Pharmaceuticals and Medical Devices Safety Information

No. 295 October 2012

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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).

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

Translated by
Pharmaceuticals and Medical Devices Agency

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Pharmaceuticals and Medical Devices Safety Information
No. 295 October 2012

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

[Outline of Information]

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

ACTH	Adrenocorticotropic hormone
ADRs	Adverse drug reactions
ALK	Anaplastic lymphoma kinase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
ALP	Alkaline phosphatase
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CEA	Carcinoembryonic antigen
CRP	C-reactive protein
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
FISH	Fluorescence in situ hybridization
FY	Fiscal year
IHC	Immunohistochemistry
IU	International unit
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
NSAID	Nonsteroidal antiinflammatory drug
PCR	Polymerase chain reaction
PLT	Platelet
PS	Performance status
RANKL	Receptor activator for nuclear factor-kB ligand
RBC	Red blood cell count
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone
VZV	Varicella-zoster virus
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Serious Hypocalcaemia Associated with Denosumab (Genetical Recombination)

Active Ingredient Brand Name (name of company)	Active Ingredient	Brand Name (name of company)
	Denosumab (Genetical Recombination)	RANMARK SUBCUTANEOUS INJECTION 120mg (Daiichi Sankyo Company, Limited)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous	
Indications	Bone lesion associated with multiple myeloma or bone metastasis of solid carcinoma	

1. Introduction

Denosumab (Genetical Recombination) (RANMARK SUBCUTANEOUS INJECTION 120mg, hereinafter "RANMARK") is a human monoclonal antibody that prevents bone-related events caused by bone destruction, including pathological fracture, by binding to receptor activator for nuclear factor-κB ligand (hereinafter "RANKL"), which is believed to be involved in osteoclast activation. It was approved in Japan for the treatment of "Bone lesion associated with multiple myeloma or bone metastasis of solid carcinoma" in January 2012.

An alert has been issued for hypocalcaemia associated with RANMARK since its approval through the package insert and "Information for Proper Use," which was prepared by the marketing authorization holder (MAH) based on the data about the incidence of hypocalcaemia in clinical studies that were submitted at the time of new drug application.

Since the launch on April 17, 2012, RANMARK has been administered to approximately 7300 patients as of August 31, 2012, and 32 cases of serious hypocalcaemia, including 2 deaths, have been reported (as of August 31, 2012). In light of such information, MHLW/PMDA instructed the MAH to distribute Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter)[1)] on September 11, 2012 and took additional safety measures. The information is presented below.

2. Hypocalcaemia associated with RANMARK

(1) Occurrence of hypocalcaemia

In 3 phase III studies that were submitted at the time of new drug application of RANMARK, adverse events of hypocalcaemia were reported in 9.6% (273/2841) of patients receiving RANMARK and 5.0% (141/2836) of patients receiving a control drug, zoledronic acid. Of those cases, serious hypocalcaemia occurred in 1.4% (41/2841) of patients in the RANMARK group and 0.6% (17/2836) of patients in the zoledronic acid group, showing a tendency for higher incidence and severity of hypocalcaemia with RANMARK than with zoledronic acid.[2)]

From the launch of RANMARK to August 31, 2012, 32 cases of serious hypocalcaemia have been reported, including 2 deaths. Of these, one fatal case is presented below.

A Fatal Case in Japan

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Bone lesion (non-small cell lung cancer) (venous thrombosis) (renal disorder)	120 mg Once	**Hypocalcaemia** Approximately 6 years before administration: The patient developed non-small cell lung cancer. The patient was removed his right upper lobe of lung. CEA 3.4 ng/mL. Approximately 4 years before administration: Metastasis to lymph nodes was confirmed, and lymphadenectomy and removal of right lung was performed. Approximately 1 year before administration: CEA 7.9 ng/mL. 18 days before administration: CEA 41.4 ng/mL. Day 1 of administration: The patient was diagnosed with multiple metastatic bone tumors and started receiving denosumab for bone lesion due to bone metastases from non-small cell lung cancer. The patient was diagnosed with renal disorder that was attributed to NSAIDs. Supplementation of calcium and vitamin D was not administered because hypercalcaemia (corrected serum calcium level 12.4 mg/dL) was present. Phosphorus 5.0 mg/dL, serum creatinine 3.9 mg/dL. PS 2. 6 days after administration: Corrected calcium level 8.5 mg/dL, phosphorus 3.6 mg/dL, serum creatinine 3.20 mg/dL. The patient was admitted to the hospital. 10 days after administration (day of onset): Hypocalcaemia occurred. Corrected serum calcium level 8.2 mg/dL, phosphorus 2.7 mg/dL, serum creatinine 2.72 mg/dL. 13 days after administration: Corrected serum calcium level 7.8 mg/dL, phosphorus 2.2 mg/dL, serum creatinine 2.43 mg/dL. 17 days after administration: Corrected serum calcium level 7.2 mg/dL, phosphorus 2.2 mg/dL, serum creatinine 1.81 mg/dL. No abnormality was observed in electrocardiogram. There were no clinical symptoms associated with hypocalcaemia. 19 days after administration: Corrected serum calcium level 6.8 mg/dL, phosphorus 2.3 mg/dL, serum creatinine 1.89 mg/dL, CEA 95.5 ng/mL. 20 days after administration: Pre-existing disease was progressed rapidly. ALK lung cancer was suspected (IHC: positive, FISH; indeterminant) and the administration of crizotinib was started, but clinical improvement was not observed within a few days of treatment. 24 days after administration: Corrected serum calcium level 5.5 mg/dL, phosphorus 3.4 mg/dL, serum creatinine 2.88 mg/dL, PS 3. The patient experienced sudden cardiac arrest, and then circulation was restarted by resuscitation. Respiratory management by mechanical ventilation was started. Calcium gluconate 8.5% (850 mg × 1) was intravenously injected. 25 days after administration: Corrected serum calcium level 6.1 mg/dL, phosphorus 3.1 mg/dL, serum creatinine 3.01 mg/dL. 27 days after administration: Corrected serum calcium level 5.8 mg/dL, phosphorus

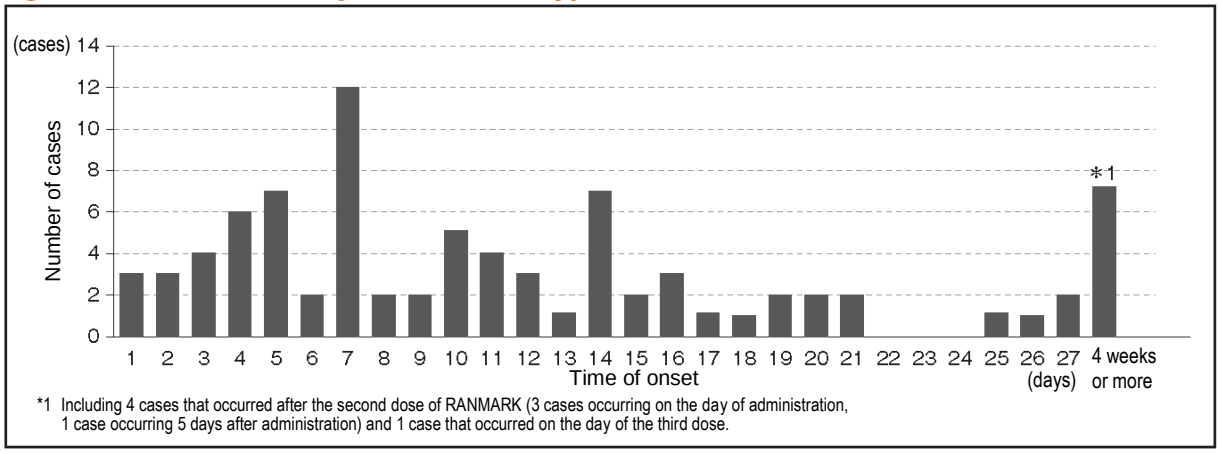
				10.7 mg/dL, serum creatinine 9.21 mg/dL. Calcium gluconate 8.5% (850 mg × 1) was intravenously injected. 28 days after administration: Calcium gluconate 8.5% (850 mg × 1) was intravenously injected. 31 days after administration: The patient died. (Cause of death: cancer. According to his physician, a direct cause of death was considered to be an aggravation of non-small cell lung cancer, but the possibility of sudden cardiac arrest due to obvious hypocalcaemia cannot be ruled out.).
	Concomitant medications: ketoprofen tape, sodium rabeprazole, warfarin potassium, flavin adenine dinucleotide sodium, celecoxib, loxoprofen sodium, crizotinib			

Laboratory Examination

	9 days before administration	Day 1 of administration	6 days after administration	10 days after administration (day of onset)	13 days after administration	17 days after administration	19 days after administration	24 days after administration	25 days after administration	27 days after administration
Corrected serum calcium (mg/dL)	10.7	12.4	8.5	8.2	7.8	7.2	6.8	5.5	6.1	5.8
Serum calcium (mg/dL)	10.2	12.1	8.2	7.8	7.3	6.8	6.5	5.2	5.7	4.4
Serum albumin (g/dL)	3.5	3.7	3.7	3.6	3.5	3.6	3.7	3.7	3.6	2.6
Serum potassium (mEq/L)	4.5	5.0	4.6	5.7	5.1	4.9	4.2	4.5	4.3	6.0
phosphorus (mg/dL)	4.8	5.0	3.6	2.7	2.2	2.2	2.3	3.4	3.1	10.7
BUN (mg/dL)	26.2	29.8	34.7	25.7	24.7	18.0	20.8	32.1	32.0	97.3
Creatinine (mg/dL)	2.94	3.90	3.20	2.72	2.43	1.81	1.89	2.88	3.01	9.21
eGFR	19	14	17	21	23	32	31	19	18	5
AST (GOT) (IU/L)	36	26	31	28	39	39	33	60	342	447
ALT (GPT) (IU/L)	15	12	11	13	15	15	17	34	112	103
LDH (IU/L)	1060	784	1215	1235	1634	1911	1754	1594	2571	3271
ALP (IU/L)	677	583	616	591	535	525	514	472	590	373
CRP (mg/dL)	4.52	2.91	5.09	8.37	6.05	9.00	12.07	18.85	35.83	19.08
WBC ($\times 10^2/\mu L$)	132	109	126	106	100	121	125	139	142	220
RBC ($\times 10^4/\mu L$)	363	377	357	369	331	320	320	278	408	370
PLT ($\times 10^4/\mu L$)	27.9	29.5	25.0	30.9	31.4	32.5	35.7	38.8	35.4	12.7

As of August 31, 2012, the MAH received 91 cases of hypocalcaemia, including non-serious case. In 85 of these cases, data on the number of days from the start of administration of RANMARK to the onset of hypocalcaemia were obtained, as shown in Figure 1[3)].

Figure 1. Number of days to onset of hypocalcaemia



*1 Including 4 cases that occurred after the second dose of RANMARK (3 cases occurring on the day of administration, 1 case occurring 5 days after administration) and 1 case that occurred on the day of the third dose.

This indicates that hypocalcaemia associated with RANMARK may occur at any time from within a few days after first administration. Therefore, blood tests should be frequently performed, and patients should be closely monitored after administration of RANMARK.

(2) Need for calcium and vitamin D supplementation

The protocols for 3 phase III studies that were submitted at the time of new drug application of RANMARK specified that "It is highly recommended that all patients receive supplementation of at least 500 mg of calcium (Ca) and at least 400 IU of natural vitamin D every day unless hypercalcaemia occurs during the study period." The results of the 3 phase III studies showed that the incidence and severity of hypocalcaemia were higher in patients who did not receive calcium or vitamin D supplementation than patients who received supplementation (see Table 1).[2)]

Table 1 Occurrence of adverse event hypocalcaemia*1 with or without Ca or vitamin D supplementation in phase III studies

Hypocalcaemia	With Ca or vitamin D supplementation*2	Without Ca and vitamin D supplementation*3
	RANMARK group: 2374 patients*4 Number of cases (%)	RANMARK group: 467 patients*4 Number of cases (%)
All grades	126 (5.3)	147 (31.5)
Grade 3	48 (1.9)	24 (6.7)
Grade 4	9 (0.4)	7 (2.0)

*1 Decrease in serum calcium levels corrected for albumin

*2 Patients who received oral calcium or oral vitamin D during the study period, excluding those who did not receive oral Ca or oral vitamin D until the onset of hypocalcaemia.

*3 Patients who never received oral calcium and oral vitamin D and patients who did not receive oral calcium or oral vitamin D until the onset of hypocalcaemia.

*4 Patients included in the safety analysis set among those enrolled in the studies.

Among cases of hypocalcaemia that were reported after the marketing of RANMARK, including fatal cases, there were several cases of possible insufficient Ca and vitamin D supplementation, for example, no vitamin D was given, or the dose of Ca was not sufficient even if Ca was given.[3)]

Therefore, in order to reduce the risk of onset of hypocalcaemia, it is necessary to ensure supplementation of Ca and vitamin D. The vitamin D to be used should be a natural type and not an activated type, because (i) natural vitamin D was used in clinical studies and thus no data of clinical

studies using activated vitamin D are available; and (ii) in general, administration of activated vitamin D over a long period of time may cause hypercalcaemia and patients using RANMARK have metastases to bone and are thus vulnerable to hypercalcaemia. However, since no prescription natural vitamin D drug is available, patients should be instructed to purchase and take an appropriate over-the-counter drug.

In addition, supplementation of Ca and vitamin D in patients with renal impairment requires the cautions provided in the next section.

(3) Cautions for patients with renal impairment when RANMARK is administered

Cases of hypocalcaemia reported after marketing in Japan included patients with possible severe renal impairment.[3)]

Acoording to the data of 3 phase III studies that were submitted at the time of new drug application of RANMARK, patients with severe renal disease with creatinine clearance of <30 mL/min and patients with end stage renal failure requiring dialysis were excluded from the studies, and usage experience of the drug is quite limited in patients with severe renal impairment.[2)] An overseas phase I study was conducted in patients with renal impairment. As a result, it has been determined that renal impairment does not affect the pharmacokinetics of RANMARK and no dose adjustment is required when the drug is administered to patients with renal impairment. However, the incidence of hypocalcaemia as an adverse event in this study was higher in patients with severe renal disease (creatinine clearance <30 mL/min) and patients with end stage renal failure requiring dialysis (29.4%, 5/17 patients) than in patients with mild and moderate renal disease and subjects with normal renal function (13.2%, 5/38 patients).[2)] Therefore, RANMARK should be carefully administered in patients with severe renal impairment.

In general, patients with renal impairment and renal failure require careful electrolyte management. When RANMARK is administered to such patients, careful evaluation, including measurement of blood and urine Ca and phosphorus, should be performed to determine the need for Ca treatment and to adjust the dosage of Ca. In addition, because activation of vitamin D may be impaired in patients with renal impairment, activated vitamin D, not natural vitamin D, should be supplemented depending on the degree of renal impairment.

When RANMARK is administered to patients with renal impairment, healthcare professionals are encouraged to evaluate and manage electrolyte levels appropriately and consider a consultation with a nephrologist as needed to ensure further careful administration of RANMARK.

3. Precautions

Based on the above information, healthcare professionals are encouraged to pay special attention to the following recommendations for proper use of RANMARK.

(i) Before administration of RANMARK, corrected serum Ca levels should be checked, and if hypocalcaemia is observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy.
(ii) RANMARK should be administered with oral supplementation of Ca and vitamin D.
(iii) Serum Ca should be measured frequently after the start of treatment.
(iv) Patients with severe renal impairment are at a greater risk of developing hypocalcaemia and therefore should use the drug cautiously.
(v) If hypocalcaemia is observed, when requiring emergency treatment, appropriate measures such as concomitant use of IV administration of Ca should be taken immediately in addition to oral administration of Ca and vitamin D.

No prescription natural vitamin D drug is available at present and patients need to purchase an over-the-counter drug by themselves. Patients should be fully informed of this and monitored appropriately for administration of vitamin D.

Various adverse reactions other than hypocalcaemia may also occur during treatment with RANMARK. Healthcare professionals are encouraged to fully understand the safety profile of RANMARK prior to administration of the drug and provide continued cooperation for proper use.

The current package insert includes precautions against hypocalcaemia in the sections of "Warnings", "Precautions of Dosage and Administration", "Careful Administration," "Important Precautions", "Clinically Significant Adverse Reactions", and "Clinical Studies" (see Table 2). (See "2. Important Safety Information (page 12)" of this document for revisions to Precautions section dated September 11, 2012.)

Table 2

[Warnings]	• Serious hypocalcaemia may occur at any time from within a few days after initiating the administration of this drug, resulting in fatal outcomes in some cases. During treatment with this drug, blood tests should be frequently performed and patients should be carefully monitored. To reduce the risk of onset of serious hypocalcaemia due to this drug, this drug should be administered with oral supplementation of calcium and vitamin D unless the corrected serum calcium levels are high. • Patients with severe renal impairment are at a greater risk of developing hypocalcaemia and therefore use the drug cautiously. • If hypocalcaemia is observed after the initiation of the drug, when requiring emergency treatment, appropriate measures such as concomitant use with IV administration of calcium should be taken immediately in addition to oral administration of calcium and vitamin D.
[Precautions of Dosage and Administration]	To reduce the risk of onset of hypocalcaemia, at least 500 mg of calcium and at least 400 IU of natural vitamin D should be administered every day unless the corrected serum calcium levels are high. For patients with renal impairment, activated vitamin D should be used depending on the degree of renal impairment, due to the impaired activation of vitamin D. The dose of calcium should be appropriately adjusted after consideration of the necessity of administration.
[Careful Administration]	• Patients with hypocalcaemia or patients at a risk of hypocalcaemia [Hypocalcaemia may occur or be aggravated.] • Patients with severe renal impairment [Hypocalcaemia may occur. In phase III clinical studies of this drug, patients with severe renal impairment (creatinine clearance <30 mL/min) or patients with end stage renal failure requiring dialysis were excluded from the studies and there is only limited experience with the drug in these patients.]
[Important Precautions]	• Hypocalcaemia may occur. Serum electrolyte levels such as serum calcium and phosphorus should be measured before the start of treatment. The level of corrected serum calcium should be checked, and if hypocalcaemia is observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy. • Hypocalcaemia can occur at any time from within a few days after initiating the administration of the drug. Serum electrolyte levels such as serum calcium and phosphorus should be measured frequently and patients should be carefully monitored after the start of the treatment.
[Clinically Significant Adverse Reactions]	**Hypocalcaemia (5.8%)**: Hypocalcaemia with symptoms including prolonged QT, convulsion, tetany, numbness, disorientation may occur, resulting in fatal outcomes in some cases. Patients should be carefully monitored, and if hypocalcaemia is observed, when requiring emergency treatment, appropriate measures such as concomitant use with intravenous administration of calcium should be taken immediately in addition to oral administration of calcium and vitamin D.
[Clinical Studies]	Incidence of hypocalcaemia • Phase III Clinical Studies Adverse events of hypocalcaemia occurred in 273/2841 patients (9.6%) in the denosumab group and 141/2836 patients (5.0%) in the zoledronic acid group. Of them, serious hypocalcaemia occurred in 41/2841 patients (1.4%) in the denosumab group and 17/2836 patients (0.6%) in the zoledronic acid group. It was highly recommended that all patients receive supplementation of at least 500 mg of calcium and at least 400 IU of natural vitamin D every day unless hypercalcaemia occurred during the study period. • Pharmacokinetic study in subjects with different renal function levels In this study, 12 subjects with normal renal function and 43 patients with renal

	impairment (13 with mild renal disease, 13 with moderate renal disease, 9 with severe renal disease, 8 with end stage renal failure requiring dialysis) received a single subcutaneous dose of denosumab 60 mg. Adverse events of hypocalcaemia occurred in 5/17 (29.4%) patients with severe renal impairment (creatinine clearance <30 mL/min) and patients with end stage renal failure requiring dialysis, with a higher incidence than in patients with mild and moderate renal disease and subjects with normal renal function (5/38 subjects, 13.2%). (overseas data) Note) The approved dosage and administration of denosumab was 120 mg given subcutaneously once every 4 weeks.

<References> (including provisionally translated titles)

1) Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter): RANMARK SUBCUTANEOUS INJECTION 120mg (denosumab) -Risk of severe hypocalcaemia, including fatal cases http://www.pmda.go.jp/english/service/pdf/letter/120911-denosumabu.pdf
2) Review Report dated November 24, 2011 for RANMARK SUBCUTANEOUS INJECTION 120mg http://www.info.pmda.go.jp/shinyaku/P201200013/430574000_22400AMX00035000_A100_4.pdf (only available in Japanese language)
3) Information for Proper Use about RANMARK SUBCUTANEOUS INJECTION 120mg: Daiichi Sankyo Company, Limited https://www.daiichisankyo.co.jp/med/contents/announce/0001347498291804/pdf/yp_ranmark_sep13.pdf (Directed to a website for healthcare professionals) (only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated September 11 and September 25, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Denosumab (Genetical Recombination)

Brand Name (name of company)	RANMARK SUBCUTANEOUS INJECTION 120 mg (Daiichi Sankyo Company, Limited)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous
Indications	Bone lesion associated with multiple myeloma or bone metastasis of solid carcinoma

PRECAUTIONS (underlined parts are revised)

Warnings

WARNINGS

Serious hypocalcaemia may occur at any time from within a few days after initiating the administration of this drug, resulting in fatal outcomes in some cases. During treatment with this drug, blood tests should be frequently performed and patients should be carefully monitored. To reduce the risk of onset of serious hypocalcaemia due to this drug, this drug should be administered with oral supplementation of calcium and vitamin D unless the corrected serum calcium levels are high.

Patients with severe renal impairment are at a greater risk of developing hypocalcaemia and therefore use the drug cautiously.

If hypocalcaemia is observed after the initiation of the drug, when requiring emergency treatment, appropriate measures such as concomitant use with IV administration of calcium should be taken immediately in addition to oral administration of calcium and vitamin D.

Precautions of Dosage and Administration

To reduce the risk of onset of hypocalcaemia, at least 500 mg of calcium and at least 400 IU of natural vitamin D should be administered every day unless the corrected serum calcium levels are high. For patients with renal impairment, activated vitamin D should be used depending on the degree of renal impairment, due to the impaired activation of vitamin D. The dose of calcium should be appropriately adjusted after consideration of the necessity of administration.

Careful Administration

Patients with severe renal impairment [Hypocalcaemia may occur. In phase III clinical studies of this drug, patients with severe renal impairment (creatinine clearance <30 mL/min) or patients with end stage renal failure requiring dialysis were excluded from the studies and there is only limited experience with the drug in these patients.]

Important Precautions

Hypocalcaemia may occur. Serum electrolyte levels such as serum calcium and phosphorus should be measured before the start of treatment. The

	level of corrected serum calcium should be checked, and if hypocalcaemia is observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy. Hypocalcaemia can occur at any time from within a few days after initiating the administration of the drug. Serum electrolyte levels such as serum calcium and phosphorus should be measured frequently and patients should be carefully monitored after the start of the treatment.
Adverse Reactions (clinically significant adverse reactions)	The sentence, "If hypocalcaemia with any clinical symptom (tetany, numbness, etc.) is observed, intravenous administration of calcium is effective." was deleted. **Hypocalcaemia**: Hypocalcaemia with symptoms including prolonged QT, convulsion, tetany, numbness, disorientation may occur, resulting in fatal outcomes in some cases. Patients should be carefully monitored, and if hypocalcaemia is observed, when requiring emergency treatment, appropriate measures such as concomitant use with IV administration of calcium should be taken immediately in addition to oral administration of calcium and vitamin D.
Reference Information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 5 months (from initial marketing to August 31, 2012) • Hypocalcaemia: 32 cases (2 fatal cases) The number of patients using this drug estimated by MAHs: approximately 7,300 (from initial marketing to August 31, 2012) Launched in Japan: April 2012

Case Summary

See fatal cases in Japan (p. 6 and 7) in "1. Serious Hypocalcaemia Associated with Denosumab (Genetical Recombination)" of this Bulletin.

2 Tetracosactide Acetate (0.5 mg preparation)

Brand Name (name of company)	CORTROSYN Z INTRAMUSCULAR INJECTION 0.5 mg (Daiichi Sankyo Company, Limited)
Therapeutic Category	Pituitary hormone preparations
Indications	Adrenal cortical function test, infantile spasms, bronchial asthma, rheumatoid arthritis, nephrotic syndrome (to be used only when the patient does not respond to other drugs except corticosteroids and corticosteroid therapy is inappropriate)

PRECAUTIONS (underlined parts are revised)

Important Precautions	If infection with varicella occurs during administration of this drug, it may lead to a fatal course. Caution should be exercised for the following points: 1) Patients should be monitored for a past history of varicella and the prophylactic vaccination before administration of this drug. 2) In patients with no history of varicella, they should be monitored with sufficient attention to prevent infection with varicella as much as possible. If infection is suspected or actually occurs, patients should be instructed to see their doctor immediately, and appropriate measures should be taken. 3) Even patients who have a history of varicella or have received a prophylactic vaccine in the past may develop varicella during administration of this drug. Caution should be exercised in those patients.

Adverse Reactions (clinically significant adverse reactions)

Induced infection, aggravated infection: Induced infection or aggravated infection may occur. Patients should be carefully monitored, 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 and 6 months (April 1, 2009 to September 6, 2012)

- Infection-associated cases: 1 case (1 fatal case)

The number of patients using this drug estimated by MAHs: approximately 1,000 (FY 2011)

Launched in Japan: June 1970

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female Under age of 1	West's syndrome, tuberous sclerosis (none)	0.0050 mg/kg for 16 days	**Varicella** Day 1 of administration: The patients started receiving adrenocorticotropic hormone (ACTH) therapy (tetracosactide acetate) for infantile spasms. Day 4 of administration: Mild bad mood occurred. A follow-up observation was performed. Day 15 of administration: Marked bad mood and sleep loss occurred. A follow-up observation was performed. Day 16 of administration (day of discontinuation): Administration of tetracosactide acetate was discontinued. 1 day after discontinuation (day of onset): Rash appeared and abnormal blood test values were observed. Based on the possible severe varicella and drug eruption, administration of aciclovir and gamma globulin was started, and administration of sodium valproate and zonisamide was discontinued. 2 days after discontinuation: Blood test values worsened, disseminated intravascular coagulation (DIC), haemorrhagic shock, and respiratory failure occurred. Blood transfusion and ventilator management were started. 8 days after discontinuation: The result of polymerase chain reaction (PCR) analysis of peripheral blood was positive for varicella-zoster virus (VZV) DNA. 15 days after discontinuation: The patient died of multi-organ failure.
	Concomitant medications: sodium valproate, zonisamide			

3 Levocabastine Hydrochloride

(1) Levocabastine Hydrochloride (ophthalmic solution)

Brand Name (name of company)	Livostin Eye Drops 0.025% (Janssen Pharmaceutical K.K.) Levocabastine Hydrochloride Ophthalmic Solution 0.025% "TOA" (TOA Pharmaceuticals Co., Ltd.) LEVOCABASTINE HYDROCHLORIDE OPHTHALMIC SOLUTION 0.025% "WAKAMOTO" (Wakamoto Co, Ltd.) LEVOCABASTINE HYDROCHLORIDE Ophthalmic Solutions 0.025% "SANWA" (Sanwa Kagaku Kenkyusho Co., Ltd.) LEVOCABASTINE OPHTHALMIC SUSPENSION 0.025% "TS" (Teika Pharmaceutical Co., Ltd.) LEVOCABASTINE HYDROCHLORIDE ophthalmic solution 0.025% "Sawai" (Sawai Pharmaceutical Co., Ltd.) LEVOCABASTINE Ophthalmic Solution 0.025% [Pfizer] (Pfizer Japan Inc.) LEVOCABASTINE Ophthalmic Suspension 0.025% "FFP" (Fujifilm Pharma Co., Ltd.) LEVOCABASTINE Eye Drops 0.025% "Isei" (Isei Co., Inc.)
Therapeutic Category	Ophthalmic Agents
Indications	Allergic conjunctivitis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis (dyspnoea, face oedema, etc.) 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.

(2) Levocabastine Hydrochloride (nasal solution)

Brand Name (name of company)	Livostin Nasal Solution 0.025 mg 112 metered sprays (Janssen Pharmaceutical K.K.)
Therapeutic Category	Otological agents
Indications	Allergic rhinitis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis (dyspnoea, face oedema, etc.) associated with the ophthalmic solution of this drug has been reported. 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, 2009 to July 22, 2012)

- Shock, anaphylaxis-associated cases: 1 case (no fatal case)

The number of patients using this drug estimated by MAHs:

(1) approximately 2,496,000 (FY 2011)

(2) approximately 193,000 (FY 2011)

Launched in Japan: (1) January 2001

(2) November 1999

Case Summary

No.	Patient	Daily dose/	Adverse reactions

	Sex/ Age	Reason for use (complications)	Treatment duration	Clinical course and therapeutic measures
1	Female 70s	Allergic conjunctivitis (cataract) (dry eye) (asthma)	Once in both eyes for 1 day	**Anaphylactic shock** The patient received levocabastine hydrochloride for allergic conjunctivitis about 2 years ago. Day of administration (day of discontinuation): After levocabastine hydrochloride was given in both eyes around noon, swelling rapidly occurred in both eyelids. The patient had difficulty breathing after a while. She visited a nearby hospital for internal medicine. The patient was referred to another hospital, which she immediately visited. At the other hospital, the patient was treated with epinephrine 0.3 mg intramuscular injection, prednisolone tablets 5 mg (6T × 3 days), and d-chlorpheniramine maleate tablets 2 mg (3T × 3 days) and was admitted to the hospital. 1 day after discontinuation: The patient progressed favorably, and eyelid oedema and dyspnoea remitted. The patient was discharged from the hospital.
	Concomitant medications: pirenoxine ophthalmic solution, purified sodium hyaluronate ophthalmic solution			

3

Revision of Precautions (No. 240)

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 September 25, 2012 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 Ophthalmic Agents

Diclofenac Sodium (ophthalmic solution)

Brand Name	DICLOD OPHTHALMIC SOLUTION 0.1% (Wakamoto Co, Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylaxis**: Shock or anaphylaxis (urticaria, angioedema, dyspnoea, etc.) associated with other dosage forms of this drug (oral, dermatologic, etc.) has been reported. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2 Analgesics, anti-itchings, astringents, anti-inflammatory agents

Diclofenac Sodium (dermatologic preparation)

Brand Name	Voltaren Tape 15 mg, 30 mg, Voltaren Gel 1%, Voltaren Lotion 1% (Dojin Iyaku-kako Co., Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylaxis**: Shock or anaphylaxis (urticaria, angioedema, dyspnoea, etc.) 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.

3 Psychotropics

Lithium Carbonate

Brand Name	LIMAS tab. 100, 200 (Taisho Pharmaceutical Co., Ltd.) and the others
Precautions of Dosage and Administration	Lithium poisoning may occur as a result of an overdose. The serum lithium level should be measured about once weekly at the initial phase of administration and during the dose-increase phase until the maintenance dose is fixed, and about once every 2 to 3 months during the maintenance dose phase. Lithium carbonate should be used while assessing a trough level based on the results of lithium level measurement. If the patient has any factor that may increase the serum lithium level (e.g., lack of food and water intake, susceptibility to dehydration, concomitant use of drugs that may increase the serum lithium level such as nonsteroidal anti-inflammatory drugs), or any initial symptom of lithium poisoning, serum lithium level should be measured.
Important Precautions	Manifestation of characteristic electrocardiogram changes (coved type elevated ST in the right-sided chest lead [V_1 - V_3]) of Brugada syndrome has been reported.

Ventricular fibrillation, ventricular tachycardia, ventricular extrasystoles associated with such a change may occur. If the drug is administered to patients with suspected Brugada-type electrocardiogram, the use of this drug should be carefully considered by means such as consultation with a physician specializing in cardiology.

Precautions for Patients and Their Families

Patients and their families should be sufficiently informed of possible lithium poisoning in cases of lack of food and water intake, susceptibility to dehydration during administration of this drug, and concomitant use of a nonsteroidal anti-inflammatory drug with this drug. And they should be instructed to consult their physician if any initial symptom of lithium poisoning occurs.

Adverse Reactions (clinically significant adverse reactions)

Acute renal failure, interstitial nephritis, nephrotic syndrome: Acute renal failure, interstitial nephritis, or nephrotic syndrome may occur. Patients should be carefully monitored through the renal function test (measurement of blood creatinine, blood urea nitrogen, urine protein, etc.), and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Hypothyroidism, thyroiditis: Hypothyroidism or thyroiditis may occur. Patients should be carefully monitored through thyroid function tests (measurement of blood TSH, blood free T_3, blood free T_4, etc.), and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Hyperparathyroidism: Hyperparathyroidism may occur. Patients should be carefully monitored by checking serum calcium, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

4 Antiarrhythmic agents

Cibenzoline Succinate

Brand Name

Cibenol Tablets 50 mg, 100 mg, Cibenol Intravenous Injection 70 mg (Astellas Pharma Inc.), and the others

Contraindications

Patients with a history of hypersensitivity to ingredients of this drug

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if a distressed feeling in the chest, cold sweat, dyspnoea, decreased blood pressure, rash, oedema are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Liver disorder associated with circulatory failure: Serious liver disorder (hepatic shock, characterized by a rapid increase in transaminase or LDH) may occur due to circulatory failure caused by the cardiac function-suppressive effect and arrhythmogenic effect of this drug. In such cases, administration of this drug should be discontinued, measures to improve the cardiac function such as administration of dopamine should be taken immediately, and appropriate measures including liver supporting therapy should be taken, if necessary. In addition, such cases may be associated with renal disorder.

Hepatic dysfunction, jaundice: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), γ-GTP, etc. or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

5 Antihypertensives

Aliskiren Fumarate

Brand Name

Rasilez Tablets 150 mg (Novartis Pharma K.K.)

Adverse Reactions (clinically significant adverse reactions)	**Anaphylaxis**: Anaphylaxis (wheezing, angioedema, urticaria, etc.) may occur. Patients should be carefully monitored, and if any symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6 Thyroid and parathyroid hormone preparations

Propylthiouracil

Brand Name	THIURAGYL tablets 50 mg (Mitsubishi Tanabe Pharma Corporation), PROPACIL Tablet 50 mg (Chugai Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Anaphylaxis**: Anaphylaxis (itching, rash, face oedema, dyspnoea, etc.) 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.

7 Antimetabolites

Tegafur/Gimeracil/Oteracil Potassium

Brand Name	TS-1 combination capsule T20, T25, TS-1 combination granule T20, T25 (Taiho Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Acute renal failure, nephrotic syndrome**: Serious renal disorders such as acute renal failure or nephrotic 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. **Lacrimal duct obstruction**: Lacrimal duct obstruction leading to surgical intervention has been reported. If any symptoms such as lacrimation are observed, appropriate measures such as ophthalmologic examination should be taken.

8 Antivirals

Telaprevir

Brand Name	TELAVIC Tablets 250 mg (Mitsubishi Tanabe Pharma Corporation)
Adverse Reactions (clinically significant adverse reactions)	**Blood disorder (pancytopenia, agranulocytosis, decreased neutropils, decreased platelets, and decreased white blood cell)**: Severe cytopenia has been reported. Patient should be carefully monitored through periodic laboratory test (blood test, etc.). If severe abnormality was observed, administration of this drug should be discontinued and appropriate measures should be taken.

9 Biological preparations-Miscellaneous

Tocilizumab (Genetical Recombination)

Brand Name	ACTEMRA 80 mg for Intravenous Infusion, 200 mg for Intravenous Infusion, 400 mg for Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)
Important Precautions	The reactivation of hepatitis B virus has been reported in hepatitis B virus carriers treated with antirheumatic biologics. If this drug is administered to hepatitis B virus carriers, attention should be paid to the occurrence of signs or symptoms related to reactivation of hepatitis B virus, by monitoring results of liver function tests or hepatitis viral markers.

10

Over-the-counter drugs

Preparations containing diclofenac sodium
(dermatologic preparation)

Brand Name

EVE OUTER Gel, EVE OUTER Tape, EVE OUTER Poultice L (SSP Co. Ltd.)
Diclotect Gel, Diclotect Tape, Diclotect Tape L, Diclotect Lotion (Dojin Iyaku-kako Co., Ltd.)
Voltaren AC Tape, Voltaren AC Tape L, Voltaren AC Gel, Voltaren AC Lotion (Dojin Iyaku-kako Co., Ltd.) FeitasZFeitasZ gelFeitasZ sip(Hisamitsu Pharmaceutical Co., Inc.)

Consultation

If the following symptoms are observed after using this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician or pharmacist for a consultation.
The following serious symptoms occur in rare cases. In such cases, immediately seek medical aid.
Shock (anaphylaxis): Immediately after taking the product, itchy skin, urticaria, hoarseness, sneezing, itchy throat, difficulty in breathing, palpitations, clouding consciousness, etc. may occur.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder 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 October 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Clopidogrel Sulfate PLAVIX 25 mg Tablets, 75 mg Tablets*1	Sanofi-aventis K.K.	September 28, 2012
Tazobactam Sodium/Piperacillin Sodium ZOSYN for Intravenous Injection 2.25 ZOSYN for Intravenous Injection 4.5*2	Taiho Pharmaceutical Co., Ltd.	September 28, 2012
Pazopanib Hydrochloride Votrient Tablets 200 mg	GlaxoSmithKline K.K.	September 28, 2012
Iguratimod 1) KOLBET Tablets 25 mg 2) Careram Tablets 25 mg	1) Toyama Chemical Co., Ltd. 2) Eisai Co., Ltd.	September 12, 2012
Teneligliptin Hydrobromide Hydrate TENELIA Tablets 20 mg	Mitsubishi Tanabe Pharma Corporation	September 10, 2012
Formoterol Fumarate Hydrate Oxis 9 μg Turbuhaler 28 doses, 60 doses*3	AstraZeneca K.K.	September 3, 2012
Inactivated Poliomyelitis Vaccine (Salk Vaccine) IMOVAX POLIO subcutaneous	Sanofi Pasteur K.K.	August 31, 2012
Axitinib Inlyta Tablets 1 mg, 5 mg	Pfizer Japan Inc.	August 30, 2012
Ropinirole Hydrochloride ReQuip CR Tablets 2 mg, 8 mg	GlaxoSmithKline K.K.	August 28, 2012
Atomoxetine Hydrochloride Strattera Capsule 5 mg, 10 mg, 25 mg, 40 mg*4	Eli Lilly Japan K.K.	August 24, 2012
Sulbactam Sodium/Ampicillin Sodium UNASYN-S for Intravenous Use 0.75 g, 1.5 g, 3 g, UNASYN-S KIT for Intravenous Use 1.5 g, 3 g*5, 6	Pfizer Japan Inc.	August 10, 2012
Budesonide/Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses*7	AstraZeneca K.K.	August 10, 2012
Perflubutane SONAZOID FOR INJECTION 16 μL*8	Daiichi Sankyo Company, Limited	August 10, 2012
Sunitinib SUTENT Capsule 12.5 mg*9	Pfizer Japan Inc.	August 10, 2012

Apomorphine Hydrochloride Hydrate Apokyn subcutaneous injection 30 mg	Kyowa Hakko Kirin Co., Ltd.	July 27, 2012
Rotavirus Vaccine, Live, Oral, Pentavalent RotaTeq Oral Solution	MSD K.K.	July 20, 2012
Gabapentin Enacarbil Regnite Tablets 300 mg	Astellas Pharma. Inc.	July 10, 2012
Bixalomer Kiklin Capsules 250 mg	Astellas Pharma. Inc.	June 26, 2012
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg ZITHROMAC 250 mg*[10]	Pfizer Japan Inc.	June 22, 2012
Aprepitant EMEND Capsules 125 mg, 80 mg, EMEND Capsules Set*[11]	Ono Pharmaceutical Co., Ltd.	June 22, 2012
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg*[12]	AstraZeneca K.K.	June 22, 2012
Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg*[13]	Pfizer Japan Inc.	June 22, 2012
Lidocaine Penles Tape 18 mg*[14]	Nitto Denko Corporation	June 22, 2012
Dornase Alfa (Genetical Recombination) PULMOZYME Inhalation Solution 2.5 mg	Chugai Pharmaceutical Co., Ltd.	June 8, 2012
Rilpivirine Hydrochloride EDURANT Tablets 25 mg	Janssen Pharmaceutical K.K.	June 8, 2012
Miglustat BRAZAVES Capsule 100 mg	Actelion Pharmaceuticals Japan Ltd.	May 30, 2012
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg	Ferring Pharmaceutical Co., Ltd.	May 29, 2012
Mogamulizumab (Genetical Recombination) POTELIGEO Injection 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 29, 2012
Azilsartan AZILVA Tablets 20 mg, 40 mg	Takeda Pharmaceutical Company Limited	May 28, 2012
Oxycodone Hydrochloride Hydrate OXIFAST Injection 10 mg, 50 mg	Shionogi & Co., Ltd.	May 28, 2012
Thalidomide THALED CAPSULE 50, 100*[15]	Fujimoto Pharmaceutical Corporation	May 25, 2012
Doripenem Hydrate FINIBAX for Intravenous Infusion 0.25 g, 0.5 g, FINIBAX Kit for Intravenous Infusion 0.25 g*[16, 17]	Shionogi & Co., Ltd.	May 25, 2012
Thyrotropin Human Alfa (Genetical Recombination) THYROGEN for Intramuscular Injection 0.9 mg*[18]	Sato Pharmaceutical Co., Ltd.	May 25, 2012
Mometasone Furoate Hydrate NASONEX Nasal 50 μg 56 sprays, NASONEX Nasal 50 μg 112 sprays*[17]	MSD K.K.	May 25, 2012
Lidocaine/Propitocaine EMLA CREAM	Sato Pharmaceutical Co., Ltd.	May 14, 2012
Brimonidine Tartrate AIPHAGAN OPHTHALMIC SOLUTION 0.1%	Senju Pharmaceutical Co., Ltd.	May 11, 2012
Alendronate Sodium Hydrate Bonalon Bag for I.V. Infusion 900 μg	Teijin Pharma Limited	May 10, 2012

Caspofungin Acetate CANCIDAS for Intravenous Drip Infusion 50 mg, 70 mg	MSD K.K.	April 19, 2012
Eszopiclone Lunesta Tablets 1 mg, 2 mg, 3 mg	Eisai Co., Ltd.	April 18, 2012
Rivaroxaban Xarelto Tablets 10 mg, 15 mg	Bayer Yakuhin Ltd.	April 18, 2012
Atovaquone SAMTIREL Oral Suspension 15%	GlaxoSmithKline K.K.	April 17, 2012
Denosumab (Genetical Recombination) RANMARK SUBCUTANEOUS INJECTION 120 mg	Daiichi Sankyo Company, Limited	April 17, 2012
Crizotinib XALKORI Capsules 200 mg, 250 mg	Pfizer Japan Inc.	March 30, 2012

*1 An additional indication for “prevention of thrombus and embolus formation in patients with peripheral arterial disease”

*2 An additional indication for “treatment of patients with peritonitis, intra-abdominal abscess, cholecystitis, or cholangitis”

*3 An additional indication for “remission of various symptoms associated with airway obstructive disorder in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)”

*4 An additional indication for “treatment of patients with attention deficit/hyperactivity disorder (AD/HD) in adulthood”

*5 An additional indication for “Streptococcus pneumonia, Moraxella (Branhamella) catarrhalis”

*6 An additional administration for “severe infections”

*7 An additional indication for “remission of various symptoms in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema) (for patients who require concomitant use of inhaled corticosteroids and long acting inhaled beta-2 agonist)”

*8 An additional indication for “contrast enhanced imaging for breast mass lesion in mammary ultrasonography”

*9 An additional indication for “treatment of patients with pancreatic neuroendocrine tumour”

*10 An additional indication for “treatment of patients with pelvic inflammatory disease”

*11 An additional administration for “pediatrics (aged 12 and older)”

*12 An additional indication for “treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low-doses aspirin”

*13 An additional indication for “treatment of pain in patients with fibromyalgia”

*14 An additional indication for “relief of pain at removal of molluscum contagiosum”

*15 An additional indication for “erythema nodosum leprosum”

*16 An additional indication for “pyogenic meningitis”

*17 An additional administration for “pediatrics”

*18 An additional indication for “adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of metastatic thyroid cancer”