Pharmaceuticals and Medical Devices Safety Information

No. 272 September 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 (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers.
The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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No. 272 September 2010

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 Bisphosphonate-related Osteonecrosis and Osteomyelitis of Jaw: Review Process and Implementation**	*P* *C*	Bisphosphonates (BPs) are drugs used as oral medications for treatment of osteoporosis and as injections for treatment of hypercalcaemia of malignancy. Since it is known to cause osteonecrosis and osteomyelitis of jaw, in October 2006, the MHLW issued an alert especially in regard to BP injections, which are associated with a higher risk of osteonecrosis and osteomyelitis of jaw. Within this alert, the MHLW asked BP manufacturers to revise the Precautions section in the package inserts of BP injection products. This time, it was concluded that equivalent safety measures as BP injections should be taken for oral BPs because, with increasing use of oral BPs, a number of adverse drug reaction (ADR) reports concerning oral BPs related-osteonecrosis and osteomyelitis of jaw have been accumulated in Japan, and because the results of various recent epidemiological studies about these events with oral BPs have been reported. Based on the risk factors for osteonecrosis and osteomyelitis of jaw, it was decided to alert physicians, ensuring that they instruct patients to, if necessary, have invasive dental procedures, such as tooth extraction, be finished before administration of BPs, as well as, 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. Accordingly, on June 1, 2010, the MHLW instructed the BP manufacturers to revise Precautions section in the package inserts of oral BP products by including the above description. Details of these safety measures are described in this section.	4
2	**Amitriptyline Hydrochloride (and 16 others)**		Revision of Precautions (No. 219)	13
3	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of September 1, 2010.	19

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.

1

Safety Measures Against Bisphosphonate-related Osteonecrosis and Osteomyelitis of Jaw: Review Process and Implementation

	Active ingredient	Brand name (name of company)
Active ingredient Brand name (name of company)	(1) Alendronate Sodium Hydrate	(1) Bonalon Tablet 5 mg, 35 mg; Teiroc Injection 5 mg, 10 mg (Teijin Pharma Limited); Fosamac Tablets-5, Fosamac Tablets 35 mg (Banyu Pharmaceutical Co., Ltd.); etc.
	(2) Incadronate Disodium Hydrate	(2) Bisphonal Injection 10 mg (Astellas Pharma Inc.)
	(3) Etidronate Disodium	(3) Didronel Tab. 200 (Dainippon Sumitomo Pharma Co., Ltd.)
	(4) Zoledronic Acid Hydrate	(4) ZOMETA for i.v. infusion 4 mg (Novartis Pharma K.K.)
	(5) Pamidronate Disodium Hydrate	(5) Aredia for i.v. infusion 15 mg, 30 mg (Novartis Pharma K.K.), etc.
	(6) Minodronic Acid Hydrate	(6) Bonoteo Tablets 1 mg (Astellas Pharma Inc.) RECALBON Tablets 1 mg (Ono Pharmaceutical Co., Ltd.)
	(7) Sodium Risedronate Hydrate	(7) Actonel Tablet 2.5 mg, 17.5 mg (Ajinomoto Pharmaceuticals Co. Ltd.) BENET Tablets 2.5 mg, 17.5 mg (Takeda Pharmaceutical Company Limited)
Therapeutic category	Miscellaneous metabolism agents-Miscellaneous	
Indications	(1) Alendronate Sodium Hydrate • Osteoporosis (oral dosage form) • Hypercalcaemia of malignancy (injectable dosage form) (2) Incadronate Disodium Hydrate • Hypercalcaemia of malignancy (3) Etidronate Disodium • Osteoporosis • Prevention of heterotopic ossification in the early or advanced stages after the following conditions Spinal cord injury, hip arthroplasty • Paget's disease of bone (4) Zoledronic Acid Hydrate • Hypercalcaemia of malignancy • Bone lesion associated with multiple myeloma or bone metastasis of solid carcinoma (5) Pamidronate Disodium Hydrate • Hypercalcaemia of malignancy • Osteolytic bone metastases of breast cancer (to be used in concomitant with chemotherapy, endocrine therapy or radiotherapy) (6) Minodronic Acid Hydrate • Osteoporosis (7) Sodium Risedronate Hydrate • Osteoporosis • Paget's disease of bone (Actonel Tablets 17.5 mg and BENET Tablets 17.5 mg only)	

1. Introduction

Bisphosphonates (BPs) are drugs that act on the calcium ion metabolism. They are used as oral medications for treatment of osteoporosis and as injections for treatment of hypercalcaemia of malignancy, bone lesion of multiple myeloma, bone lesion from bone metastasis of solid carcinoma, and osteolytic bone metastasis of breast cancer. Osteonecrosis of jaw is local death of jawbone tissues and cells, which are associated with symptoms such as pain, swelling, and pus discharge in jaw.[1)] Known risk factors for osteonecrosis of jaw include BP treatment, chemotherapy, steroid therapy, malignancy, radiotherapy, poor oral hygiene, and past dental procedures such as tooth extraction.[1,2)]

In October 2006, the MHLW issued an alert especially in regard to BP injections, which are associated with higher risks of octeonecrosis of jaw,[3,4)] and required BP manufacturers to revise Precautions in package inserts of BP injection products.

On the other hand, in Japan, with increasing use of oral BPs, a number of adverse drug reaction (ADR) reports concerning oral BPs-related osteonecrosis of jaw have been accumulated. The results of various recent epidemiological studies about osteonecrosis of jaw with oral BPs have been reported.[5,6)]

Based on this recent situation, from the standpoint of prevention of ADRs resulting in poor prognosis, which may interfere with treatment in individual patients, and from the standpoint of ensuring the usefulness of BPs, it was concluded that safety measures should be taken to prevent osteonecrosis of jaw associated with oral BPs in cooperation with healthcare professionals. Based on the risk factors associated with osteonecrosis and osteomyelitis of jaw, it was decided to alert physicians, ensuring that they instruct patients to, if necessary, have invasive dental procedures, such as tooth extraction, be finished before administration of BPs, as well as, 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. Accordingly, on June 1, 2010, the MHLW instructed the BP manufacturers to revise Precautions section in the package inserts of oral BP products by including the above description. Details of these safety measures are described below.

2. ADR reports of osteonecrosis and osteomyelitis of jaw

(1) Summary on incidences of osteonecrosis and osteomyelitis of jaw

According to an Australian report, incidence of osteonecrosis and osteomyelitis of jaw was 0.01% to 0.04% in patients treated with oral BPs and 0.09% to 0.34% in those patients who had had their teeth extracted.[4)] The incidence of osteonecrosis and osteomyelitis of jaw was 0.88% to 1.15% in patients with malignant tumor treated with BP injections and 6.67% to 9.1% in those patients who had had their teeth extracted.[4)] Osteonecrosis and osteomyelitis of jaw associated with BP injection occurred in 16 (1.2%) of 1,338 patients with breast cancer and 13 (2.4%) of 548 patients with multiple myeloma.[7)] Another study reported osteonecrosis and osteomyelitis of jaw occurred in 22 out of 80 cancer patients (28%).[8)] A recent survey showed the incidence of osteonecrosis and osteomyelitis of jaw was 8.5% in patients with multiple myeloma, 3.1% in patients with breast cancer, and 4.9% in patients with prostate cancer.[9)]

(2) Recent epidemiological studies on oral BPs

Sedghizadeh et al. investigated the use of alendronate, past tooth extraction, and treatment of osteonecrosis and osteomyelitis of jaw in 13,730 patients based on the electronic medical records database of the School of Dentistry, University of Southern California.[5)] Osteonecrosis and osteomyelitis of jaw occurred in 9 (approximately 4%) out of 208 patients treated with alendronate and none of the 13,522 patients who had never used alendronate.

An investigation conducted by Lo et al. in patients treated with oral BPs in the U.S.A. showed that osteonecrosis and osteomyelitis of jaw occurred in 1 out of 952 to 1,537 patients.[6)]

The Japanese Society of Oral and Maxillofacial Surgeons followed patients who had osteonecrosis and osteomyelitis of jaw after about 2-year treatment with BPs at 248 institutions in Japan. According to the study, osteonecrosis and osteomyelitis of jaw in 263 patients (111 had been treated with oral BPs) met the diagnostic criteria in the proposition by the American Association of

Oral and Maxillofacial Surgeons, suggesting that the incidence of osteonecrosis and osteomyelitis of jaw in Japanese patients treated with oral BPs is estimated at 0.01% to 0.02%.[10)]

Although some of these recent studies reported the incidence of osteonecrosis and osteomyelitis of jaw has been increasing in patients treated with oral BPs, it is difficult to compare the risk of osteonecrosis and osteomyelitis of jaw between oral BPs and BP injections solely based on these reports. Comprehensively, however, the risk is considered to be greater in patients treated with BP injection compared with those treated with oral BPs according to past studies.

(3) ADRs reported in Japan

Osteonecrosis and osteomyelitis of jaw reported as ADRs in the past three years are shown by BP products in the table below. The data extraction was performed by using the ADR terms of "osteonecrosis of jaw" and "osteomyelitis of jaw" in the Japanese version of the Medical Dictionary for Regulatory Activities.

Treatment durations from initial dose of BPs to onset of ADRs are also tabulated together with the number of reported events.

<Oral dosage form>

Drug name (nonproprietary name)	Number of ADR cases (number of ADRs)			
	FY 2007	FY 2008	FY 2009	Total*
Alendronate Sodium Hydrate	53 (69)	74 (84)	70 (85)	197 (238) (736 days: 6 to 3,312 days)
Etidronate Disodium	6 (7)	0 (0)	1 (1)	7 (8) (1,709 days: 309 to 4,038 days)
Minodronic Acid Hydrate**	--	--	0 (0)	0 (0)
Sodium Risedronate Hydrate	21 (22)	27 (29)	13 (13)	61 (64) (818 days: 41 to 4,121 days)
Total	80 (98)	101 (113)	84 (99)	265 (310) (736 days: 6 to 4,121 days)

* Treatment duration from initial dose to onset of ADR; median, minimum and maximum shown in brackets in second lines.

** Marketed in Japan in: April 7, 2009

<Injectable dosage form>

Drug name (nonproprietary name)	Number of ADR cases (number of ADRs)			
	FY 2007	FY 2008	FY 2009	Total*
Alendronate Sodium Hydrate	0 (0)	1 (1)	0 (0)	1 (1) (365 days)
Incadronate Disodium Hydrate	10 (10)	3 (3)	5 (5)	18 (18) (1,095 days: 30 to 3,044 days)
Zoledronic Acid Hydrate	69 (80)	94 (105)	127 (132)	290 (317) (592 days: 52 to 2,580 days)
Pamidronate Disodium Hydrate	27 (32)	7 (10)	7 (8)	41 (50) (867 days: 90 to 2,024 days)
Total	106 (122)	105 (119)	139 (145)	350 (386) (635 days: 23 to 3,044 days)

* Treatment duration from initial dose to onset of ADR; median, minimum and maximum shown in brackets in second lines.

This tabulation does not necessarily demonstrate the causality between BPs and osteonecrosis and osteomyelitis of jaw, but approximately 80 to 100 cases of osteonecrosis and osteomyelitis of jaw have been reported as ADRs of oral BPs annually. A detailed review of reports on patients who developed osteonecrosis and osteomyelitis of jaw associated with oral BP treatment showed that some patients had received dental procedures such as tooth extraction by dentists who had been unaware of the treatment. There were also patients who had failed to maintain oral hygiene while taking BP. (See "4. Case summary.")

While it is difficult to demonstrate incidences of osteonecrosis and osteomyelitis of jaw based on the number of ADRs shown in the above tables, information on estimated number of patients treated with BPs is considered to be useful for incidence estimation in Japan. The table below shows the estimated number of patients treated with BPs based on the medical fee claim from the database of Japan Medical Data Center, Ltd. (n = approximately 350,000; 2007 to 2008) and the sales figures reported by the BP manufacturers.

BP dosage form	Information source for estimation of patients treated with BPs	Estimated number of patients treated with BPs	
		2007	2008
Oral dosage form	Medical fee claim*	2,082,928	2,470,979
	Sales figures**	1,543,198	1,656,317
Injectable dosage form	Medical fee claim*	31,393	47,455
	Sales figures†	41,290	46,974

* Estimation method of patients treated with BPs based on the medical fee claim: The number of patients who had received BP prescriptions was obtained from the medical fee claim and divided by the population (total number of subscribers to the health insurance societies contracted with Japan Medical Data Center, Ltd.) to obtain the proportion of patients who had received BP prescriptions. Estimation was done using the proportion of patients who had received BP prescriptions and the estimated population according to the demographic estimates reported by Statistics Bureau, Ministry of Internal Affairs and Communications (as of October 1). The total estimates were calculated based on separate estimates for sex and specific age brackets.

** Estimation method of patients treated with BPs based on the sales figures (oral dosage form): With the assumed mean treatment duration of ≥ one year, the annual tablet shipments were divided by the total number of tablets specified in the Dosage and Administration section of the package insert (e.g., 52 tablets if the recommended dosage is one tablet per week).

† Estimation method of patients treated with BPs based on the sales figures (injectable dosage form): The annual shipments were divided by the mean dose per patient based on the use-results survey.

Based on the above-mentioned epidemiological studies on oral BPs[5,6] and the ADR reports in Japan, it was concluded that equivalent safety measures as BP injection should be taken for oral BPs in regards to osteonecrosis and osteomyelitis of jaw. Considering the median time to onset of BP-related osteonecrosis and osteomyelitis of jaw (1.7 to 2.0 years) shown in the review of ADR reports in Japan, attention should be paid to the fact that osteonecrosis and osteomyelitis of jaw may occur even during relatively short-term BP treatment.

Therefore, the MHLW issued an alert requiring BP manufacturers to revise the Precautions as described in the following section.

3. Details and implementation of safety measures

The section "Important Precautions" in the Precautions section in the package inserts of oral BPs and BP injections will be revised to include the following descriptions.

(1) Administration of BPs may increase possible risks of osteonecrosis and osteomyelitis of jaw regardless of the route of administration. The risk may be higher in patients treated with BP injections.

(2) Physicians need to advise patients of the following things; to receive appropriate dental examinations before using this drug and, if necessary, to have invasive dental procedures such as tooth extraction be finished before treatment, as well as to receive periodic dental checkups at dental clinics and to avoid invasive dental procedures in the jaw bone, such as tooth extraction,

as much as possible during treatment.

The phrase "to receive appropriate dental examinations before using this drug" was included in the Precautions section to advise healthcare professionals to ensure appropriate patient management as much as possible by checking how oral hygiene care is managed, e.g., whether the patient is receiving periodic dental check-ups and oral care management, and whether he/she is currently treated by a dentist, and by recommending a dental check-up as necessary so that potential local risk factors for osteonecrosis and osteomyelitis of jaw (e.g., poor oral hygiene, past dental procedures such as tooth extraction, periodontal disease [history of inflammatory disease including pyorrhea]) can be identified. Treatment with BP and dental procedures may be considered to be provided at the same time if the physician considers that there is no time to check for potential risk factors for osteonecrosis and osteomyelitis of jaw in advance.

The revised Precautions are also meant to recommend healthcare professionals to advise patients, if necessary, to receive dental procedures such as tooth extraction before treatment with BP, as well as, to receive periodic dental checkups, and to avoid dental procedures, such as tooth extraction during treatment with BP as much as possible. Necessity of pretreatment dental procedures is to be determined based on the potential risk factors for osteonecrosis and osteomyelitis of jaw in individual patients. The position paper "Bisphosphonate-related osteonecrosis of the jaw" issued by the Allied Task Force Committee of the Japanese Society for Bone and Mineral Research, the Japan Osteoporosis Society, the Japanese Society for Oral and Maxillofacial Radiology, the Japanese Society of Periodontology, and the Japanese Society of Oral and Maxillofacial Surgeons[10)] may be used as a reference.

Cooperation of healthcare professionals involved in medicine, dentistry and oral surgery is expected to prevent BP-related osteonecrosis and osteomyelitis of jaw as much as possible. BP manufacturers were instructed to prepare and distribute the patient cards for BP users so as to help healthcare professionals inform patients of precautions concerning BP use, as well as to help their use of BP be known at dental or oral surgery services. The Patient Cards are expected to be utelized in clinical practice.

The mechanism of onset of osteonecrosis and osteomyelitis of jaw is not clear. However, the MHLW will continuously collect and evaluate latest information about osteonecrosis and osteomyelitis of jaw, in cooperation with the relevant manufacturers and organizations, and will review the Precautions section in the package inserts of BP products as necessary to take appropriate and effective measures to ensure safety of clinical practice and patient management.

Specific revisions of the Precautions in the package inserts of the BP products are listed below. (The underlined parts are revised.)

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

[Important Precautions]	Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates including this drug <u>regardless of route of administration</u>. <u>In most of</u> reported cases, the events 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, patients <u>should be instructed 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. Patients should be instructed 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, patients should be thoroughly informed of the importance of oral hygiene and notifying his/her dentist about use of this drug. Patients</u> also should be advised to see a dentist/oral surgeon, if any abnormalities occur.

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

[Important Precautions]

Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates including this drug regardless of route of administration. In most of reported cases, the events 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, patients should be instructed 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. Patients should be instructed 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, patients should be thoroughly informed of the importance of oral hygiene and notifying his/her dentist about use of this drug. Patients also should be advised to see a dentist/oral surgeon, if any abnormalities occur.

Minodronic Acid Hydrate

[Important Precautions]

Osteonecrosis or osteomyelitis of jaw may occur in patients treated with bisphosphonates regardless of route of administration. In most of reported cases, the events 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, patients should be instructed 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. Patients should be instructed 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, patients should be thoroughly informed of the importance of oral hygiene and notifying his/her dentist about use of this drug. Patients also should be advised to see a dentist/oral surgeon, if any abnormalities occur.

4. Case summary

<Alendronate Sodium Hydrate>

No.	Patient		Weekly dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Osteoporosis (Hypertension)	35 mg for 2 years and 2 months	**Osteonecrosis and osteomyelitis of jaw** The patient had no history of adverse drug reaction. She had not received periodic dental checkups. Her oral hygiene was poor. The patient had been wearing a full denture. She had not taken corticosteroid. 2 months before administration: Administration of sodium risedronate hydrate was started. 17 days before administration: Administration of sodium risedronate hydrate was discontinued. Day 1 of administration: Administration of alendronate sodium hydrate was

				started. Year 1 and Month 6 of administration: The patient received dental treatment including removal of sutures. (With a residual root) Year 1 and Month 8 of administration: The patient started outpatient visits to an orthopedist. Year 1 and Month 9 of administration: The patient was admitted to the orthopedic department for fracture of the left femoral neck. Date unknown: The patient was discharged from the hospital after a surgery. Year 2 and Month 1 of administration: Administration of alendronate sodium hydrate was discontinued. Administration of alendronate sodium hydrate was resumed 13 days after the discontinuation. Year 2 and Month 2 of administration (day of discontinuation): Swelling and pain in the left lower jaw and mouth ulcer occurred. The patient consulted a dentist. On the same day, the patient was admitted to the hospital to receive IV drip infusion. Jaw x-ray showed a residual root of the upper tooth and osteolysis around it. IV drip infusion of an antibiotic (cefazolin) was started. Administration of alendronate sodium hydrate was discontinued. Oral disinfection was started. 2 days after discontinuation: Oral disinfection was completed. 4 days after discontinuation: Drip infusion was completed. 5 days after discontinuation: An oral administration of an antibiotic (cefcapene pivoxil hydrochloride 100 mg × 3) was started. 9 days after discontinuation: The treatment with the oral antibiotic was completed. Swelling and pain in the left lower jaw remitted. 10 days after discontinuation: The patient was discharged from the hospital. Osteomyelitis and osteonecrosis of the jaw remitted.
	Concomitant medications: none			

<Alendronate Sodium Hydrate>

No.	Patient		Weekly dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 80s	Osteoporosis (None)	35 mg for 1 year and 9 months	**Osteonecrosis of jaw** Year 1 and Month 7 of administration: The patient had her 7th and 8th lower right teeth extracted at a nearby dental clinic. Use of alendronate sodium hydrate was not mentioned by the patient. Healing of the extraction site was impaired, and pus discharge, pain and swelling persisted. Year 1 and Month 8 of administration: The patient consulted the reporting physician for the first time. Intraoral swelling and pus discharge from the fistulae in the right lower jaw formed after the removal of the teeth number 7 and 8 occurred. Panoramic x-ray showed dish-shaped osteonecrosis and sequestration where the teeth

				number 7 and 8 had been in the right lower jaw. The patient was diagnosed with bisphosphonate-related osteonecrosis of jaw based on the clinical and image findings. The patient had 18 to 21 remaining teeth. She had visited periodically her former dentist. Presence of periodontal pockets had never been checked. No corticosteroid had been administered. Treatment given to the patient included mouth washing, administration of an analgesic and long-term administration of a macrolide antimicrobial. Year 1 and Month 9 of administration (day of discontinuation): Administration of alendronate sodium hydrate was discontinued. Alendronate sodium hydrate was not readministered. Jaw MRI showed osteomyelitis image and the patient was diagnosed with osteomyelitis. Date unknown: Long-term administration of a macrolide antimicrobial was started. Pus discharge in the mouth persisted. 1 month after discontinuation: No change was seen in the patient's condition. 2 months after discontinuation: Pus discharge stopped. 3 months after discontinuation: The patient visited the outpatient clinic. No change was seen in the patient's condition. The scheduled operation was canceled since the patient's condition was stable. 5 months after discontinuation: No significant change was seen in panoramic x-ray. Osteonecrosis of jaw remitted.
	Concomitant medications: none			

<Sodium Risedronate Hydrate>

No.	Patient		Weekly dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 80s	Osteoporosis (Hypertension)	17.5 mg for 2 months	**Osteomyelitis of the lower jaw** 21 months before administration: The patient started taking alendronate sodium hydrate. Day 1 of administration: Administration of sodium risedronate hydrate was started. Day 17 of administration: The patient had her tooth extracted at Dental Clinic A. Day 62 of administration: The patient visited Oral Surgical Clinic B for persistent pus discharge. The patient was diagnosed with osteomyelitis of the lower jaw and admitted to the hospital for treatment (drip infusion of an antibiotic was given). Bone scintigraphy and CT showed sequestration. Bacterial tests were performed 3 times, but only indigenous oral bacteria were detected. Day 94 of administration: Sequestrectomy was performed. Day 99 of administration: Pus discharge stopped. Epithelialization occurred with no bone exposure. The patient had no pain. Day 101 of administration: The patient was discharged from the hospital.

	Concomitant medications: betahistine mesilate, cefteram pivoxil, olmesartan medoxomil, atorvastatin calcium hydrate, benidipine hydrochloride, flurbiprofen, preparation containing an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus, diclofenac sodium, mosapride citrate

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2

Revision of Precautions (No. 219)

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 August 10, 2010.

[Brand name]: Major product names are showed.

1

< Psychotropics >

Amitriptyline Hydrochloride
Amoxapine
Imipramine Hydrochloride
Clomipramine Hydrochloride
Setiptiline Maleate
Duloxetine Hydrochloride
Dosulepin Hydrochloride
Trazodone Hydrochloride
Trimipramine Maleate
Nortriptyline Hydrochloride
Maprotiline Hydrochloride
Mianserin Hydrochloride
Mirtazapine
Milnacipran Hydrochloride
Lofepramine Hydrochloride

[Brand Name]

Tryptanol tablets-10, 25 (Banyu Pharmaceutical Co., Ltd.)
AMOXAN CAPSULES 10 mg, 25 mg, 50 mg, AMOXAN FINE GRANULES 10% (Pfizer Japan Inc.)
IMIDOL SUGAR-COATED TABLETS (10), (25) (Mitsubishi Tanabe Pharma Corporation), TOFRANIL Tablets 10 mg, 25 mg (Alfresa Pharma Corporation)
ANAFRANIL Tablets 10 mg, 25 mg, ANAFLANIL Intravenous Drip Infusion 25 mg (Alfresa Pharma Corporation)
TECIPUL Tab. 1 mg (Mochida Pharmaceutical Co., Ltd.)
Cymbalta Capsule 20 mg, 30 mg (Shionogi & Co., Ltd.)
PROTHIADEN Tab. 25 (Kaken Pharmaceutical Co., Ltd.)
Desyrel Tablets 25, 50 (Pfizer Japan Inc.), RESLIN TABLETS 25, 50 (Schering-Plough K.K.)
Surmontil Tablet 10 mg, 25 mg, Surmontil Powder 10% (Shionogi & Co., Ltd.)
NORITREN Tablet 10 mg, 25 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Ludiomil Tablets 10 mg, 25 mg, 50 mg (Novartis Pharma K.K.)

Tetramide Tablets 10 mg, 30 mg (Schering-Plough K.K.)
REFLEX TABLETS 15 mg (Meiji Seika Kaisha, Ltd.), Remeron tablets 15 mg (Schering-Plough K.K.)
Toledomin Tablets 12.5 mg, 15 mg, 25 mg, 50 mg (Asahi Kasei Pharma Corporation)
AMPLIT TABLETS 10 mg, 25 mg (Daiichi Sankyo Company, Limited)

[Other Precautions] Overseas epidemiological studies in patients aged 50 or older have been reported the risk of fracture increased in patients treated with antidepressants including selective serotonin reuptake inhibitors and tricyclic antidepressants.

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2 **< Psychotropics >**

Sertraline Hydrochloride
Paroxetine Hydrochloride Hydrate

[Brand Name] J ZOLOFT Tablets 25 mg, 50 mg (Pfizer Japan Inc.)
PAXIL Tablets 10 mg, 20 mg (GlaxoSmithKline K.K.)

[Other Precautions] Overseas epidemiological studies in patients aged 50 or older have reported the risk of fracture increases in patients treated with antidepressants including selective serotonin reuptake inhibitors and tricyclic antidepressants.
Overseas clinical studies have reported that selective serotonin reuptake inhibitors including this drug may change the sperm characteristics and affect fertility.

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3 **< Psychotropics >**

Fluvoxamine Maleate

[Brand Name] DEPROMEL TABLETS 25, 50, 75 (Meiji Seika Kaisha, Ltd.), Luvox Tablets 25, 50, 75 (Abbott Japan Co., Ltd.)

[Other Precautions] Overseas epidemiological studies in patients aged 50 or older have reported the risk of fracture increased in patients treated with antidepressants including selective serotonin reuptake inhibitors and tricyclic antidepressants.
Overseas clinical studies have reported that other selective serotonin reuptake inhibitors may change the sperm characteristics and affect fertility.

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4 **< Hormones-Miscellaneous >**

Dienogest

[Brand Name] DINAGEST Tab. 1 mg (Mochida Pharmaceutical Co., Ltd.)

[Contraindications] Patients with a history of hypersensitivity to ingredients of this drug

[Adverse Reactions (clinically significant adverse reactions)] **Anaphylactoid symptoms**: Anaphylactoid symptoms (e.g., dyspnoea, angioedema, urticaria, and pruritus) may occur. If any such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

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5 **< Antineoplastics-Miscellaneous >**

Cladribine

[Brand Name] LEUSTATIN Injection 8 mg (Janssen Pharmaceutical K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Acute renal failure**: Serious renal disorders such as acute renal failure may occur. Patients should be carefully monitored through renal function analyses and if abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6

< Acting mainly on mold >

Amphotericin B (liposome preparation)

[Brand Name] AmBisome 50 mg for Intravenous Drip Infusion (Dainippon Sumitomo Pharma Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Hypokalaemia: Serious hypokalaemia may occur. Arrhythmia including ventricular tachycardia, general malaise, and feelings of weakness associated with abnormal changes in serum potassium may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

Cardiac arrest, cardiac failure, arrhythmia (e.g., ventricular tachycardia, ventricular fibrillation, atrial fibrillation): Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

7

< Acting mainly on mold >

Amphotericin B [non-liposome preparation (injectable dosage form)]

[Brand Name] FUNGIZONE FOR INFUSION 50 mg (Bristol Myers K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Cardiac arrest, cardiac failure, arrhythmia (e.g., ventricular tachycardia, ventricular fibrillation, atrial fibrillation): Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Hypokalaemia: Serious hypokalaemia may occur. Arrhythmia including ventricular tachycardia, general malaise,and feelings of weakness associated with abnormal changes in serum potassium may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

8

< Sulfonamides >

Salazosulfapyridine (tablet, suppository)

[Brand Name] Salazopyrin Tablets 500 mg, Salazopyrin Suppositories 500 mg (Pfizer Japan Inc.)

[Important Precautions]

Before administration of this drug, haematology test (haemogram including differential leukocyte count) and liver and renal function tests should be performed. Patients should be carefully monitored for changes in their clinical symptoms during treatment with this drug and periodic haematological and liver function tests should be performed (once every 2 weeks in the first 3 months, once every 4 weeks in the next 3 months and once every 3 months after 6 months of administration in principle). Periodic renal function tests should also be performed.

9

< Synthetic antibacterials >

Enoxacin Hydrate
Tosufloxacin Tosilate Hydrate (oral dosage form)
Pazufloxacin Mesilate
Lomefloxacin Hydrochloride (oral dosage form)

[Brand Name]	FLUMARK Tablet 100 mg, 200 mg (Dainippon Sumitomo Pharma Co., Ltd.) OZEX TAB. 75, 150, OZEX fine granules 15% for pediatric (Toyama Chemical Co., Ltd.), Tosuxacin Tablets 75 mg, 150 mg (Abbott Japan Co., Ltd.) PASIL INTRAVENOUS DRIP INFUSION 300 mg, 500 mg (Toyama Chemical Co., Ltd.), Pazucross INJECTION 300, 500 (Mitsubishi Tanabe Pharma Corporation) Bareon Capsule 100 mg, Bareon Tablet 200 mg (Abbott Japan Co., Ltd.), Lomebact Capsules 100 mg (Shionogi & Co., Ltd.)
[Careful Administration]	Patients with myasthenia gravis
[Clinically significant adverse reactions (similar drug)]	**Exacerbation of myasthenia gravis:** Exacerbation of myasthenia gravis associated with other new quinolone preparation have been reported. Patients should be carefully monitored, if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

10 **< Synthetic antibacterials >**

Garenoxacin Mesilate Hydrate

[Brand Name]	Geninax Tablets 200 mg (Toyama Chemical Co., Ltd.)
[Careful Administration]	Patients with myasthenia gravis
[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia, eosinophilic pneumonia**: Interstitial pneumonia or eosinophilic pneumonia associated with pyrexia, cough, dyspnoea, abnormal chest x-ray and/or increased eosinophils may occur. If any such symptoms are observed, administration of this drug should be discontinued and appropriate measures such as administration of corticosteroids should be taken. **Exacerbation of myasthenia gravis**: Patients with myasthenia gravis may experience exacerbation of symptoms. Such patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

11 **< Synthetic antibacterials >**

Sitafloxacin Hydrate
Prulifloxacin

[Brand Name]	GRACEVIT TABLETS 50 mg, Gracevit FINE GRANULES 10% (Daiichi Sankyo Company Limited) SWORD TABLETS 100 (Meiji Seika Kaisha Ltd.)
[Careful Administration]	Patients with myasthenia gravis
[Clinically significant adverse reactions (similar drug)]	Exacerbation of myasthenia gravis

12 **< Synthetic antibacterials >**

Ciprofloxacin
Ciprofloxacin Hydrochloride

[Brand Name]	Ciproxan-I.V. 200, 300 (Bayer Yakuhin Ltd.) Ciproxan Tablet 100, 200 (Bayer Yakuhin Ltd.)

[Careful Administration]	Patients who may have prolonged QT
[Adverse Reactions (clinically significant adverse reactions)]	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme **Prolonged QT, ventricular tachycardia (including Torsades de pointes)**: Prolonged QT or ventricular tachycardia (including torsades de pointes) 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.

13 **< Synthetic antibacterials >**

Sparfloxacin

[Brand Name]	SPARA Tablet 100 mg (Dainippon Sumitomo Pharma Co., Ltd.)
[Careful Administration]	Patients with myasthenia gravis
[Clinically significant adverse reactions (similar drug)]	**Exacerbation of myasthenia gravis**: Exacerbation of myasthenia gravis associated with other new quinolone preparation have been reported. Patients should be carefully monitored, if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

14 **< Synthetic antibacterials >**

Norfloxacin (oral dosage form)

[Brand Name]	BACCIDAL Tablets 100 mg, 200 mg, BACCIDAL Tablets for Children 50 mg (Kyorin Pharmaceutical Co., Ltd.)
[Careful Administration]	Patients with myasthenia gravis

15 **< Antivirals >**

Didanosine

[Brand Name]	VIDEX CHEWABLE/DISPERSIBLE BUFFERED TABLETS 25, 50, 100, VIDEX EC CAPSULES Enteric-Coated Beadlets 125, 200 (Bristol Myers K.K.)
[Important Precautions]	Lactic acidosis, hepatomegaly with severe hepatic steatosis, serious hepatic disorder, or portal hypertension (including non-cirrhotic portal hypertension) may occur in association with administration of this drug. Patients should be carefully monitored through periodic clinical and laboratory tests, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. Life-threatening lactic acidosis has been reported in several pregnant women treated with this drug and concomitant sanilvudin. This drug should be used in concomitant with sanilvudin only when the potential benefit outweighs the risks during pregnancy.
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic disorder, portal hypertension (including non-cirrhotic portal hypertension)**: Hepatomegaly with severe hepatic steatosis, serious hepatic disorder, or portal hypertension (including non-cirrhotic portal hypertension) may occur. Patients should be carefully monitored through periodic clinical and laboratory tests, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

16

< Antivirals >

Raltegravir Potassium

[Brand Name] ISENTRESS Tablets 400 mg (Banyu Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Rhabdomyolysis, myopathy**: Rhabdomyolysis characterized by myalgia, feeling of weakness, increased CK (CPK), and increased blood myoglobin or increased urine myoglobin may be followed by serious renal disorder such as acute renal failure. Patients should be carefully monitored and if such symptoms are observed, administration of this drug should be discontinued immediately. Myopathy may also occur. If muscular weakness, myalgia, or marked increased CK(CPK) are observed, administration of this drug should be discontinued.

17

< Biological preparations-Miscellaneous >

Tocilizumab (Genetical Recombination)

[Brand Name] ACTEMRA 80 mg for Intravenous Infusion, ACTEMRA 200 mg for Intravenous Infusion, ACTEMRA 400 mg for Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)

[Careful Administration] Patients with decreased white blood cell, decreased neutrophils or decreased platelets

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

3

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 September 1, 2010)

Nonproprietary name Brand name on	Name of the marketing authorisation holder	Date of EPPV initiate
Everolimus AFINITOR tablets 5 mg	Novartis Pharma K.K.	March 8, 2010
Rasburicase (Genetical Recombinant) 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
Metformin Hydrochloride Metgluco Tablets 250 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 10, 2010
Thalidomide THALED capsule 50	Fujimoto Pharmaceutical Corporation	May 25, 2010
Epoetin Kappa (Genetical Recombinant) [Epoetin Alfa Biosimilar 1] Epoetin Alfa BS Injection 750 syringe [JCR], Epoetin Alfa BS Injection 1500 syringe [JCR], Epoetin Alfa Injection 3000 syringe [JCR], Epoetin Alfa BS Injection 750 [JCR], 1500 [JCR], 3000 [JCR]	JCR Pharmaceuticals Co., Ltd.	May 27, 2010
Travoprost/Timolol Maleate DuoTrav Combination Ophthalmic Solution	Alcon Japan Ltd.	June 11, 2010

Dorzolamide Hydrochloride/Timolol Maleate COSOPT Ophtalmic Solution	Banyu Pharmaceutical Co., Ltd.	June 11, 2010
Eculizumab (Genetical Recombination) Soliris Intravenous Drip Infusion 300 mg	Alexion Pharmaceuticals, Inc.	June 14, 2010
Alogliptin Benzoate NESINA Tablets 6.25 mg., 12.5 mg., 25 mg.	Takeda Pharmaceutical Company Limited	June 15, 2010
Candesartan Cilexetil/Amlodipine Besilate UNISIA Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 15, 2010
Panitumumab (Genetical Recombination) Vectibix Intravenous Drip Infusion 100 mg	Takeda Pharmaceutical Company Limited	June 15, 2010
Pregabalin Lyrica Capsules 25 mg, 75 mg, 150 mg	Pfizer Japan Inc.	June 22, 2010
Fentanyl Citrate Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	June 24, 2010
Metformin Hydrochloride/Pioglitazone Hydrochloride METACT Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	July 6, 2010
Ramelteon Rozerem Tablets 8 mg	Takeda Pharmaceutical Company Limited	July 6, 2010
Lenalidomide Hydrate	Celgene K.K.	July 20, 2010*1
Revlimid Capsules 5 mg		August 20, 2010*2
Olopatadine Hydrochloride ALLELOCK Tablets 2.5, 5*3	Kyowa Hakko Kirin Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate PASIL INTRAVENOUS DRIP INFUSION 300 mg, 500 mg*4	Toyama Chemical Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate Pazucross INJECTION 300 mg, 500 mg*4	Mitsubishi Tanabe Pharma Corporation	July 23, 2010
Budesonide Pulmicort 100 μg Turbuhaler 112 doses, Pulmicort 200 μg Turbuhaler 56, 112 doses*5	AstraZeneca K.K.	July 23, 2010
Lansoprazole	Takeda Pharmaceutical Company Limited	July 23, 2010*6
Takepron capsules 15, Takepron OD Tablets 15		August 20, 2010*7
Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 10 μg/1 mL PLASTIC SYRINGE, NEPS INJECTION 15 μg/1 mL PLASTIC SYRINGE, NESP 20 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 30 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 40 μg/1 mL PLASTIC SYRINGE, NEPS INJECTION 60 μg/0.6 mL PLASTIC SYRINGE, NESP 120 μg/0.6 mL PLASTIC SYRINGE, NESP INJECTION 180 μg/0.9 mL PLASTIC SYRINGE	Kyowa Hakko Kirin Co., Ltd.	August 26, 2010

*1 The originally approved indication for "treatment of patients with relapsed or refractory multiple myeloma"
*2 An additional indication for "treatment of patients with myelodysplastic syndrome associated with a chromosome 5q deletion"
*3 An additional administration for "pediatrics (aged 7 and older)"
*4 An additional indication for "treatment of patients with sepsis, applicable microorganism; *Streptococcus pneumonia*"
*5 An additional administration for "pediatrics"
*6 An additional indication for "treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of low-dose aspirin"
*7 An additional indication for "treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of non-steroidal anti-inflammatory drugs"