Pharmaceuticals and Medical Devices Safety Information

No. 285 November 2011

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

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Pharmaceuticals and Medical Devices Safety Information
No. 285 November 2011

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Safety Measures against Nephrogenic Systemic Fibrosis associated with Gadolinium Contrast Media**	*P*	MHLW issued a notification about gadolinium contrast media in April and October 2009 and required marketing authorization holders (MAHs) to revise the "Precautions" section of the package insert to issue alerts for nephrogenic systemic fibrosis (NSF) associated with the drug. Based on review results of reported adverse reaction and situations overseas, MHLW issued an additional notification on September 20, 2011 and required MAHs to revise the "Precautions" section. The details are described in this section.	6
2	**Carbamazepine-induced Serious Drug Eruption and Genetic Polymorphism**	*P*	A number of cases of serious drug eruption such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with carbamazepine have been reported. The causality between carbamazepine-induced serious drug eruption and HLA genetic polymorphism in Han Chinese is already included in the package insert of carbamazepine. This time MHLW reviewed the cases reported in Japanese patients and required MAHs to provide the information in the package insert. The details are described in this section.	11
3	**Important Safety Information**	*P* *C*	Anastrozole (and 2 others): Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated October 25, 2011, the contents of important revisions and case summaries that served as the basis for these revisions will be provided in this section.	14
4	**Revision of Precautions (No. 231)**		Atomoxetine Hydrochloride (and 6 others)	23
5	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of November 1, 2011.	27

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

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADRs	Adverse drug reactions
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
Al-P	Alkaline phosphatase
APTT	Activated partial thromboplastin time
BUN	Blood urea nitrogen
CA15-3	Carbohydrate antigen 15-3
CEA	Carcinoembryonic antigen
CMAJ	Canadian medical association journal
CPK	Creatine phosphokinase
CPM	Count per minute
CRP	C-reactive protein
CT	Computed tomography
dBP	Diastolic blood pressure
DLST	Drug lymphocyte stimulation test
EF	Ejection fraction
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPPV	Early Post-marketing Phase Vigilance
ER	Estrogen receptor
FDA	Food and Drug Administration
FT_3	Free triiodothyronine
FT_4	Free thyroxine
FY	Fiscal year
GFR	Glomerular filtration rate
HbA_{1c}	Hemoglobin A1c
HDL	High-density lipoprotein
HER2	Human epidermal growth factor receptor 2
HLA	Human leukocyte antigens
HLA-A*3101	Human leukocyte antigens-A*3101
HLA-B*1502	Human leukocyte antigens-B*1502
HR	Heart rate
I-CTP	Carboxy-terminal telopeptide of type I collagen
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IU	International unit
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lungen-6)
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LVIDd	Left ventricular internal dimension in diastole
MAH	Marketing authorization holder
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NSF	Nephrogenic Systemic Fibrosis

NT-proBNP	N-terminal pro-Brain natriuretic peptide
PGR	Progesterone receptor
PLT	Platelet
PS	Performance status
PT	Prothrombin Time
PT INR	Prothrombin time - international normalized ratio
PTH-INT	Intact parathyroid hormone
RBC	Red blood cell count
sBP	Systolic blood pressure
S.I.	Stimulation index
SJS	Stevens-Johnson syndrome
SP-A	Surfactant protein A
TEN	Toxic epidermal necrolysis
TSH	Thyroid-stimulating hormone
US	the United States
WBC	White blood cell count
ZTT	Zinc sulfate turbidity test
γ-GTP	gamma-glutamyl transpeptidase

1

Safety Measures against Nephrogenic Systemic Fibrosis associated with Gadolinium Contrast Media

	Active ingredient	Brand Name (name of company)
Active ingredient Brand Name (name of company)	(1) Gadodiamide hydrate	(1) OMNISCAN INTRAVENOUS INJECTION 32%, OMNISCAN INTRAVENOUS INJECTION 32% SYRINGE 5 mL, 10 mL, 15 mL, 20 mL (Daiichi Sankyo Company, Limited)
	(2) Gadopentetate dimeglumine	(2) Magnevist iv inj., Magnevist iv inj. Syringe (Bayer Yakuhin, Ltd.)
	(3) Gadoxetate sodium	(3) EOB・Primovist Inj. Syringe (Bayer Yakuhin, Ltd.)
	(4) Gadoteridol	(4) ProHance for Intravenous Injection, 5 mL, 10 mL, 15 mL, 20 mL, ProHance for Intravenous Injection Syringe 13 mL, 17 mL (Bracco-Eisai Co., Ltd.)
	(5) Gadoterate meglumine	(5) Magnescope intravenous injection 38% Syringe 10 mL, 15 mL, 20 mL, MAGNESCOPE Syringe (Guerbet Japan K.K.)
Therapeutic Category	Diagnostic Agents-Miscellaneous	
Indications	(1) Magnetic resonance imaging of the following parts Brain and spinal cord Trunk and extremities (2) Magnetic resonance imaging of the following parts Brain and spinal cord Trunk and extremities (3) Magnetic resonance imaging of hepatic tumor (4) Magnetic resonance imaging of the following parts Brain and spinal cord Trunk and extremities (5) Magnetic resonance imaging of the following parts Brain and spinal cord Trunk and extremities	

1. Introduction

Nephrogenic systemic fibrosis (NSF) associated with gadolinium contrast media used for magnetic resonance imaging (MRI) was described in Pharmaceuticals and Medical Device Safety Information No. 237 issued in June 2007 and No. 242 issued in December 2007.

Gadolinium contrast media approved in Japan include gadodiamide hydrate, gadopentetate dimeglumine, gadoxetate sodium, gadoteridol and gadoterate meglumine. Based on the review results and reported adverse reactions to the five compounds and situations overseas, MHLW issued a notification on September 20, 2011 and required marketing authorization holders (MAHs) to revise the "Precautions" section of the package insert. The details are described below.

2. Adverse reaction reports of NSF

(1) Situations in Japan

Of the cases of adverse reactions to gadolinium contrast media reported as of July 26, 2011 (since the initial marketing), reports of nephrogenic systemic fibrosis (Medical Dictionary for Regulatory Activities [MedDRA/J]) are shown in the table below.

	NSF (number of cases)	Cases for which a causality could not be ruled out (number of cases)
Gadodiamide hydrate	13	12
Gadopentetate dimeglumine	8	2
Gadoxetate sodium	0	0
Gadoteridol	1	0
Gadoterate meglumine	0	0

The causality with the contrast media was evaluated in 22 cases. The causality between the gadolinium contrast media and NSF could not be ruled out in 12 cases of adverse reaction to gadodiamide hydrate and 2 cases of adverse reaction to gadopentetate dimeglumine. Many of the adverse reactions for which a causality to the gadolinium contrast media could not be ruled out were reported in patients with serious renal disorder requiring haemodialysis.

All NSF cases following the administration of gadolinium contrast media,including these 14 cases, occured before the alert had been issued in 2007. After the alert issuance, no NSF associated with gadolinium contrast media has been reported in Japan.

(2) Situations Overseas

Measures to minimize the risk of NSF associated with gadolinium contrast media have been taken in overseas countries because (i) several adverse reactions have continued to be reported since around 2006, (ii) NSF is a rare disease involving skin and connective tissue fibrosis and may result in death after adversely affecting joint (impaired joint mobility) and other organs, (iii) NSF develops in patients with renal impairment and (iv) there is no established treatment for NSF.

The European Medicines Agency (EMA) determined that the onset of NSF depends on the structural characteristics of gadolinium contrast media and classified the risk of NSF associated with individual compounds into 3 levels (high risk, medium risk and low risk)[Note)], based on a comprehensive review of the stability of gadolinium ion and the reported NSF case series. The US Food and Drug Administration (FDA) has classified the risk of these agents in a similar way to the EMA's.

Note) EMA's risk classification

High risk:	Gadodiamide hydrate, gadopentetate dimeglumine
Medium risk:	Gadoxetate sodium
Low risk:	Gadoteridol, gadoterate meglumine

(3) Guidelines for the use of gadolinium contrast media

The Japan Radiological Society and the Japanese Society of Nephrology issued "Guidelines for Administering Gadolinium Based Contrast Agents to Patients with Renal Dysfunction"[1)] for physicians performing contrast enhanced MRI. The guidelines specify, "Before performing a contrast enhanced MRI, renal function (glomerular filtration rate, GFR) should be evaluated except in emergency situations. In the clinical setting, it is recommended this be done by calculating the estimated GFR (estimated glomerular filtration rate, eGFR) based on the patient's gender, age and

serum creatinine level. The serum creatinine level should be as recent as possible." For patients with end-stage renal dysfunction, chronic renal failure or acute renal failure, the guidelines recommend that, "Gadolinium based contrast agent enhanced MRI should be replaced with an alternative examination." and "If gadolinium based contrast agent is absolutely necessary, it is preferable to avoid gadolinium based contrast agent for which there are many reported cases of NSF."

In patients with GFR that exceeds 60 mL/min/1.73 m^2, "there is little evidence suggesting high risk for developing NSF after use of gadolinium contrast agent." In patients with GFR greater than 30 mL/min/1.73 m^2 and less than 60 mL/min/1.73 m^2, however, "there have been reports of such patients developing NSF, the risk and benefit of a gadolinium based contrast agent enhanced MRI should be carefully considered before the administration of a gadolinium based contrast agent."

3. Review results and safety measures

Based on the above information and the expert's review, a revision of the "Precautions" section, e.g., inclusion of an alert for NSF in the "Warnings" section, was considered appropriate to additionally alert healthcare professionals. MHLW issued a notification on September 20, 2011 and required MAHs to revise the "Precautions" section of the package inserts. Healthcare professionals are encouraged to ensure safety through promotion of proper use of gadolinium contrast media.

Gadodiamide Hydrate

Warnings	**WARNINGS** It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Sufficient caution should be exercised with patients who have renal disorder or patients who may have decreased renal function.
Contraindications	Patients with serious renal disorder (Nephrogenic systemic fibrosis may occur. The main route of excretion of this drug is the kidney, and therefore, symptoms such as acute renal failure may be aggravated due to delayed excretion in patients with decreased renal function.)
Careful Administration	Patients with renal disorder or patients who may have decreased renal function.
Important Precautions	If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function. It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, administration of this drug should be avoided.

Gadopentetate Dimeglumine

Warnings	**WARNINGS** It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Sufficient caution should be exercised with patients with renal disorder or patients who may have decreased renal function.

Contraindications	Patients with serious renal disorder (Nephrogenic systemic fibrosis may occur. The main organ that excretes this drug is the kidney, and therefore, symptoms such as acute renal failure may be aggravated due to delayed excretion in patients with decreased renal function.)
Careful Administration	Patients with renal disorder or patients who may have decreased renal function.
Important Precautions	If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function. It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, administration of this drug should be avoided.

Gadoxetate Sodium

Warnings	**WARNINGS** It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Sufficient caution should be exercised with patients who have renal disorder or patients who may have decreased renal function.
Careful Administration	Patients with renal disorder or patients who may have decreased renal function.
Important Precautions	If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function. It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, it is encouraged to avoid administration of this drug and to replace it with other alternative examination methods.
Clinically significant adverse reactions (similar drug)	**Nephrogenic Systemic Fibrosis (NSF)**: It has been reported that nephrogenic systemic fibrosis developed after using drugs of the same class in patients with serious renal disorder. Patients should continue to be carefully monitored after administration, and caution should be exercised for the occurrence of abnormalities including itching, swelling, sclerosis of the skin, joint stiffness, and muscular weakness.

Gadoteridol

Warnings	**WARNINGS** It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Sufficient caution should be exercised with patients who have renal disorder or patients who may have decreased renal function.
Careful Administration	Patients with renal disorder or patients who may have decreased renal function.

Important Precautions	If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function. It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, it is encouraged to avoid administration of this drug and to replace it with other alternative examination methods.
Adverse Reactions (clinically significant adverse reactions)	**Nephrogenic Systemic Fibrosis (NSF)**: It has been reported overseas that nephrogenic systemic fibrosis developed after using this drugs in patients with serious renal disorder. Patients should continue to be carefully monitored after administration, and caution should be exercised for the occurrence of abnormalities including itching, swelling, sclerosis of the skin, joint stiffness, and muscular weakness.

Meglumine Gadoterate

Warnings	**WARNINGS** It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Sufficient caution should be exercised with patients who have renal disorder or patients who may have decreased renal function.
Careful Administration	Patients with renal disorder or patients who may have decreased renal function.
Important Precautions	If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function. It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, it is encouraged to avoid administration of this drug, and to replace it with other alternative examination methods.
Adverse Reactions (clinically significant adverse reactions)	**Nephrogenic Systemic Fibrosis (NSF)**: It has been reported overseas that nephrogenic systemic fibrosis developed after using this drugs in patients with serious renal disorder. Patients should continue to be carefully monitored after administration, and caution should be exercised for the occurrence of abnormalities including itching, swelling, sclerosis of the skin, joint stiffness, and muscular weakness.

<Reference> (including provisionally translated titles)

1) Guidelines for Administering Gadolinium Based Contrast Agents to Patients with Renal Dysfunction (version 2; revised on September 2, 2009) [Joint Committee for NSF and Use of Gadolinium Based Contrast Agents (Japan Radiological Society and Japanese Society of Nephrology)

2

Carbamazepine-induced Serious Drug Eruption and Genetic Polymorphism

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Carbamazepine	Tegretol Tablet 100 mg, 200 mg, Tegretol Fine granule 50% (Novartis Pharma K.K.) and others
Therapeutic Category	Antiepileptics, Psychotropics	
Indications	1. Psychomotor seizure, mental disorder associated with epileptic personality or epilepsy, epileptic convulsive seizure: tonic-clonic seizure (generalized convulsive seizure, grand mal) 2. Mania, manic state in manic depressive illness, excitement in schizophrenia 3. Trigeminal neuralgia	

1. Introduction

Carbamazepine was approved as a treatment for patients with epilepsy and trigeminal neuralgia in March 1965. The additional indication for the treatment of "mania, manic state in manic depressive illness and excitement in schizophrenia" was approved in March 1990. As of October 2011, 8 products under 4 brand names including generic drugs (brand names: Tegretol Tablet/Fine Granule, CARBAMAZEPINE Tab./Fine Gran., TELESMIN TABLETS/FINE GRANULES, and LEXIN TABLETS/FINE GRANULES) have been approved in Japan. An estimated 275000 patients per year are using Tegretol Tablet/Fine Granule (2010 data).

Like antibiotics, antipyretic/analgesic/anti-inflammatory drugs and other anti-epileptics, a number of serious drug eruptions such as oculomucocutaneous syndrome (Stevens-Johnson syndrome, SJS) and toxic epidermal necrolysis (TEN) associated with carbamazepine have been reported. Although the reporting frequency of serious drug eruption is quite low, the outcome can be serious once it has developed. Recently, predictors of serious drug eruption have been investigated to avoid the occurrence of such drug eruption. Human leukocyte antigen (HLA) genetic polymorphism is attracting attention as a biomarker to predict the onset of severe drug eruption.

Chung et al.[1)] and Hung et al.[2)] reported in their studies in patients of Han-Chinese descent that almost all of the patients who had SJS/TEN after receiving carbamazepine were carriers of *HLA-B*1502*. Based on the study reports, the following description of the association between serious drug eruption and *HLA-B*1502* in the Han-Chinese was included in the package insert of carbamazepine in April 2008.

Other Precautions

Retrospective studies in patients of Han Chinese descent have found that in almost all cases, patients with carbamazepine-induced oculomucocutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) were carriers of *HLA-B*1502* allele. The prevalence of carriers of *HLA-B*1502* allele appears to be above 15% of the population in the Philippines, Thailand, Hong Kong and Malaysia, around 10% in Taiwan and less than 1% in Japan and Korea. The association between oculomucocutaneous syndrome/toxic epidermal necrolysis and Japanese carriers of *HLA-B*1502* allele is unknown.

Since an association between serious drug eruption and HLA genetic polymorphism has

recently been reported in Japanese patients, the package insert of carbamazepine has been revised to provide information. The details are described below.

2. Review and information provision

The following 3 study reports of carbamazepine-induced serious drug eruption and genetic polymorphism submitted by the MAH by the end of August 2011 were reviewed.

Report No.	Authors Reference No.)	Major outcomes
1	Ozeki et al.[3)]	• Association between serious drug eruption and *HLA-A*3101* was suggested. • No *HLA-B*1502* carrier was identified.
2	Kashiwagi et al.[4)]	• Association between serious drug eruption and *HLA-A*3101* was suggested. • No *HLA-B*1502* carrier was identified.
3	Kaniwa a et al.[5)]	• *HLA-B*1511* was suggested as a risk factor for SJS/TEN. • No *HLA-B*1502* carrier was identified.

The genome-wide association study[Note 1)] of Ozeki et al. [3)] suggested that there was an association between carbamazepine-induced serious drug eruption and *HLA-A*3101*. Kashiwagi et al. [4)] reported the same in their study using the candidate gene approach[Note 2)]. Reproducibility was demonstrated in the studies conducted by different groups using different approaches. The absence of *HLA-B*1502* carrier in the Japanese study population reported by Ozeki et al. [3)] is consistent with the reports by Kashiwagi et al. [4)] and Kaniwa et al.[5)]

Note 1) An approach to search for responsible gene/polymorphism in each polymorphism in whole genomic regions
Note 2) An approach to evaluate the target gene alone

Based on the above information and the experts' review, provision of new information concerning the association between carbamazepine-induced serious drug eruption and gene polymorphism was considered necessary. MHLW issued a notification on September 20, 2011 and required MAHs to revise the "Precautions" section of the package insert as follows (underlined parts are revised).

As of November 4, 2011, the estimated frequency of *HLA-A*3101* allele is 0.071 to 0.120 and that of *HLA-B*1502* allele is 0.001 in the Japanese.[6)]

Other Precautions

A retrospective genome-wide association analysis in Japanese reported that *HLA-A*3101* carriers accounted for 58% (45/77) of patients who developed carbamazepine-induced serious drug eruption such as oculomucocutaneous syndrome, toxic epidermal necrolysis, and hypersensitivity syndrome, while *HLA-A*3101* carriers accounted for 13% (54/420) of patients who did not develop severe drug eruption. [3)]
Studies in patients of Han Chinese descent have found that almost all of the patients with carbamazepine-induced oculomucocutaneous syndrome or toxic epidermal necrolysis were carriers of *HLA-B*1502*. On the other hand, apparent association between carbamazepine-induced severe drug eruption and carriers of *HLA-B*1502* was not suggested in the research conducted in Japanese. [3)]
Meanwhile, it was reported that the frequency of *HLA-B*1502* allele is 0.019 - 0.124 in Han Chinese and 0.001 in Japanese.[6)]

3. Analysis studies of factors causing serious adverse reactions

The National Institute of Health Sciences has been conducting an analysis study of causative factors for the skin disorder SJS/TEN[7)] since 2006. Biomarker exploratory studies for rhabdomyolysis[8)] and interstitial lung disease were also started in 2009 and 2011, respectively.

When a serious adverse reaction is reported to MHLW from a medical institution directly or through the MAH according to the "Pharmaceuticals and Medical Device Safety Information Reporting System[9)]", the reporting institution is asked to cooperate in the study.

It is important to predict onset of serious adverse reaction, although the incidence frequency is low, because the outcome could be life-threatening. Since different causative factors have been reported in different races, collection of adverse reaction cases in the Japanese is quite important to obtain useful analysis results for successful prediction.

If a patient develops "SJS/TEN," "rhabdomyolysis" or "interstitial lung disease" after drug use, healthcare professionals are requested to report the case to the MHLWor the MAH of the suspected drug. Cooperation in the analysis study is also encouraged.

<References> (including provisionally translated titles)

1) Chung, W. H. et al.: Nature 428 (6982), 486, 2004
2) Hung, S. I. et al.: Pharmacogenet. Genomics 16 (4), 297-306, 2006
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8) http://www.nihs.go.jp/mss/myo/index-1.html (only available in Japanese language)
9) http://www.info.pmda.go.jp/info/houkoku.html (only available in Japanese language)

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated October 25, 2011, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Anastrozole

Brand Name (name of company)	Arimidex Tablets 1 mg (AstraZeneca K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Postmenopausal breast cancer

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored for changes in their clinical symptoms including cough, dyspnoea, and pyrexia. If any abnormalities are observed, examinations including chest X-ray and chest CT scan should be performed. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

Thromboembolism: Deep vein thrombosis or pulmonary embolism, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to July 24, 2011)

- Interstitial pneumonia: 2 cases (no fatal cases)
- Thromboembolism: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 100,000 (2011)

Launched in Japan: February 2001

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Breast cancer (hypertension)	1 mg for approx. 2 years and 5 months	**Interstitial pneumonia** The patient underwent breast cancer surgery. Left partial mastectomy was performed. Day 1 of administration: The patient started receiving anastrozole. 2 years and 4 months after administration (day of onset): Interstitial pneumonia occurred. The CT scan showed interstitial opacities in both lung fields. <Diagnosis for interstitial pneumonia> Diagnostic method: X-ray, CT

				Disease that required differentiation when the diagnosis was made: Viral pneumonia, bacterial pneumonia, pulmonary oedema, cardiac failure Steroid therapy: Responded (prednisolone 10 - 20 mg/day) 2 years and 5 months after administration (day of discontinuation): The above were pointed out at a routine outpatient visit of surgery, and the patient visited the department of respiratory internal medicine. Administration of anastrozole was discontinued. 5 days after discontinuation: Dry cough, productive cough, rales were noted. 7 days after discontinuation: The patient was admitted to the hospital. 9 days after discontinuation: X-ray showed no improvement. 10 days after discontinuation: Administration of prednisolone 10 mg was started. 12 days after discontinuation: Drug lymphocyte stimulation test (DLST) was positive for anastrozole and olmesartan medoxomil. Administration of all oral medications was discontinued. Dry cough, productive cough, rales were noted. 14 days after discontinuation: The patient had not recovered from interstitial pneumonia. 19 days after discontinuation: Dry cough, productive cough, rales were noted. 26 days after discontinuation: Rales were noted.
	Concomitant medications: olmesartan medoxomil, alendronate sodium hydrate, shoseiryuto, menatetrenone, alfacalcidol			

Laboratory Examination

	2 years and 3 months after administration	2 years and 5 months after administration (day of discontinuation)	5 days after discontinuation	9 days after discontinuation	12 days after discontinuation	19 days after discontinuation	26 days after discontinuation
Total protein (g/dL)	7.2	6.8	6.9	6.4	6.4	—	—
BUN (mg/dL)	15	12	13	15	16	—	—
Serum creatinine (mg/dL)	0.48	0.51	0.56	0.58	0.53	—	—
Uric acid (mg/dL)	3.9	—	—	—	—	—	—
Total cholesterol (mg/dL)	—	225	215	208	202	—	—
LDL-cholesterol (mg/dL)	110	133	—	—	—	—	—
HDL-cholesterol (mg/dL)	—	85	—	—	—	—	—
Triglyceride (mg/dL)	95	70	—	—	—	—	—
ZTT (U)	9.4	—	—	—	—	—	—
Total bilirubin (mg/dL)	0.6	0.8	0.7	1.0	0.8	—	—
AST (GOT) (IU/L)	19	19	18	18	15	—	—
ALT (GPT) (IU/L)	12	13	11	13	10	—	—
Al-P (IU/L)	261	265	264	219	213	—	—
LDH (IU/L)	220	222	231	176	187	—	—
Cholinesterase (ChE) (IU/L)	221	—	—	—	—	—	—
γ-GTP (IU/L)	14	—	—	—	—	—	—
CPK (IU/L)	70	—	—	—	34	—	—
Amylase (IU/L)	118	—	—	—	—	—	—
Na (mEq/L)	144	142	141	142	141	—	—
K (mEq/L)	4.5	4.5	4.1	4.1	4.0	—	—
Cl (mEq/L)	106	104	104	105	104	—	—
Ca (mg/dL)	10.2	—	—	—	—	—	—

Blood glucose (mg/dL)	—	97	96	96	87	—	—
Albumin (g/dL)	4.0	4.0	4.0	3.9	3.8	—	—
Chyle	—	(—)	(—)	(—)	(—)	—	—
Haemolysis	—	(—)	(—)	(—)	(—)	—	—
KL-6 (U/mL)	—	823	—	—	—	—	—
Rheumatoid factor determinations (IU/mL)	—	4	—	—	—	—	—
CRP (mg/dL)	—	0.75	0.22	0.12	0.08	—	—
IgG (mg/dL)	—	1352	—	—	—	—	—
IgE (IU/mL)	—	17	—	—	—	—	—
Antinuclear antibody (double)	—	40	—	—	—	—	—
β-D-glucan (pg/mL)	—	<5.0	—	—	—	—	—
Thyroid stimulating hormone (TSH) (μIU/mL)	1.209	—	—	—	—	—	—
Free thyroxine (FT_4) (ng/dL)	1.28	—	—	—	—	—	—
Free triiodothyronine (FT_3) (pg/mL)	3.1	—	—	—	—	—	—
Thyroglobulin (ng/mL)	160.5	—	—	—	—	—	—
CEA (ng/mL)	2.2	—	—	—	—	—	—
CA15-3 (U/mL)	8.8	—	—	—	—	—	—
WBC (/mm^3)	4300	3700	4000	3300	4700	—	—
Eosinophils (%)	3.5	4.5	4.7	6.0	3.2	—	—
Basophils (%)	1.2	1.1	0.7	1.5	0.8	—	—
Lymphocytes (%)	30.4	36.8	37.1	39.9	40.4	—	—
Monocytes (%)	6.5	6.9	12.4	8.4	6.3	—	—
Neutrophils (%)	58.4	50.7	45.1	44.2	49.3	—	—
RBC (× 10^4/mm^3)	385	402	370	399	388	—	—
Hemoglobin (g/dL)	11.8	12.3	11.4	12.3	11.8	—	—
Hematocrit (%)	37.3	37.7	34.2	37.2	36.2	—	—
PLT (× 10^4/mm^3)	25.8	26.1	26.6	25.8	24.9	—	—
MCV (fL)	97	93	92	93	93	—	—
MCH (pg)	30.6	30.6	30.8	30.8	30.4	—	—
MCHC (%)	31.6	32.6	33.3	33.1	32.6	—	—
HbA_{1c} (%)	—	5.4	—	—	—	—	—
I CTP (ng/mL)	5.1	—	—	—	—	—	—
SP-A (ng/mL)	—	—	115.6	—	—	—	—
PS	—	—	1	—	—	—	—
Body weight (kg)	—	—	53	—	—	—	—
Blood pressure (mmHg)	—	—	152/78	—	113/64	130/72	126/62
Pulse rate (beats/min)	—	—	88	—	74	74	80
Maximum body temperature (°C)	—	—	36.4	—	36.8	36.6	36.4

Before start of administration: [Chest X-ray]: (shrinking of lung field) None
2 years and 4 months after administration:
[Chest X-ray]: Interstitial opacities were noted in both lung fields. (distribution of opacities) Bilateral/lower lung fields/subpleural, (characteristic of opacities) Ground-glass opacities (light infiltrative opacities)
Day of discontinuation of administration:
[DLST] Shoseiryuto: false positive, anastrozole: (+), olmesartan medoxomil: (+), [Chest X-ray: (shrinking of lung field) None, (distribution of opacities) Bilateral /lower lung fields, (characteristic of opacities) Ground-glass opacities (light infiltrative opacities), [Chest X-ray]: (distribution of opacities) Bilateral /lower lung fields/subpleural, (characteristic of opacities) Ground-glass opacities (light infiltrative opacities)
5 days after discontinuation: [Chest X-ray]: (shrinking of lung field) None, (distribution of opacities) Bilateral /lower lung fields, (characteristic of opacities) Ground-glass opacities (light infiltrative opacities)
9 days after discontinuation: [Chest X-ray]: No improvement
12 days after discontinuation: [Chest X-ray]: (shrinking of lung field) None, (distribution of opacities) Bilateral/lower lung fields, (characteristic of opacities) Ground-glass opacities (light infiltrative opacities)

19 days after discontinuation: [Chest X-ray]: (shrinking of lung field) None, (distribution of opacities) Bilateral/lower lung fields, (characteristic of opacities) Ground-glass opacities (light infiltrative opacities)
26 days after discontinuation: [Chest X-ray]: (shrinking of lung field) None, (distribution of opacities) Bilateral/lower lung fields, (characteristic of opacities) Ground-glass opacities (light infiltrative opacities)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Breast cancer (diabetes mellitus, hypertension, hyperlipidaemia)	1 mg for 884 days (= for approx. 2 years and 5 months)	**Portal vein thrombosis, Mesenteric vein thrombosis** 36 days before administration: The patient underwent surgery for left breast cancer. Surgical findings: $T_1N_0M_X$, Stage 1 Pathological diagnosis: Estrogen receptor (ER) (+), Progesterone receptor (PGR) (+), Human epidermal growth factor receptor 2 (HER2) (-) Day 1 of administration: Administration of anastrozole was started. 880 days after administration (day of onset): Vomiting and abdominal pain were noted. Portal-superior mesenteric vein thrombosis and small intestinal necrosis developed. 883 days after administration (day of discontinuation): The patient was transferred to another hospital. Emergency surgery due to the above diagnosis by CT. Administration of anastrozole was discontinued. 1 day after discontinuation: Administration of dalteparin sodium was started. 12 days after discontinuation: CT was performed and showed shrinking of thrombus. Administration of warfarin potassium was started. 16 days after discontinuation: The patient was discharged from the hospital. Portal-superior mesenteric vein thrombosis and small intestinal necrosis remitted.
	Concomitant medications: glimepiride, human monocomponent insulin, candesartan cilexetil, atorvastatin calcium hydrate			

Laboratory Examination

	42 days before administration	224 days after administration	336 days after administration	497 days after administration	735 days after administration	868 days after administration	877 days after administration	883 days after administration (day of discontinuation)	
								Daytime	Evening
Total bilirubin (mg/dL)	0.30	0.39	0.24	0.41	0.36	0.39	0.81	0.60	0.58
Direct bilirubin (mg/dL)	0.02	0.04	0.02	0.04	0.05	0.05	0.10	0.10	0.12
AST (GOT) (IU/L)	20	24	17	33	21	40	52	17	17
ALT (GPT) (IU/L)	23	32	20	50	22	117	108	26	23
Blood glucose (mg/dL)	261	181	285	168	360	235	300	438	390
Serum creatinine (mg/dL)	0.9	0.9	1.0	0.9	1.0	1.3	1.2	1.2	1.0
BUN (mg/dL)	20.8	18.7	20.7	22.2	23.2	25.4	24.8	26.4	25.0
Total cholesterol (mg/dL)	166	141	171	141	152	155	167	117	94
Triglyceride (mg/dL)	245	193	253	118	183	192	84	—	62
CRP(mg/dL)	—	—	—	—	—	—	—	10.4	15.0
WBC (/mm^3)	9100	11400	10900	10700	12200	11300	15200	36500	33800
Granulocytes (%)	—	—	—	—	—	—	69	95	—
Lymphocytes (%)	—	—	—	—	—	—	21	2	—

Monocytes (%)	—	—	—	—	—	—	8	3	—
Eosinophils (%)	—	—	—	—	—	—	2	—	—
RBC (× 10^4/mm^3)	403	389	423	398	467	457	462	505	460
Hemoglobin (g/dL)	12.3	11.7	12.9	12.2	14.2	13.9	14.1	15.3	14.0
Hematocrit (%)	37.6	35.6	38.7	36.3	42.9	42.7	42.7	46.1	41.5
PLT (× 10^4/mm^3)	34.8	35.4	35.1	37.2	41.9	41.0	29.5	21.9	23.8
Bleeding time (min)	2.0	—	—	—	—	—	—	—	—
APTT (sec)	32.2	—	—	—	—	—	—	34.2	—
PT (sec)	10.1	—	—	—	—	—	—	14.3	—
PT INR (INR)	0.85	—	—	—	—	—	—	1.21	—
Fibrinogen (mg/dL)	—	—	—	—	—	—	—	229	—
D-dimer (μg/mL)	—	—	—	—	—	—	—	5.2	—

2 Temozolomide

Brand Name (name of company)	TEMODAL Capsules 20 mg, 100 mg, TEMODAL Infusion 100 mg (MSD K.K.)
Therapeutic Category	Alkylating agents
Indications	Malignant glioma

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome): Toxic epidermal necrolysis or oculomucocutaneous syndrome may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to September 14, 2011)

- Toxic epidermal necrolysis: 1 case (no fatal cases)
- Oculomucocutaneous syndrome: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 3800 (2011)

Launched in Japan: September 2006 (Capsules)
May 2010 (injectable dosage form)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Malignant glioma (none)	120 mg for 42 days	**Systemic toxic epidermal necrosis** 12 days before administration: The patient started receiving dexamethasone. Day 1 of administration: Administration of temozolomide and radiotherapy (2 Gy × 30) were started. Performance status of the patient at start of administration of temozolomide: 1. Day 42 of administration (day of completion): Administration of temozolomide was completed without skin symptoms. 1 day after completion: At the beginning, dull red papule measuring about 3 mm with no tendency toward confluence were scattered symmetrically

				from the chest/abdomen to the back. Itching also occurred. The event was not wheals. Drug eruption was suspected, administration of sulfamethoxazole/trimethoprim, lansoprazole was discontinued. 4 days after completion: The patient had no pyrexia but complained of chills. Drug eruption spread to the neck, body trunk, arms, and thighs. Administration of juzentaihoto was also discontinued. 7 days after completion: Since temozolomide was judged most suspected, administration of lansoprazole and juzentaihoto were resumed, in addition to ointment. 8 days after completion: Radiotherapy was completed. 9 days after completion: Eruption progressed to epidermolysis on the back. The patient was diagnosed with systemic toxic epidermal necrosis at the dermatology department. Dermatological findings: Blister/erosion and Nikolsky's sign were observed. There were no mucosal findings. Steroid pulse therapy (methylprednisolone sodium succinate, 1000 mg/day per time) was performed for 3 days, followed by prednisolone injection 40 mg for 3 days and 20 mg for 9 days, and then treatment at the dermatology department was completed. 14 days after completion: DLST test was positive (maximum stimulation index (SI): 4.5, maximum response level (CPM): 708). Approximately 20 days after completion: Mesh-like red flare was observed systematically, but was disappearing.Symptoms such as itching also remitted. Infection: No herpes simplex virus, no mycoplasma. Multi-organ disorder did not develop.
	Concomitant medications: granisetron hydrochloride, concentrated glycerin/fructose, maintenance solution, lansoprazole, juzentaihoto, dexamethasone, sulfamethoxazole/trimethoprim, heparin sodium			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Brain neoplasm (intracranial aneurysm)	100 mg for 5 days	**Stevens-Johnson syndrome** 15 days before administration: The patient underwent tumour resection by craniotomy. 14 days before administration: Administration of phenytoin was started. Day 1 of administration: Administration of temozolomide and radiotherapy were started. Day 5 of administration: Red eruption occurred from the left cheek to lower jaw (with itching). Herpes was suspected on the lips. Also, the lips were swollen, and bilateral eye discharge was confirmed. Considering the possibility of herpes zoster, aciclovir drip infusion and glycyrrhizin were administered. Day 6 of administration (day of discontinuation): The patient visited the ophthalmology and dermatology departments. As Stevens-Johnson syndrome was suspected, oral administration of temozolomide and phenytoin were discontinued. Steroid pulse therapy was performed for 3 days (the dose was gradually reduced thereafter). At that time, red papule spread systemically, with erosion in the palpebral

				conjunctiva, lips, and hard palate. DLST showed negative results for temozolomide and phenytoin before administration of steroids. 2 days after discontinuation: Blisters were scattered systemically. 8 days after discontinuation: Facial rash remitted. 23 days after discontinuation: Toe nail loss. 30 days after discontinuation: Stevens-Johnson syndrome remitted.
	Concomitant medications: phenytoin			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 60s	Glioblastoma multiforme (hypertension)	120 mg for 10 days	**Stevens-Johnson syndrome** 14 days before administration: The patient started receiving phenytoin and lansoprazole. Day 1 of administration: Administration of temozolomide was started. Day 6 of administration: Administration of temozolomide and radiotherapy were started. Day 8 of administration: Administration of diphenhydramine and diprophylline were started. Day 9 of administration: Administration of difenidol hydrochloride and milnacipran hydrochloride were started. Pharynx pain developed in the evening. Day 10 of administration (Day of discontinuation): Oedema, redness, genital erythema, and systemic grain-size erythema, and multiple red papule developed. Body temperature was 38.9°C. Based on the above, the patient was diagnosed with Stevens-Johnson syndrome, and administration of medications including temozolomide that were started within 1 month were discontinued. Administration of prednisolone succinate (60 mg/day) was started. Radiotherapy was continued. The patient has not recovered from Stevens-Johnson syndrome. Administration of prednisolone sodium succinate was continued with gradual dose reduction.
	Concomitant medications: phenytoin, lansoprazole, diphenhydramine/diprophylline, difenidol hydrochloride, milnacipran hydrochloride			

3 **Ritodrine hydrochloride** (injectable dosage form)

Brand Name (name of company)	UTEMERIN injection 50 mg (Kissei Pharmaceutical Co., Ltd.) UTEMENAL FOR INTRAVENOUS INFUSION 50 mg (Yell Pharmaceutical Co., Ltd.) UTEROTOP For I.V. Infusion 50 mg (Kyoritsu Seiyaku Corporation) Uteron Intravenous Infusion 50 mg (Sandoz K.K.) PIROSDEN Intravenous Injection 50 mg (Taiyo Pharmaceutical Co., Ltd.),Ritodol for I.V. infusion 50 mg (I'rom Pharmaceutical Co., Ltd.)

	RITODRINE For I.V. Infusion 50 mg "PP" (Pola Pharma Inc.) REMETRERK intravenous infusion 50 mg (Fuji Pharma Co., Ltd.) RINDOLF Intravenous Injection 50 mg (Nichi-Iko Pharma Factory Co., Ltd.) LUTEONIN FOR I.V. INFUSION 50 mg (Aska Pharmaceutical Co., Ltd.)
Therapeutic Category	Urogenital and anal organ agents-Miscellaneous
Indications	Threatened abortion/premature labour that requires emergency treatment

PRECAUTIONS (underlined parts are revised)

Important Precautions

Cardiac failure, tachycardia, and arrhythmia may occur in fetuses. Intestinal obstruction, cardiac failure, reversible hypertrophy of the interventricular septum wall, hypoglycaemia, tachycardia, and renal impairment may occur in neonates.

Adverse Reactions (clinically significant adverse reactions)

Cardiac failure in fetuses and neonates: Cardiac failure may occur in fetuses and neonates. Especially, cardiac failure has been reported in children whose mothers were treated for 2 weeks or longer. Caution should be exerted to signs of cardiac failure such as cardiomegaly from the fetal stage, and if any abnormalities are observed, appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to July 26, 2011)

- Cardiac failure in fetuses and neonates: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 150,000 (2011)

Launched in Japan: August 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 1 day	Mother Threatened premature labour (none)	(transplacenta) 73 - 180 μg/ min for 40 days	**Cardiomegaly, cardiac function disturbance** [Clinical course of mother] Day 1 of administration (Week 30 and Day 6 of pregnancy): The patient' mother started receiving ritodrine hydrochloride 120 μg/min for threatened premature labour. Day 4 - 39 of administration: Dose of ritodrine hydrochloride was adjusted between 133 and 180 μg/min. Day 40 of administration (Week 36 and Day 3 of pregnancy): The dose of ritodrine hydrochloride was reduced to 73 μg/min in the morning. Administration of ritodrine hydrochloride was completed after 3 hours. After about 6 hours and a half, she delivered a baby with a normal delivery. No abnormalities were found at the time of delivery. [Clinical course of neonate] Findings at birth: Girl, body weight 2980 g, height 49.4 cm Apgar score: 8 after 1 minutes, 9 after 5 minutes Day 1 after birth (day of completion): Echocardiography showed cardiomegaly (Left ventricular internal dimension in diastole [LVIDd]: 1.81cm), cardiac function disturbance (Ejection fraction [EF]: 52.6%), and moderate mitral regurgitation at 2 hours after birth.

				Transnasal administration of oxygen was started. Day 2 after birth: Percutaneous ultrafine central venous catheterisation was performed. Continuous administration of calcium gluconate hydrate injection was started for hypocalcaemia. Day 4 after birth: EF: 65.8%. Oxygen therapy was discontinued. Day 7 after birth: Administration of calcium gluconate hydrate injection was discontinued. Day 9 after birth: Hypocalcaemia improved. Day 12 after birth: Mitral regurgitation disappeared. Day 15 after birth (14 days after completion): Cardiomegaly and cardiac function disturbance improved.
	Concomitant medications (mother): bifidobacteria preparation, ulinastatin, metronidazole, magnesium oxide, acetated Ringer solution (containing glucose), ampicillin sodium			

Laboratory Examination

		Day 1 after birth (day of completion)	Day 2 after birth	Day 3 after birth	Day 4 after birth	Day 5 after birth	Day 7 after birth	Day 9 after birth	Day 12 after birth	Day 15 after birth
Ca (mg/dL)	First	—	6.6	7.1	8.9	9.6	—	9.7	10.3	—
	Second	—	—	8.1	—	—	—	—	—	—
Mg (mg/dL)		—	1.9	2.1	2.3	—	—	2.3	2.0	—
P (mg/dL)		—	5.3	5.4	6.2	—	—	6.7	7.0	—
NT-proBNP (pg/mL)		—	52244	—	10259	—	—	2696	1397	—
PTH-INT (pg/mL)		—	—	44	—	—	—	—	—	—
dBP (mmHg)		36	29	37	47	—	41	34	22	32
sBP (mmHg)		64	62	61	65	—	67	63	60	61
HR (/min)		137	125	114	115	—	142	135	139	138

4

Revision of Precautions (No. 231)

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 October 25 and November 8, 2011 (excluding those presented in 3. Important Safety Information of this Bulletin).

1 Psychotropics

Atomoxetine Hydrochloride

Brand Name

Strattera Capsule 5 mg, 10 mg, 25 mg (Eli Lilly Japan K.K.)

Contraindications

Patients with serious cardiovascular disorder

Important Precautions

To monitor influences on the cardiovascular system, blood pressure and heart rate (pulse rate) should be measured before and periodically during the administration of this drug.
This drug may influence blood pressure and heart rate. When this drug is administered to patients with cardiovascular disorder, the use of this drug should be carefully considered by means such as consultation with a physician specializing in cardiology. In addition, when administration of this drug is considered for patients who have any cardiac abnormality (non-serious) or who may have such an abnormality based on the patient's history of heart disease, family history regarding sudden death or serious heart disease, or other history, the status of the cardiovascular system should be evaluated by electrocardiography, etc. before the start of administration.

2 Antineoplastics-Miscellaneous

Dasatinib Hydrate

Brand Name

Sprycel Tablets 20 mg, 50 mg (Bristol-Myers K.K.)

Adverse Reactions (clinically significant adverse reactions)

Pulmonary arterial hypertension: Pulmonary arterial hypertension may occur. Some cases have been also reported in patients treated with this drug for a long period. Patients should be carefully monitored, and if any symptoms including dyspnoea or chest pain are observed, administration of this drug should be discontinued, and appropriate measures should be taken after making differential diagnosis versus other causes of disease (e.g. pleural effusion, pulmonary oedema).

3 Non-main therapeutic purpose agents-Miscellaneous

Varenicline Tartrate

Brand Name

CHAMPIX Tablets 0.5 mg, 1 m (Pfizer Japan Inc.)

Other Precautions

In an overseas randomized, double-blind study conducted in 703 patients with cardiovascular disease to evaluate the efficacy of this drug, it was reported that the incidence of cardiovascular events was 7.1% (25/353) in the group treated with this drug and 5.7% (20/350) in the placebo group [risk difference: 1.4%, 95% confidence

interval: -2.3% - 5.0%]. And in a meta-analysis to evaluate the safety of this drug, it was reported that the incidence of cardiovascular events was 1.06% (52/4908) in the group treated with this drug and 0.82% (27/3308) in the placebo group [Peto odds ratio: 1.72, 95% confidence interval: 1.09 - 2.71].

Reference Information

Rigotti, N. A., et al. : Circulation 2010 ; 121 : 221-229
Singh, S., et al. : CMAJ 2011 ; 183 (12): 1359-1366

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4 **Miscellaneous metabolism agents-Miscellaneous**

Zoledronic Acid Hydrate
Pamidronate Disodium Hydrate

Brand Name

ZOMETA for i.v. infusion 4 mg (Novartis Pharma K.K.)
Aredia for i.v. infusion 15 mg, 30 mg (Novartis Pharma K.K.)

Important Precautions

Osteonecrosis or osteomyelitis of the jaw may occur in patients treated with bisphosphonates including this drug. In most reported cases, the events occurred in association with invasive dental procedures in the jaw bone, 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, the status of oral care management should be checked. Patients should be instructed to receive an appropriate dental examination, if necessary, and to have invasive dental procedures be finished before treatment as much as possible. If dental procedures are required during administration of this drug, patients should be instructed to receive non-invasive dental procedures as much as possible. In addition, patients should be thoroughly informed of the importance of oral hygiene, receiving periodic dental examination, notifying his/her dentist about use of this drug to avoid invasive dental procedures as much as possible. Patients also should be advised to see a dentist/oral surgeon, if any abnormalities occur.
It is reported that nontraumatic atypical fracture of subtrochanteric femur and proximal femoral shaft occurred in patients treated with long-term bisphosphonate. In some of these reports, precursor pain in the femur, inguinal, or other area starts several weeks to months before a complete fracture. If such symptoms are observed, X-ray examination, etc. should be performed, and appropriate measures should be taken. In addition, a bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the other femur and performing an X-ray examination. Characteristic findings such as a thickened bone cortex have been noted in X-rays. If such symptoms are observed, appropriate measures should be taken.

Adverse Reactions (clinically significant adverse reactions)

Atypical fracture of subtrochanteric femur and proximal femoral shaft:
Atypical fracture of subtrochanteric femur and proximal femoral shaft may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

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5 **Miscellaneous metabolism agents-Miscellaneous**

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

Brand Name

FOSAMAC Tablets 5, 35 mg (MSD K.K.), Bonalon Tablet 5 mg, 35 mg (Teijin Pharma Limited.)
Didronel Tab. 200 (Dainippon Sumitomo Pharma Co., Ltd.)
Actonel Tab. 2.5 mg, 17.5 mg (Ajinomoto Pharmaceuticals Co., Ltd.), BENET Tablets 2.5 mg, 17.5 mg (Takeda Pharmaceutical Company Limited.)

Important Precautions	Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates including this drug. In most reported cases, the events occurred in association with invasive dental procedures in the jaw bone, 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, the status of oral care management should be checked. Patients should be instructed to receive an appropriate dental examination, if necessary, and to have invasive dental procedures be finished before treatment as much as possible. If dental procedures are required during administration of this drug, suspension of this drug should be considered. In addition, patients should be thoroughly informed of the importance of oral hygiene, receiving periodic dental examination and notifying his/her dentist about use of this drug to avoid invasive dental procedures as much as possible. Patients should also be advised to see a dentist/oral surgeon, if any abnormalities occur. It is reported that nontraumatic atypical fracture of subtrochanteric femur and proximal femoral shaft occurred in patients treated with long-term bisphosphonate. According to these reports, precursor pain in the femur, inguinal, or other areas starts several weeks to months before complete fracture. If such symptoms are observed, X-ray examination, etc. should be performed, and appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the other femur and performing X-ray examination. Characteristic findings such as a thickened bone cortex have been noted in X-rays. If such symptoms observed, appropriate measures should be taken.
Adverse Reactions (clinically significant adverse reactions)	**Atypical fracture of subtrochanteric femur and proximal femoral shaft**: Atypical fracture of subtrochanteric femur and proximal femoral shaft may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

6 **Miscellaneous metabolism agents-Miscellaneous**

Alendronate Sodium Hydrate (injectable dosage form)

Brand Name	Teiroc Injection 5 mg, 10 mg (Teijin Pharma Limited.)
Important Precautions	Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates including this drug. In most reported cases, the events occurred in association with invasive dental procedures in the jaw bone, 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, the status of oral care management should be checked. Patients should be instructed to receive an appropriate dental examination, if necessary, and to have invasive dental procedures be finished before treatment as much as possible. If dental procedures are required during administration of this drug, patients should be instructed to receive non-invasive dental procedures as much as possible. In addition, patients should be thoroughly informed of the importance of oral hygiene, receiving periodic dental examination, notifying his/her dentist about use of this drug to avoid invasive dental procedures as much as possible. Patients should also be advised to see a dentist/oral surgeon, if any abnormalities occur.

7 **Miscellaneous metabolism agents-Miscellaneous**

Minodronic Acid Hydrate

Brand Name	Bonoteo Tablets 1 mg, 50 mg (Astellas Pharma Inc.), RECALBON Tablets 1 mg, 50 mg (Ono Pharmaceutical Co., Ltd.)

Important Precautions	Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates including this drug. In most reported cases, the events occurred in association with invasive dental procedures in the jaw bone, 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, the status of oral care management should be checked. Patients should be instructed to receive an appropriate dental examination, if necessary, and to have invasive dental procedures be finished before treatment as much as possible. If dental procedures are required during administration of this drug, suspension of this drug should be considered. In addition, patients should be thoroughly informed of the importance of oral hygiene, receiving periodic dental examination, notifying his/her dentist about use of this drug to avoid invasive dental procedures as much as possible. Patients also should be advised to see a dentist/oral surgeon, if any abnormalities occur. It is reported that nontraumatic atypical fracture of the subtrochanteric femur and proximal femoral shaft occurred in patients treated with long-term bisphosphonate. In some of these reports, precursor pain in the femur, inguinal, or other areas starts several weeks to months before complete fracture. If such symptoms are observed, X-ray examination, etc. should be performed, and appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the other femur and performing X-ray examination. Characteristic findings such as a thickened bone cortex have been noted in X-rays. If such symptoms are observed, appropriate measures should be taken.
Adverse Reactions (clinically significant adverse reactions)	**Osteonecrosis and osteomyelitis of jaw**: Osteonecrosis and osteomyelitis of jaw may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. **Atypical fracture of subtrochanteric femur and proximal femur shaft**: Atypical fracture of subtrochanteric femur and proximal femur shaft may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

5

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of November 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Repaglinide SUREPOST Tablets 0.25 mg, 0.5 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 16, 2011
Febuxostat Feburic Tablet 10 mg, 20 mg, 40 mg	Teijin Pharma Limited	May 17, 2011
Levonorgestrel NORLEVO 0.75 mg Tablet	Sosei Co. Ltd.	May 24, 2011
Pioglitazone Hydrochloride/Glimepiride SONIAS Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	June 6, 2011
Memantine Hydrochloride MEMARY TABLETS 5 mg, 10 mg, 20 mg	Daiichi Sankyo Company, Limited	June 8, 2011
Adalimumab (Genetical Recombination) HUMIRA for s.c. injection syringe 40 mg/0.8 mL, HUMIRA for s.c. injection syringe 20 mg/0.4 mL*1	Abbott Japan Co., Ltd.	July 1, 2011
Erlotinib Hydrochloride TARCEVA Tablets 25 mg, 100 mg*2	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Gabapentin GABAPEN Tablets 200 mg, 300 mg, 400 mg*3	Pfizer Japan Inc.	July 1, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 µg, 180 µg	Chugai Pharmaceutical Co., Ltd.	July 1, 2011*4 September 26, 2011*5
Lamotrigine Lamictal Tablets 25 mg, 100 mg*6	GlaxoSmithKline K.K.	July 1, 2011
Ribavirin COPEGUS Tablet 200 mg*7	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Edoxaban Tosilate Hydrate LIXIANA TABLETS 15 mg, 30 mg	Daiichi Sankyo Company, Limited	July 19, 2011
Eribulin Mesilate Halaven injection 1 mg	Eisai Co., Ltd.	July 19, 2011
Tramadol Hydrochloride/Acetaminophen TRAMCET Combination Tablets	Janssen Pharmaceutical K.K.	July 19, 2011
Rivastigmine EXELON PATCH 4.5 mg, 9 mg, 13.5 mg, 18 mg	Novartis Pharma K.K.	July 19, 2011

Rivastigmine RIVASTACH Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Ono Pharmaceutical Co., Ltd.	July 19, 2011
Epoetin Beta Pegol (Genetical Recombination) MIRCERA Injection Syringe 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg	Chugai Pharmaceutical Co., Ltd.	July 20, 2011
Pramipexole Hydrochloride Hydrate Mirapex-LA Tablets 0.375 mg, 1.5 mg	Nippon Boehringer Ingelheim Co., Ltd.	July 20, 2011
Mitiglinide Calcium Hydrate/Voglibose GLUBES Combination Tab.	Kissei Pharmaceutical Co., Ltd.	July 22, 2011
Desflurane Suprane Inhalational Anesthetic Solution	Baxter Limited	July 29, 2011
Buprenorphine NORSPAN TAPE 5 mg, 10 mg, 20 mg	Mundipharma K.K.	August 4, 2011
Escitalopram Oxalate LEXAPRO Tab. 10mg	Mochida Pharmaceutical Co., Ltd.	August 22, 2011
Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (Yeast Origin) GARDASIL Aqueous Suspension for Intramuscular Injection, GARDASIL Aqueous Suspension for Intramuscular Injection Syringe	MSD K.K.	August 26, 2011
Pancrelipase LipaCreon Granules 300mg Sachet, LipaCreon Capsules 150mg	Abbott Japan Co., Ltd.	August 30, 2011
Vorinostat ZOLINZA Capsules 100 mg	MSD K.K.	September 14, 2011
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg	AstraZeneca K.K.	September 15, 2011
Landiolol Hydrochloride COREBETA for Intravenous 12.5 mg	Ono Pharmaceutical Co., Ltd.	September 15, 2011
Linagliptin Trazenta Tablets 5 mg	Nippon Boehringer Ingelheim Co., Ltd.	September 15, 2011
Golimumab (Genetical Recombination) Simponi Subcutaneous Injection Syringe 50 mg	Janssen Pharmaceutical K.K.	September 16, 2011
Minodronic Acid Hydrate Bonoteo Tablets 50 mg	Astellas Pharma Inc.	September 16, 2011
Minodronic Acid Hydrate RECALBON Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	September 16, 2011
Mirabegron Betanis Tablets 25 mg, 50 mg	Astellas Pharma Inc.	September 16, 2011
Alogliptin Benzoate / Pioglitazone Hydrochloride LIOVEL Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	September 20, 2011
Indacaterol Maleate onbrez inhalation capsules 150 μg	Novartis Pharma K.K.	September 20, 2011
Daptomycin CUBICIN IV 350 mg	MSD K.K.	September 22, 2011
Itraconazole ITRIZOLE Oral Solution 1%*[8]	Janssen Pharmaceutical K.K.	September 26, 2011
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*[9]	Chugai Pharmaceutical Co., Ltd.	September 26, 2011

*1 An additional indication for “treatment of patients with active polyarticular juvenile idiopathic arthritis”

*2 An additional indication for “treatment of patients with non-resectable pancreatic carcinoma”

*3 An additional administration for “pediatrics”

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

*5 An additional indication for “improvement of viraemia in chronic active hepatitis B

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

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

*8 Additional indications for “treatment of patients with fungal infection caused by *Aspergillus*, *Cryptococcus*, *Blastomyces*, or *Histoplasma* (fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, blastomycosis, histoplasmosis)”, “treatment of patients with febrile neutropenia of suspected fungal infection”, and “prophylaxis of deep mycosis in patients with haematological malignancy possibly associated with neutropenia or patients who underwent hematopoietic stem cell transplantation”

*9 An additional indication for “treatment of patients with inoperable or recurrent breast cancer”