant lymphoma in patients with chronic inflammation such as rheumatoid arthritis. <u>In addition, malignancies such as malignant lymphoma has been reported in children and adolescents treated with TNF blockers including this drug.</u> A possible association between the use of TNF blockers and malignancies is unclear; however, patients should be carefully monitored for occurrence of malignancies. (See "Clinical Studies".) All patients (especially patients who have been on long-term immunosuppressant therapy, or patients with psoriasis who have received PUVA therapy) should be checked for non-melanoma skin cancer in advance and continuously monitored during treatment with this drug.

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 June 1, 2010

[Brand Name]:Major product names are showed.

1 Deferasirox

Brand Name (name of company)	Exjade Dispersible Tablets 125 mg, 500 mg (Novartis Pharma K.K.)
Therapeutic Category	Antidotes
Indications	Chronic iron overload due to blood transfusions (cases when injection of iron chelating agent is inappropriate)

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

[Warning]

WARNING

Liver disorder, renal disorder, and gastrointestinal haemorrhage, some fatal, have been reported associated with administration of this drug. Blood tests including transaminase and creatinine should be periodically performed to check serum These adverse reactions occur especially in elderly patients, patients with high-risk myelodysplastic syndrome, those with liver disorder or renal disorder, and those with platelet count of less than 50,000/mm^3.

[Contraindications]

Patients with severe renal impairment
Patients with high-risk myelodysplastic syndrome with poor general condition
Patients with advanced malignant tumor with poor general condition

[Precautions of Dosage and Administration]

Patients treated with this drug may develop abnormal liver function test results. Serum transaminase, bilirubin and Al-P should be checked at baseline, every 2 weeks in the first month and every 4 weeks after 1 month of administration. If serum transaminase etc. persistently increases in association with the treatment, administration should be discontinued and appropriate measures should be taken. When resuming this drug after confirming abnormal liver function test results is unrelated to this drug and returned to normal, the dose should be reduced.

[Careful Administration]

Patients with platelet count of less than 50,000/mm^3
Elderly patients
Patients with high-risk myelodysplastic syndrome
Patients with advanced malignant tumor

[Important Precautions]

This drug should be used by physicians with adequate knowledge and experience of treating patients with refractory anaemia. Physicians should refer to the latest information about this drug before use. This drug should be administered only if potential benefit outweighs the risks.

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Oculomucocutaneous syndrome or erythema multiforme may occur. The patient 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 2 years (from initial marketing to April 22, 2010)

- Serious liver disorder: 6 cases (no fatalities)
- Serious renal disorder: 17 cases (including 2 fatalities)
- Gastrointestinal haemorrhage: 3 cases (no fatalities)
- Skin disorder: 3 cases (no fatalities)

The number of patients treated with this drug per year estimated by marketing authorization holder (MAH): approximately 2300 (2009)

Marketed in Japan: June 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Iron overload (myelodysplastic syndrome, chronic renal failure, liver disorder, aortic valve incompetence, pulmonary hypertension, aortic aneurysm)	500 mg for 8 days	**Renal failure** The patient had aortic valve incompetence (III°) and chronic renal failure. Cardiac and renal functions had been further aggravated by iron overload. 2 days before administration: Creatinine level was 3.2 mg/dL Day 1 of administration: Administration of deferasirox was started at half a dose (500 mg/day). Day 2 of administration: Renal impairment was aggravated/advanced. Day 8 of administration (day of discontinuation): Administration of deferasirox was discontinued. 3 days after discontinuation: Creatinine level was 4.4 mg/dL 7 days after discontinuation: The patient died of renal failure.
	Concomitant medications: levothyroxine sodium, carvedilol, cilnidipine, allopurinol, alfacalcidol, sodium bicarbonate, famotidine, valsartan, spherical adsorptive carbon			

Clinical Laboratory Values

	2 days before administration	3 days after discontinuation
Creatinine (mg/dL)	3.2	4.4
BUN (mg/dL)	85	112
Urine protein (qualitative)	(+)	(+)

BUN: Blood urea nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 20s	Iron overload (acute myeloid leukaemia, graft versus host disease, haemochromatosis, type 2 diabetes mellitus)	875 mg for 8 days	**Stevens-Johnson syndrome** The patient had no history of adverse drug reaction or was not predisposed to hypersensitivity. Day 1 of administration: Administration of deferasirox was started at 875 mg/day. Day 8 of administration (day of discontinuation): Administration of deferasirox was discontinued. 1 day after discontinuation: Pyrexia (38°C) and skin eruption occurred. 2 days after discontinuation: The patient visited the emergency outpatient department for pyrexia (39°C), pharynx pain, and enlarged skin eruption. General oedematous erythema, palpebra conjunctival hyperaemia, and oral mucosal erythema were present. Erosion or blisters was seen in 0% of the body surface area. The patient was admitted to the hospital based on a definitive diagnosis of Stevens-Johnson syndrome (SJS) made by a dermatologist. SJS-related symptoms included pyrexia, ocular hyperaemia, redness and swelling of eyelids, pharynx pain, erythema and increased CRP. Urine analysis was performed (protein, 30 mg/dL; sugar, 0.1 g/dL; ketone body, 1+; occult blood, 1+). Chest Xray showed no abnormality. No histopathological examination of skin, stool analysis, simple chest CT, or endoscopy was performed. Administration of prednisolone, olopatadine hydrochloride, and famotidine were started. Extermal dosage form (ointment and eye drops) were used. 4 days after discontinuation: The dose of prednisolone was reduced because fever had resolved and skin eruption had improved. 7 days after discontinuation: Keratitis and corneal infiltrates were found by an ophthalmologist. Eye drops of sodium hyaluronate and betamethasone sodium phosphate were given. 8 days after discontinuation: Skin eruption resulted in pigmentation. 12 days after discontinuation: SJS remitted 55 days after discontinuation: Administration of prednisolone was discontinued.
	Concomitant medication: tacrolimus hydrate			

Clinical Laboratory Values

	1 day before administration	2 days after discontinuation	5 days after discontinuation	6 days after discontinuation	11 days after discontinuation
Hemoglobin (g/dL)	15.2	14.9	13.3	13.6	13.9
WBC (/mm^3)	11500	12400	16800	17900	26700
Neutrophils (%)	-	81.8	-	-	-
Stab cell (%)	1.0	-	3.0	2.0	4.0
Segmented cell (%)	62.0	-	82.0	75.0	77.0
Lymphocytes (%)	24.0	10.4	10.0	12.5	8.0
Eosinophils (%)	3.0	1.1	-	0.5	-
Basophils (%)	1.0	0.1	-	-	-
Monocytes (%)	8.0	6.6	4.0	8.5	6.0
Creatinine (mg/dL)	0.5	0.6	0.6	0.6	0.5
BUN (mg/dL)	15.6	13.0	17.9	15.7	18.6
AST (GOT) (IU/L)	119	49	37	27	30
ALT (GPT) (IU/L)	244	108	96	91	134
γ-GTP (IU/L)	472	314	254	252	335
ALP (IU/L)	432	290	268	260	326
LDH (IU/L)	225	228	218	215	243
Total bilirubin (mg/dL)	0.9	1.2	0.5	0.5	0.7
CRP (mg/dL)	<0.30	2.94	0.98	0.38	<0.30

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

2 Furosemide

Brand Name (name of company)	Lasix 4% Fine granule, Lasix 20 mg Tablet, 40 mg Tablet, Lasix 20 mg Injection, 100 mg Injection, Eutensin 40 mg Capsule (sanofi-aventis K.K.)
Therapeutic Category	Diuretics
Indications	(Fine granule, tablet) Hypertension (e.g. essential, renal), malignant hypertension, cardiac induced oedema (congestive heart failure), renal oedema, hepatic oedema, premenstrual tension, oedema due to peripheral vascular disorder, promotion of elimination of urinary calculi (Capsules) Essential hypertension (Injectable dosage form) Oliguria due to acute or chronic renal failure [Only Lasix 100 mg Injection and LOWPSTON Injection 20 mg(Nichi-Iko Pharmaceutical Co., Ltd.)] Hypertension (e.g. essential, renal), malignant hypertension, cardiac oedema (congestive heart failure), renal oedema, hepatic oedema, brain oedema, elimination of urinary calculi (Except Lasix 100 mg Injection)

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

[Adverse Reactions (clinically significant adverse reactions)]

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome or erythema multiforme may occur. If such symptoms are observed, appropriate measures, such as discontinuing administration, should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to March 30, 2010)

- Toxic epidermal necrolysis: 2 cases (no fatalities)

The number of patients treated with this drug per year estimated by MAH: approximately 2.66 million (2009)
Marketed in Japan: May 1965

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Heart failure (Ventricular tachycardia, Arrhythmia, Sepsis)	40 mg for 14 days	**Toxic epidermal necrolysis** 2 days before administration: The patient was admitted to the hospital to have a detailed examination and treatment for ventricular tachycardia and cardiac failure. Oral administration of spironolactone was started. Day 1 of administration: Administration of furosemide 40 mg/day was started for treatment of cardiac failure. Day 4 of administration: Pyrexia occurred after catheter examination. CT showed bacterial emboli in the lung. She was diagnosed with sepsis based on blood culture. Administration of antibiotics was started. Day 7 of administration: IV drip infusion of vancomycin hydrochloride was started. Generalized rash appeared after administration. Day 11 of administration: Oral administration of spironolactone was discontinued. Day 14 of administration (day of discontinuation): Skin lesion was aggravated, and vancomycin hydrochloride was switched to teicoplanin. 4 days after discontinuation: All oral and IV treatment was discontinued. Skin lesion was further aggravated. Blisters and erosion were seen all over the body. 5 days after discontinuation: Administration of prednisolone 40 mg/day was started but not effective. 11 days after discontinuation: Methylprednisolone 2500 mg/day and human immune globulin 17.5 g/day were given. 13 days after discontinuation: Erythema disappeared, resulting in pigmentation. Blisters and erosion also improved with time. 47 days after discontinuation: Oral administration of steroid was discontinued. 54 days after discontinuation: The patient was still hospitalized for treatment of ventricular tachycardia and new-onset depression. 153 days after discontinuation: The patient was discharged; treatment for skin pigmentation and xerosis is ongoing on an outpatient basis. [Information concerning skin disorder] Initial symptoms: Multiple fog-drop to rice-grain sized blisters on the face and extremities Accompanied symptom: Infection Skin biopsy: Marked lymphocytic infiltration in epidermis and upper dermis, subepidermal blisters, epidermal necrosis
	Concomitant medications: loxoprofen sodium, vancomycin hydrochloride, gentamicin sulfate, aspirin, clarithromycin, spironolactone, rebamipide, temocapril hydrochloride, teicoplanin			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Renal disorder (Protein urine, Hypertension, Glomerulonephritis chronic, Nephrosclerosis)	20 mg for 7 days	**Toxic epidermal necrolysis** 5 days before administration: The patient had been on amlodipine besilate 5 mg q.d. in the morning since admission. Coadministration of losartan potassium 25 mg was started. Day 1 of administration: Blood pressure was 110 to 150 mmHg. The dose of losartan potassium was increased to 50 mg. Oral trichlormethiazide 1 mg had been used before admission but was switched to furosemide 20 mg/day. Day 4 of administration: Toxicoderma occurred. Eruption appeared on both legs on Day 9 of administration of losartan potassium/Day 4 of administration of furosemide. Despite discontinuation of these drugs, the symptoms did not improve and was aggravated, resulting in generalized rash, including oral mucosa. Skin eruption appeared in the trunk and lower extremities. Administration of fexofenadine hydrochloride was started after the discontinuation of losartan potassium. Day 7 of administration (day of discontinuation): Administration of furosemide was discontinued because skin eruption did not improve. A dermatologist was consulted and toxicoderma was diagnosed. 3 days after discontinuation: Skin eruption did not improve. Oral administration of prednisolone 30 mg was started. The symptoms still did not improve despite topical and oral steroids. DLST was positive for furosemide and losartan potassium. 5 days after discontinuation: Skin eruption was further aggravated. Pyrexia (38.8°C), hyperaemia and eye discharge occurred. Skin eruption was also seen in the face and mouth. Skin biopsy showed toxic epidermal necrolysis. Steroid pulse therapy (1000 mg) was performed for 2 days. 7 days after discontinuation: Oral prednisolone 30 mg was given. Erosion increased (++). (Nikolsky's sign) 11 days after discontinuation: Esophageal epithelial detachment and gastrointestinal haemorrhage were seen. Administration of steroid was discontinued, and plasma exchange was started. (6 sessions in total, until 28 days after discontinuation) 28 days after discontinuation: Skin eruption gradually improved. General condition also improved. Symptoms remitted. [Information concerning skin disorder] Initial symptom: Multiple skin eruption in the trunk and lower extremities Accompanied symptoms: Pyrexia, conjunctivitis Skin biopsy: Toxic epidermal necrolysis
	Concomitant medications: losartan potassium, atorvastatin calcium hydrate, allopurinol, amlodipine besilate, spherical adsorptive carbon			

3

Revision of PRECAUTIONS

(No.217)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated June 1, 2010 (excluding those presented in "2. Important Safety Information" of this Bulletin).

[Brand Name]: Major product names are showed.

<Pituitary hormone preparations>

1 Oxytocin

[Brand Name] ATONIN-O INJECTION 1u, 5u (ASKA Pharmaceutical Co., Ltd.)

[Warning]

WARNING

The indication of this drug should be carefully determined based on thorough observation of the mother and the fetus and expected risks and benefits of this drug. Attention should be paid that multiparous women and those who have undergone caesarean section or hysterotomy are especially prone to uterine rupture and cervical laceration.

Sensitivity to this drug varies greatly depending on individuals. It is reported that some women had severe labour pain with a small dose of oxytocin.

Administration of this drug should be started by an IV drip infusion at a very small dose and adjusted gradually depending on individual labour pain. In addition, this drug should be administered using a syringe pump (device of precision continuous drip infusion).

The patient should be thoroughly informed on the necessity and risk of inducing labour or treating a patient for weak labour with this drug.Informed consent should be obtained from patients before administration.

[Precautions of Dosage and Administration] This drug should be administered using a syringe pump (device of precision continuous drip infusion).

[Important Precautions] With or without drug use, life-threatening emergency events (e.g. uterine rupture, amniotic fluid embolus, intra-cerebral haemorrhage, subarachnoid haemorrhage, premature separation of placenta, eclampsia, massive bleeding during delivery) may occur to the mother during delivery. Patients should be monitored by using a delivery monitoring device (cardiotocography) and checking periodic vital sign when inducing labour or treating a patient for weak labour with this drug. If any abnormalities are observed, appropriate measures should be taken.

<Hormones-Miscellaneous>

2 Dinoprost

[Brand Name] PROSTARMON·F Injection 1000, 2000 (Ono Pharmaceutical Co., Ltd.)

[Warning]

WARNING

The indication of this drug should be carefully determined based on thorough observation of the mother and the fetus and expected risks and benefits of this drug. Attention should be paid that multiparous women and those who have undergone caesarean section or hysterotomy are especially prone to uterine rupture and cervical laceration.
Sensitivity to this drug varies greatly depending on individuals. It is reported that some women had severe labour pain with a small dose of dinoprost.
Administration of this drug should be started by an IV drip infusion at a very small dose and adjusted gradually depending on individual labour pain. In addition, this drug should be administered using a syringe pump (device of precision continuous drip infusion).
The patient should be thoroughly informed on the necessity and risk of induction/ augmentation /stimulation of labour. Informed consent should be obtained from patients before administration.

[Precautions of Dosage and Administration] This drug should be administered using a syringe pump (device of precision continuous drip infusion) for induction/ augmentation /stimulation of labour.

[Important Precautions] With or without drug use, life-threatening emergency events (e.g. uterine rupture, amniotic fluid embolus, intra-cerebral haemorrhage, subarachnoid haemorrhage, premature separation of placenta, eclampsia, massive bleeding during delivery) may occur to the mother during delivery. Patients should be monitored by using a delivery monitoring device (cardiotocography) and checking periodic vital sign when inducing/ augmentation /stimulating labour with this drug. If any abnormalities are observed, appropriate measures should be taken.

<Hormones-Miscellaneous>

3 Dinoprostone

[Brand Name] Prostaglandin E_2 tablets 0.5 mg (Kaken pharmaceutical Co., Ltd.)

[Warning]

WARNING

The indication of this drug should be carefully determined based on thorough observation of the mother and the fetus and expected risks and benefits of this drug. Attention should be paid to that multiparous women and those who have undergone caesarean section or hysterotomy are especially prone to uterine rupture and cervical laceration.
The patient should be thoroughly informed on the necessity of and risks from induction/ augmentation of labour. Informed consent should be obtained from patients before administration.

[Important Precautions] With or without drug use, life-threatening emergency events (e.g. uterine rupture, amniotic fluid embolus, intra-cerebral haemorrhage, subarachnoid haemorrhage, premature separation of placenta, eclampsia, massive bleeding during delivery) may occur to the mother during delivery. Patients should be monitored by using a delivery monitoring device (cardiotocography) and checking periodic vital sign when inducing/ augmentation labour with this drug. If any abnormalities are observed, appropriate measures should be taken.

<Gout preparations>

4 Colchicine

[Brand Name]	Colchicine Tablet 0.5 mg (Takata Seiyaku Co., Ltd.)
[Contraindications]	Patients with hepatic or renal disorder treated with any drug that strongly inhibits the hepatic drug-metabolizing enzyme CYP3A4 or that inhibits P-glycoprotein
[Precautions of Dosage and Administration]	Incidence of gastrointestinal disorders such as diarrhoea increases with dose. It is advisable that usual adult dose is up to 1.8 mg/day of colchicine for gout attack relief.
[Careful Administration]	Patients with hepatic disorder
[Important Precautions]	This drug is administered 0.5 mg at a time for gout attack relief and every 3 to 4 hours until the pain attack is relieved. It is advisable that the daily dose is up to 1.8 mg.
[Interactions]	This drug is mainly metabolized by the hepatic drug-metabolizing enzyme CYP3A4. It is a substrate of P-glycoprotein.
[Interactions (precautions for concomitant use)]	Drugs that inhibit the hepatic drug-metabolizing enzyme CYP3A4 [strong inhibitors (include atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, ritonavir, saquinavir, telithromycin) ; moderate inhibitors (include amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil)]Drug that inhibits P-glycoprotein (ciclosporin)
[Other Precautions]	Overseas clinical studies showed no difference in efficacy for pain attack relief between low-dose colchicine (1.8 mg/day) and high-dose colchicine (4.8 mg/day). Incidence of gastrointestinal adverse events such as diarrhoea was higher in patients treated with high-dose colchicine.

<Psychotropics>

5 Mirtazapine

[Brand Name]	REFLEX TABLETS 15 mg (Meiji Seika Kaisha, Ltd.), Remeron tablets 15mg (Schering-Plough K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Oculomucocutaneous syndrome or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

<Antihypertensives>

6 Efonidipine Hydrochloride Ethanolate

[Brand Name]	Landel Tablet 10, 20, 40 (Nissan Chemical Industries, Ltd.)
[Important Precautions]	Excessive decrease in blood pressure may occur in association with administration of this drug. If such symptoms occurs, appropriate measures such as dose reduction or drug suspension should be taken.
[Adverse Reactions (clinically significant adverse reactions)]	**Shock**: Shock associated with excessive decrease in blood pressure may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Peptic ulcer agents>

7 Famotidine

[Brand Name] Gaster Powder 2%, 10%, Gaster Tablets 10 mg, 20 mg, Gaster D Tablets 10 mg, 20 mg, Gaster injection 10 mg, 20 mg (Astellas Pharma Inc.)

[Adverse Reactions (clinically significant adverse reactions)] **Aplastic anaemia, pancytopenia, agranulocytosis, haemolytic anaemia, decreased platelets**: Aplastic anaemia, pancytopenia, agranulocytosis, haemolytic anaemia, decreased platelets (initial symptoms include general malaise, weakness, subcutaneous/submucosal haemorrhage, pyrexia) may occur. Periodic blood tests should be performed. If any abnormalities are observed, administration should be discontinued immediately and appropriate measures should be taken.

<Pituitary hormone preparations>

8 Purified Human Menopausal Gonadotrophin Human Menopausal Gonadotrophin

[Brand Name] FOLYRMON-P injection 75(Fuji Pharma Co., Ltd.)
HMG INJECTION TEIZO 75 (ASKA Pharmaceutical Co., Ltd.)

[Contraindications] Patients with confirmed or suspected oestrogen-dependent malignant tumor (e.g. breast cancer, endometrial cancer)

[Careful Administration] Patients with uterine myoma
Patients with endometriosis
Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray

<Pituitary hormone preparations>

9 Human Chorionic Gonadotrophin

[Brand Name] GONATROPIN FOR INTRAMUSCULAR INJECTION 1000U (ASKA Pharmaceutical Co., Ltd.)

[Careful Administration] Patients with confirmed or suspected oestrogen-dependent malignant tumor (e.g. breast cancer, endometrial cancer)
Patients with uterine myoma
Patients with endometriosis
Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray

<Pituitary hormone preparations>

10 Follitropin Beta (Genetical Recombination)

[Brand Name] Follistim Injection 50 (Schering-Plough K.K.)

[Careful Administration] Patients with uterine myoma
Patients with endometriosis
Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray

<Pituitary hormone preparations>

11 Follitropin Alfa (Genetical Recombination) (75IU, 450IU, 900IU)

[Brand Name] Gonalef for Subcutaneous Injection 75, Gonalef for Subcutaneous Injection Pen 450, 900 (Merck Serono Co., Ltd.)

[Contraindications]

Patients with confirmed or suspected oestrogen-dependent malignant tumor (e.g. breast cancer, endometrial cancer)
Patients with confirmed or suspected androgen-dependent malignant tumor (e.g. prostate cancer)

[Careful Administration]

Patients with uterine myoma
Patients with endometriosis
Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray
Patients with prostatic hypertrophy

<Pituitary hormone preparations>

12 Follitropin Alfa (Genetical Recobmination) (150IU)

[Brand Name] Gonalef for Subcutaneous Injection 150 (Merck Serono Co., Ltd.)

[Contraindications]

Patients with confirmed or suspected oestrogen-dependent malignant tumor (e.g. breast cancer)
Patients with confirmed or suspected androgen-dependent malignant tumor (e.g. prostate cancer)

[Careful Administration]

Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray
Patients with prostatic hypertrophy

<Estrogen and progesterone preparations, Mixed hormone preparations>

13 Estriol (injectable dosage form)
Chlormadinone Acetate/Mestranol
Norethisterone/Mestranol
Norgestrel/Ethinylestradiol
Hydroxyprogesterone Caproate/Estradiol Benzoate
Hydroxyprogesterone Caproate/Estradiol Dipropionate

[Brand Name] HOLIN FOR INTRAMUSCULAR INJECTION 10 mg (ASKA Pharmaceutical Co., Ltd.)
LUTEDION TABLETS (ASKA Pharmaceutical Co., Ltd)
SOPHIA-A TABLETS, C TABLETS (ASKA Pharmaceutical Co., Ltd.)
Planovar Combination Tablets (Pfizer Japan Inc.)
LUTES DEPOT Inj. (Mochida Pharmaceutical Co., Ltd.)
E･P･HORMONE DEPOT INTRAMUSCULAR INJECTION (ASKA Pharmaceutical Co., Ltd.)

[Careful Administration]

Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast

nodule, mastopathy, or abnormal breast x-ray

<Mixed hormone preparations>

14 Norethisterone/Ethinylestradiol (preparation with the indication for dysmenorrhoea)

[Brand Name] LUNABELL tablets (Nobelpharma Co., Ltd.)

[Careful Administration] Patients with a history of breast cancer

<Hormones-Miscellaneous>

15 Clomifene Citrate Cyclofenil

[Brand Name] Clomid Tablet 50 mg (Shionogi & Co., Ltd.)
SEXOVID TABLETS 100 mg (ASKA Pharmaceutical Co., Ltd)

[Contraindications]

Patients with confirmed or suspected oestrogen-dependent malignant tumor (e.g. breast cancer, endometrial cancer)

[Careful Administration] Patients with uterine myoma
Patients with endometriosis
Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray

<Hormones-Miscellaneous>

16 Gonadorelin Acetate (1.2 mg, 2.4 mg)

[Brand Name] HYPOCRINE Injection 1.2, 2.4 (Mitsubishi Tanabe Pharma Corporation)

[Contraindications]

Patients with confirmed or suspected oestrogen-dependent malignant tumor (e.g. breast cancer, endometrial cancer)
Patients with confirmed or suspected androgen-dependent malignant tumor (e.g. prostate cancer)

[Careful Administration] Patients with uterine myoma
Patients with endometriosis
Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray
Patients with prostatic hypertrophy

<Genital organ agents>

17 Estriol (vaginal tablet)

[Brand Name] ESTRIEL VAGINAL Tab. 0.5 mg (Mochida Pharmaceutical Co., Ltd.)

[Careful Administration] Patients with uterine myoma
Patients with endometriosis
Patients with a history of breast cancer
Patients with genetic predisposition of breast cancer and those with breast nodule, mastopathy, or abnormal breast x-ray

<Miscellaneous metabolism agents-Miscellaneous>

18 Alendronate Sodium Hydrate (oral dosage form)
Etidronate Disodium
Sodium Risedronate Hydrate

[Brand Name] Fosamac Tablets -5 (Banyu Pharmaceutical Co., Ltd.), Bonalon Tablet 5mg (Teijin Pharma Ltd.)
Didronel Tab. 200 (Dainippon Sumitomo Pharma Co., Ltd.)
Actonel Tablet 2.5 mg, 17.5 mg (Ajinomoto Pharmaceuticals Co., Ltd.), BENET Tablets 2.5mg (Takeda Pharmaceutical Company Limited.)

[Important Precautions] Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates including this drug regardless of route of administration. In many of reported cases, the event occurred in association with dental procedures such as tooth extraction or local infection. Known risk factors include malignant tumor, chemotherapy, corticosteroid therapy, radiotherapy, poor oral hygiene, and past dental procedure.
Before using this drug, physicians should instruct the patient to receive an appropriate dental examination and, if necessary, to have invasive dental procedures in the jaw bone such as tooth extraction be finished before treatment. Physicians should instruct the patient to receive periodic dental checkups and to avoid invasive dental procedures in the jaw bone, such as tooth extraction, as much as possible during treatment. In addition, physicians should thoroughly inform the patients of the importance of oral hygiene and notifying his/her dentist about use of this drug. Physicians also should advise the patient to see a dentist/oral surgeon, if any abnormalities occur.
It is reported that nontraumatic stress fracture of subtrochanteric and proximal femur shaft occurred in patients treated with long-term bisphosphonate. Physicians should performed x-ray examinations and should administer cautiously with adequate monitoring. This stress fracture appears in x-rays as a characteristic image such as a thickened bone cortex. Precursor pain in the affected area starts several weeks to months before complete fracture. If such signs observed, appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral femoral fracture occurs, diagnostic imaging on the other femur should be performed.

<Reference Information> Sedghizadeh, P.P., et al. : JADA 2009 ; 140(1) : 61-66

<Miscellaneous metabolism agents-Miscellaneous>

19 Alendronate Sodium Hydrate (injectable dosage form)
Incadronate Disodium
Zoledronic Acid Hydrate
Pamidronate Disodium

[Brand Name]

Teiroc Injection 5 mg, 10 mg (Teijin Pharma Limited.)
Bisphonal Injection 10 mg (Astellas Pharma Inc.)
ZOMETA for i.v. infusion 4 mg (Novartis Pharma K.K.)
Aredia for Intravenous Infusion 15 mg (Novartis Pharma K.K.)

[Important Precautions]

Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates including this drug regardless of route of administration. In many of reported cases, the event occurred in association with dental procedures such as tooth extraction or local infection. Known risk factors include malignant tumor, chemotherapy, corticosteroid therapy, radiotherapy, poor oral hygiene, and past dental procedure.
Before using this drug, physicians should instruct the patient to receive an appropriate dental examination and, if necessary, to have invasive dental procedures in the jaw bone such as tooth extraction be finished before treatment. Physicians should instruct the patient to receive periodic dental checkups and to avoid invasive dental procedures in the jaw bone, such as tooth extraction, as much as possible during treatment. In addition, physicians should thoroughly inform the patients of the importance of oral hygiene and notifying his/her dentist about use of this drug. Physicians also should advise the patient to see a dentist/oral surgeon, if any abnormalities occur.

<Reference Information>

Sedghizadeh, P.P., et al. : JADA 2009 ; 140(1) : 61-66

<Miscellaneous metabolism agents-Miscellaneous>

20 Minodronic Acid Hydrate

[Brand Name]

Bonoteo Tablets 1 mg (Astellas Pharma Inc.), RECALBON Tablets 1mg (Ono Pharmaceutical Co., Ltd.)

[Important Precautions]

Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates regardless of route of administration. In many of reported cases, the event occurred in association with dental procedures such as tooth extraction or local infection. Known risk factors include malignant tumor, chemotherapy, corticosteroid therapy, radiotherapy, poor oral hygiene, and past dental procedures.
Before using this drug, physicians should instruct the patient to receive an appropriate dental examination and, if necessary, to have invasive dental procedures in the jaw bone such as tooth extraction be finished before treatment. Physicians should instruct the patient to receive periodic dental checkups and to avoid invasive dental procedures in the jaw bone, such as tooth extraction, as much as possible during treatment. In addition, physicians should thoroughly inform the patients of the importance of oral hygiene and notifying his/her dentist about use of this drug. Physicians also should advise the patient to see a dentist/oral surgeon, if any abnormalities occur.
It is reported that nontraumatic stress fracture of subtrochanteric and proximal femur shaft occurred in patients treated with long-term bisphosphonate. Physicians should performed x-ray examinations and should administered cautiously with adequate monitoring. This stress fracture appears in x-rays as a characteristic image such as a thickened bone cortex. Precursor pain in the

affected area starts several weeks to months before complete fracture. If such signs observed, appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral femoral fracture occurs, diagnostic imaging on the other femur should be performed.

<Reference Information> Sedghizadeh, P.P., et al. : JADA 2009 ; 140(1) : 61-66

<Antineoplastics-Miscellaneous>

21 Tamoxifen Citrate

[Brand Name] nolvadex tablets 10 mg (AstraZeneca K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Agranulocytosis, decreased white blood cell, decreased neutrophils, anaemia**, **decreased platelets**: Agranulocytosis, decreased white blood cell, decreased neutrophils, anaemia, decreased platelets may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

<Over-the-counter drugs>

22 Preparations containing Codeine Phosphate Hydrate
Preparations containing Dihydrocodeine Phosphate
Preparations containing Hydrocodeine Phosphate Sekisanol

[Brand Name] Aneton Cough Z Liquid (Johnson & Johnson K.K.), S.Tac EVE Tablets (SSP Co. Ltd.), Neo Cough Medicine (Tenshindo Pharmaceutical Co., Ltd.)

[When not to use the product] Overdosing and long-term use should be avoided.

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 June 1, 2010)

Nonproprietary name Brand name on	Name of the marketing authorisation holder	Date of EPPV initiate
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 800ppm	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*[1]	Abbott Japan Co., Ltd.	January 20, 2010
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion 100*[2]	Mitsubishi Tanabe Pharma Corp.	January 20, 2010
Nonacog Alfa (Genetical Recombination) BeneFIX Intravenous 500, 1000, 2000	Pfizer Japan Inc.	January 20, 2010
Fentanyl Durotep MT Patch 2.1 mg, 4.2 mg, 8.4 mg, 12.6 mg, 16.8 mg*[3]	Janssen Pharmaceutical K.K.	January 20, 2010

Pramipexole Hydrochloride Hydrate BI•Sifrol Tablets 0.125 mg, 0.5 mg*4	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, 0.5 g, Meropen Kit for Intravenous Drip Infusion 0.5 g*5	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	Pfizer Japan Inc.	February 24, 2010
Everolimus AFINITOR tablets 5 mg	Novartis Pharma K.K.	March 8, 2010
Rasburicase (Genetical Recombination) Rasuritek for I.V. Injection 1.5 mg, 7.5 mg	sanofi-aventis K.K	April 5, 2010
Olmesartan Medoxomil/Azelnidipine REZALTAS COMBINATION TABLETS LD, HD	Daiichi Sankyo Company, Limited.	April 16, 2010
Valsartan/Amlodipine Besilate EXFORGE Combination Tablets	Novartis Pharma K.K.	April 16, 2010
Vildagliptin Equa Tablets 50 mg	Novartis Pharma K.K.	April 16, 2010
Sugammadex Sodium Bridion Intravenous 200 mg, 500 mg	Schering-Plough K.K.	April 19, 2010
Duloxetine Hydrochloride Cymbalta Capsule 20 mg, 30 mg	Shionogi & Co., Ltd.	April 19, 2010
Latanoprost/Timolol Maleate Xalacom Combination Eye Drops	Pfizer Japan Inc.	April 20, 2010
Palonosetron Hydrochloride ALOXI I.V. Injection 0.75 mg	Taiho Pharmaceutical Co., Ltd.	April 22, 2010
Epoetin Kappa (Genetical Recombination) [Epoetin Alfa Biosimilar 1] Epoetin Alfa BS Injection 750 syringe [JCR], 1500 syringe [JCR], 3000 syringe [JCR], Epoetin Alfa BS Injection 750 [JCR], 1500 [JCR], 3000 [JCR]	JCR Pharmaceuticals Co., Ltd.	May 27, 2010

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

*2: 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"

*3: 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)"

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

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

Reference

Project to survey provision and availability of information on appropriate use of drugs

1. Introduction

Ministry of Health, Labour and Welfare (MHLW) conducted a survey in 2009 to use the results as reference for future communication practice on the following issues;

- if marketing authorization holders (MAHs) properly provided healthcare professionals in the medical instructions with the information on the appropriate use of drugs, such as package insert revisions which were required by MHLW to the MAHs.
- how such information was disseminated within the medical institutions.

MHLW also promoted the medical institutions to subscribe to the information E-mail service (PushMail) by Pharmaceuticals and Medical Devices Agency (PMDA) in the project. The survey report by Mitsubishi Research Institute, which implemented the survey, is now available.

2. Request to healthcare providers

The survey report revealed that the timing and and the means by which information on appropriate use of drugs is available may differ depending on the size of the medical institutions. However, it showed that healthcare providers in medical institutions which subscribed to PushMail obtained information early whether their size is big or small. Healthcare providers are encouraged to subscribe to PushMail and to take advantage of the service to ensure to obtain information on appropriate use of drugs in a timely manner.

PushMail subscription: http://www.info.pmda.go.jp/info/idx-push.html

3. Closing comments

For further information, see MHLW and Pharmaceuticals and Medical Devices information websites .

MHLW website
http://www1.mhlw.go.jp/kinkyu/iyaku_j/100519.html

Pharmaceuticals and Medical Devices information website
http://www.info.pmda.go.jp/kyoten_iyaku/tekisei_report.html