

Pharmaceuticals and Medical Devices Safety Information

No. 260 August 2009

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

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*This translation of the original Japanese text is for information purpose only
(in the event of inconsistency, the Japanese text shall prevail).*

Pharmaceuticals and Medical Devices Safety Information No. 260 August 2009

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	Tricyclic and tetracyclic antidepressants, associated with aggression	P C	Following a recent review of adverse reaction reports of aggression, regarding harmful behavior to others including injury, associated with tricyclic antidepressants, tetracyclic antidepressants, trazodone hydrochloride, and sulpiride, MHLW considered it necessary to call for a similar alert to that used for SSRIs and SNRIs. Thus, on July 3, 2009, MHLW required relevant companies to revise PRECAUTIONS of package inserts. Details of these safety measures are described hereinafter.	3
2	Telmisartan (and 1 other case)	P C	Presents contents of revisions and a summary of cases that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated July 3, 2009.	9
3	Lamotrigine (and 9 other cases)		Revision of PRECAUTIONS (No. 208)	17
4	Products subject to Early Post-marketing Phase Vigilance		Lists products subject to Early Post-marketing Phase Vigilance as of August 1, 2009.	21

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

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

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

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

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

Tricyclic and tetracyclic antidepressants, associated with aggression

	Active ingredient	Brand name (name of company)
Active ingredient Brand name (name of company)	Amitriptyline hydrochloride	Tryptanol Tablets 10 and 25 (Banyu Pharmaceutical Co., Ltd.), Amiplin Tablets (10 mg) (Kobayashi Kako Co., Ltd.), Normaln Tablets 10 mg and 25 mg (Sawai Pharmaceutical Co., Ltd.)
	Amoxapine	Amoxan Fine Granules 10%, Amoxan Capsules 10 mg, 25 mg, and 50 mg (Wyeth K.K.)
	Imipramine hydrochloride	Imidol Sugar-Coated Tablets (10 and 25) (Mitsubishi Tanabe Pharma Corporation), Tofranil Tablets 10 mg and 25 mg (Novartis Pharma K.K.)
	Clomipramine hydrochloride (oral)	Anafranil Tablets 10 mg and 25 mg (Alfresa Pharma Corporation)
	Clomipramine hydrochloride (injection)	Anafranil Intravenous Infusion 25 mg (Alfresa Pharma Corporation)
	Setiptiline maleate	Tecipul Tablets 1 mg (Mochida Pharmaceutical Co., Ltd.), Bisopool Tablets 1 mg (Medisa Shinyaku Inc.)
	Dosulepin hydrochloride	Prothiaden Tablets 25 (Kaken Pharmaceutical Co., Ltd.)
	Trazodone hydrochloride	Desyrel Tablets 25 and 50 (Pfizer Japan Inc.), Reslin Tablets 25 and 50 (Schering-Plough K.K.), Undepre Tablets 25 mg and 50 mg (Kyowa Pharmaceutical Industry Co., Ltd.)
	Trimipramine maleate	Surmontil Powder 10%, Surmontil Tablets 10 mg and 25 mg (Shionogi & Co., Ltd.)
	Nortriptyline hydrochloride	Noritren Tablets 10 mg and 25 mg (Dainippon Sumitomo Pharma Co., Ltd.)
	Maprotiline hydrochloride	Ludiomil Tablets 10 mg, 25 mg, and 50 mg (Novartis Pharma K.K.), Cronmolin Tablets 10 mg, 25 mg, and 50 mg (Takata Seiyaku Co., Ltd.), Neuomil Tablets 10 mg, 25 mg, and 50 mg (Kyowa Pharmaceutical Industry Co., Ltd.), Mapromil Tablets 10 mg (Kobayashi Kako Co., Ltd.)
	Mianserin hydrochloride	Tetramide Tablets 10 mg and 30 mg (Schering-Plough K.K.)
	Lofepamine hydrochloride	Amplit Tablets 10 mg and 25 mg (Daiichi Sankyo Co. Ltd.)
Therapeutic category	Psychotropics	
Indications	Amitriptyline hydrochloride Depression/depressed state in the psychiatric domain and nocturnal enuresis Amoxapine, setiptiline maleate, trazodone hydrochloride, maprotiline hydrochloride, mianserin hydrochloride, and lofepramine hydrochloride Depression/depressed state	

	<p>Imipramine hydrochloride Depression/depressed state in the psychiatric domain Enuresis (daytime or nighttime)</p> <p>Clomipramine hydrochloride (oral) Depression/depressed state in the psychiatric domain Enuresis</p> <p>Clomipramine hydrochloride (injection), trimipramine maleate Depression/depressed state in the psychiatric domain</p> <p>Dosulepin hydrochloride Depression and depressed state</p> <p>Nortriptyline hydrochloride Depression and depressed state in the psychiatric domain (endogenous depression, reactive depression, involuntal depression, neurotic depressed state, or depressed state of brain organic mental disorder)</p>
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1. Introduction

Following a recent review of adverse reaction reports of aggression, regarding harmful behavior to others including injury associated with selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), MHLW confirmed the necessity of alerting patients, their families and caregivers to pay due attention to changes in the patient's condition during the course of treatment. In line with this, on May 8, 2009 MHLW required relevant companies to revise PRECAUTIONS in package inserts. (See "Pharmaceuticals and Medical Devices Safety Information No. 258, June 2009".)

The antidepressants approved in Japan other than SSRIs and SNRIs include the following 13 active ingredients: tricyclic antidepressants (amitriptyline hydrochloride, amoxapine, imipramine hydrochloride, clomipramine hydrochloride [oral and injection], dosulepin hydrochloride, trimipramine maleate, nortriptyline hydrochloride, and lofepramine hydrochloride), tetracyclic antidepressants (setipiline maleate, maprotiline hydrochloride, and mianserin hydrochloride), trazodone hydrochloride, and sulpiride. MHLW recently reviewed adverse reaction reports of aggression, regarding harmful behavior to others including injury, associated with antidepressants containing any of these 13 ingredients to consider the necessity of calling for a similar alert to that for SSRIs and SNRIs, and concluded that such needed to be issued for the 12 ingredients except for sulpiride. On July 3, 2009, MHLW required marketing authorization holders (MAHs) to revise PRECAUTIONS in package inserts. Details of these safety measures, etc. are described hereinafter.

2. Reported adverse reactions including hostility/aggression and details of safety measures

The table below summarizes the number of adverse reaction reports regarding hostility/aggression (MedDRA/J) associated with tricyclic antidepressants, tetracyclic antidepressants, trazodone hydrochloride, or sulphiride between the day of launch of the respective products and May 15, 2009. And harmful behavior to others including injury among those reports are also showed.

	Hostility/Aggression, etc. (cases)	Among Hostility/Aggression cases, harmful behavior to others including injury or episodes that could have potentially resulted in harmful behavior to others including injury identified from the clinical course (episodes for which causality with the drug could not be denied) (cases)
Amitriptyline hydrochloride	5	0 (0)
Amoxapine	3	0 (0)
Imipramine hydrochloride	15	0 (0)
Clomipramine hydrochloride (oral and injectable)	29	7* (1)
Dosulepin hydrochloride	6	1 (0)
Trimipramine maleate	0	0 (0)
Nortriptyline hydrochloride	0	0 (0)
Lofepramine hydrochloride	0	0 (0)
Setiptiline maleate	5	2 (1)
Maprotiline hydrochloride	10	1 (0)
Mianserin hydrochloride	14	0 (0)
Trazodone hydrochloride	18	1 (1)
Sulpiride	9	1** (0)

*Two of these cases involved harmful behavior to others including injury, identified from the clinical course.

**Involved harmful behavior to others including injury, identified from the clinical course.

After a careful review of the 13 cases of harmful behavior to others including injury and potential episodes that could have resulted in harmful behavior to others including injury identified from the clinical course, causality between the drug and harmful behavior to others could not be denied in the reported adverse reaction cases (one case for each drug) associated with clomipramine hydrochloride, setiptiline maleate, and trazodone hydrochloride. For the remaining 10 cases of adverse reactions, causality between the drug and harmful behavior to others was considered unknown or it was evaluated that the SSRIs administered concomitantly had a greater effect.

In the most of reported adverse reactions reviewed for a causal relationship, including those for which causality could not be denied, it was suspected that patients with comorbid disorders such as a depressed state of manic depressive psychosis or schizophrenia when prescribed antidepressants developed excitement, aggression or irritability, or exacerbated comorbid disorders, which resulted in harmful behavior to others. It was admitted that these findings were similar to those seen with SSRIs or SNRIs.

Given these findings and the review by specialists, tricyclic antidepressants, tetracyclic antidepressants, and trazodone hydrochloride, including active ingredients for which adverse reactions such as “hostility/aggression” have not been reported to date, appear to exert an antidepressive effect in a similar pharmacological manner. For this reason, it was regarded as necessary to revise PRECAUTIONS and call for an alert, as done for SSRIs and SNRIs. However, although sulphiride-related adverse reactions such as “hostility/aggression” regarding harmful behavior including injury have been reported, those reactions appeared to be due mainly to the effect of SSRIs administered concomitantly. It was therefore considered appropriate to pay close attention to further adverse reaction reports without additional calling for an alert at this time.

The results of the recent careful review of reported adverse reactions of aggression associated with antidepressants highlighted not only the necessity of calling for an alert regarding aggression to be included in the PRECAUTIONS but also the importance of providing medical practice, patients, and their families with appropriate information when antidepressants are prescribed. The “Committee on Appropriate Use of Antidepressants” (Chairman: Teruhiko Higuchi, President, National Center of Neurology and Psychiatry) established by the Japanese Society of Mood Disorders published “Appropriate Use of Antidepressants—A Message to Patients with Depression and Their Families” (<http://www.secretariat.ne.jp/jsmd/img/tsukaikata.pdf>) on June 16, 2009. In cooperation with the committee, MHLW will continue deliberations on the appropriate and effective provision of information for the appropriate use of antidepressants.

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

Amitriptyline hydrochloride

Amoxapine

Imipramine hydrochloride

Clomipramine hydrochloride (oral)

Setiptiline maleate

Dosulepin hydrochloride

Trazodone hydrochloride

Trimipramine maleate

Nortriptyline hydrochloride

Maprotiline hydrochloride

Mianserin hydrochloride

Lofepamine hydrochloride

[Careful Administration] Patients with highly impulsive comorbid disorders
Patients with a medical history of suicidal ideation or suicide attempts, and patients with suicidal ideation

[Important Precautions] Patients with depressive symptoms have suicidal ideation and may attempt suicide. Such patients should be carefully monitored for changes in their clinical condition during early periods of drug therapy or at times of dose changes.
Episodes of anxiety, irritation, excitement, panic attack, insomnia, irritability, hostility, aggression, impulsivity, akathisia/psychomotor restlessness, hypomania and mania have been reported. In patients with these symptoms or behavior, exacerbation of underlying disease, suicidal ideation, suicide attempts, and harmful behavior to others have been reported, though causality with the drug is unknown. Patients should be monitored carefully for changes in their clinical condition, and if exacerbation of any of these symptoms is observed, drug dose should not be increased, and appropriate measures should be taken such as discontinuation of the drug after gradual dose reduction.
Patients’ families should be given full information on the risk of suicidal ideation, suicide attempts, changes in behavior such as excitement, aggression, irritability, etc., and exacerbation of underlying disease, and be instructed to keep in close contact with the physician.

Clomipramine Hydrochloride (injectable dosage form)

[Careful Administration] Patients with highly impulsive comorbid disorders
Patients with a medical history of suicidal ideation or suicide attempts, and patients with suicidal ideation

[Important Precautions] Patients with depressive symptoms have suicidal ideation and may attempt suicide. Such patients should be carefully monitored for changes in their clinical condition during early periods of drug therapy or at times of dose changes.
Episodes of anxiety, irritation, excitement, panic attack, insomnia, irritability, hostility, aggression, impulsivity, akathisia/psychomotor restlessness, hypomania and mania have been reported. In patients with these symptoms or behavior, exacerbation of underlying disease, suicidal ideation, suicide attempts, and harmful behavior to others have been reported, though causality with the drug is unknown. Patients should be monitored carefully for changes in their clinical condition, and if exacerbation of any of these symptoms is observed, drug dose should not be increased, and appropriate measures should be taken such as discontinuation of the drug after gradual dose reduction.
Patients' families should be given full information on the risk of suicidal ideation, suicide attempts, changes in behavior such as excitement, aggression, irritability, etc., and exacerbation of underlying disease, and be instructed to keep in close contact with the physician.

Case Summary

< Clomipramine hydrochloride (oral dosage form) > [Tricyclic antidepressant]

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 20s	Obsessive-compulsive disorder (Affective disorder)	20 mg for 13 days ↓ 40 mg for 12 days	<p>Hostility, irritability, impulsivity, insomnia</p> <p>8 years before administration: From about this time, the patient gradually developed obsessive symptoms such as turning lights off in a specific order and checking whether a clothes tag was sticking out or not a pre-determined number of times, such as three or seven times. Molysmophobia also occurred.</p> <p>On day 1 of administration: Administration of the drug was initiated at 20 mg to treat obsessive-compulsive disorder.</p> <p>On day 14 of administration: The dose of the drug was increased to 40 mg. Administration of 2 mg of ethyl loflazepate was initiated.</p> <p>On day 16 of administration: The patient showed irritability and impulsivity such as breaking a wall, desk, and bed, and started to have hostile feelings toward others. Sleep duration decreased to about 1 hour.</p> <p>On day 25 of administration (day of discontinuation): Clomipramine hydrochloride was discontinued.</p> <p>3 days after discontinuation: The patient was admitted to the hospital. Administration of 400 mg of sodium valproate was initiated to treat emotional instability.</p> <p>4 days after discontinuation: The patient recovered.</p>
Concomitant medications: ethyl loflazepate				

<Setiptiline maleate> [Tetracyclic antidepressant]

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 40s	Hypobulia (Schizophrenia, chronic hepatitis)	3 mg for 14 days ↓ 6 mg for 42 days ↓ 3 mg Continued	<p>Excitation, impulsive behavior, feeling irritated</p> <p>14 years before administration: The patient developed schizophrenia.</p> <p>On day 1 of administration: Administration of the drug was initiated at 3 mg to treat hypobulia.</p> <p>On day 15 of administration: The drug dosage was increased to 6 mg.</p> <p>On day 53 of administration: Excitation, impulsive behavior (breaking window panes and shouting), and feeling irritated developed.</p> <p>On day 57 of administration: The drug dosage was reduced to 3 mg and the patient was followed up.</p> <p>On day 84 of administration: Irrascibility, feeling irritated, and excitation disappeared.</p>
Concomitant medications: nemonapride, sultopride hydrochloride, sho-saiko-to (xiao chai hu tang) [Kampo Medicine]				

<Trazodone hydrochloride>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 40s	Bipolar depression (insomnia)	75 mg for 13 days	<p>Change to manic state</p> <p>On day 1 of administration: Administration of the drug was initiated at 75 mg.</p> <p>On day 13 of administration (day of discontinuation): Hyperthimic and excitation / aggression toward other patients, nursing staff and his family were noted. Based on these symptoms as well as the patient displaying signs of a flight of ideas, the patient was considered to have changed to manic state. This drug and concomitant drugs were discontinued.</p> <p>Administration of zotepine and lithium carbonate was initiated.</p> <p>150 days after discontinuation: The patient recovered.</p>
Concomitant medications: sulpiride, ethyl loflazepate, zopiclone, flunitrazepam				

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Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated July 3, 2009.

1 Telmisartan

Brand Name (name of company)	Micardis Tablets 20 mg and 40 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic Category	Antihypertensives
Indications	Hypertension

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

**[Adverse Reactions
(clinically significant
adverse reactions)]**

Interstitial pneumonia: Interstitial pneumonia associated with pyrexia, cough, dyspnea, or abnormal chest X-ray may occur. In such cases, administration should be discontinued and appropriate measures, such as administration of corticosteroids, should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2006 to June 16, 2009) (events for which a causality to the drug could not be denied):

- Interstitial pneumonia: 7 cases (of which 1 had a fatal case)

The number of patients treated with Telmisartan for a year estimated by MAH: approximately 1.68 million patients (May 2008 to April 2009)

Marketed in Japan in: January 2005 (Micardis Tablets)

*December 2002 to March 2006 (Micardis Capsules)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Hypertension (Diabetes, ischemic heart disease, urinary retention, diabetic nephropathy, diabetic peripheral neuropathy, and anorexia)	40 mg for 8 days	<p>Interstitial pneumonia</p> <p>4 days before administration: The patient was examined for diabetes for the first time, and found to have pronounced diabetes.</p> <p>2 days before administration: The patient came back to the hospital with urinary retention. Administration of distigmine bromide and tamsulosin hydrochloride was initiated. He was hospitalized for the control and treatment of diabetes. Diabetic nephropathy and peripheral neuropathy were found.</p> <p>On day 1 of administration: The patient was found to have hypertension as well, and administration of the drug was initiated at 40 mg. Administration of mosapride citrate hydrate and mecobalamin was initiated to treat anorexia.</p> <p>On day 5 of administration: Body temperature was 37.4°C, with pyrexia. Pyrexia persisted. Cefdinir and acetaminophen were administered to treat upper respiratory inflammation. No improvement.</p> <p>On day 8 of administration (day of discontinuation): Body temperature was 38.4°C. Chest X-ray showed ground glass opacity in both lungs, and chest CT showed signs of interstitial pneumonia. Administration of piperacillin sodium was initiated at 2g. This drug, as well as distigmine bromide, tamsulosin hydrochloride, mosapride citrate hydrate, and mecobalamin were discontinued. Steroid pulse therapy with methylprednisolone sodium succinate 500 mg was performed (for 3 days).</p> <p>1 day after discontinuation: Oxygen saturation (SaO₂) dropped to 92% and oxygen supply was initiated. The oxygen flow rate was then increased. A drip infusion of pazufloxacin mesilate was initiated. Piperacillin sodium was discontinued.</p> <p>2 days after discontinuation: SaO₂ further declined to 72%. Endotracheal intubation was performed and a ventilator was attached. Administration of sivelestat sodium hydrate was initiated.</p> <p>3 days after discontinuation: Inspired oxygen concentration (FiO₂) was 0.6 and SaO₂ was 95%. Administration of 20 mg of prednisolone was initiated.</p> <p>5 days after discontinuation: Blood pressure dropped suddenly. The patient had an acute myocardial infarction (MI) and was transferred to another hospital by ambulance. The patient underwent CHDF and CABG there, and recovered from the acute MI. He was later readmitted to the first hospital for rehabilitation.</p> <p>66 days after discontinuation: The patient recovered from the interstitial pneumonia.</p>
Concomitant medications: distigmine bromide, tamsulosin hydrochloride, mosapride citrate hydrate, and mecobalamin				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Hypertension (None)	40 mg for 20 days	<p>Interstitial pneumonia</p> <p>Approx. 5 years before administration: Administration of mefruside, amlodipine besylate, and enalapril maleate was initiated.</p> <p>4 days before administration: A slight pyrexia was noted.</p> <p>1 day before administration: The patient had a cough, throat pain, and a runny nose. It was suspected that Enalapril maleate was responsible for cough and thus it was discontinued.</p> <p>On day 1 of administration: Administration of this drug was initiated at 40 mg.</p> <p>On day 3 of administration: Cold-like symptoms remitted.</p> <p>On day 6 of administration: Dry cough developed.</p> <p>On day 20 of administration (day of discontinuation): The patient was hospitalized due to pyrexia, dyspnea, and interstitial pneumonia (ground glass opacity in both lungs) confirmed on chest CT. Methylprednisolone sodium succinate 125 mg was administered. Pneumocystis pneumonia was suspected and administration of sulfamethoxazole/trimethoprim was initiated. This drug and amlodipine besylate were discontinued because the pneumonia may have been associated with either of them. Administration of sulbactam sodium/cefoperazone sodium was initiated.</p> <p>1 day after discontinuation: Interstitial pneumonia worsened and the first course of steroid pulse therapy was carried out (methylprednisolone sodium succinate 1 g was administered for 3 days). Administration of sivelestat sodium hydrate was initiated. Medication was switched from sulbactam sodium/cefoperazone sodium to meropenem hydrate and minocycline hydrochloride. β-D glucan 9.6 pg/mL, cytomegalovirus antigen (C7-HRP) was negative. Sputum tested negative for Pneumocystis jiroveci by DNA-PCR. Antinuclear antibody negative, rheumatoid factor negative, MPO-ANCA negative, PR3-ANCA 19. DLST showed a stimulation index (S.I.) of 306%, positive for this drug and 107%, negative for amlodipine besylate.</p> <p>2 days after discontinuation: Administration of dry sulfonated human immunoglobulin was initiated (administered for 4 days). The patient's respiratory status worsened and an NPPV was attached.</p> <p>4 days after discontinuation: Administration of methylprednisolone sodium succinate 80 mg was initiated.</p> <p>5 days after discontinuation: Administration of gabexate mesilate was initiated, to treat pre-DIC.</p> <p>7 days after discontinuation: Pulse administration of cyclophosphamide 800 mg was conducted.</p> <p>8 days after discontinuation: Chest CT showed exacerbation of bilateral ground glass opacity.</p>

				<p>The second course of steroid pulse therapy was carried out (methylprednisolone sodium succinate 1 g was administered for 3 days).</p> <p>9 days after discontinuation: Medication was switched from meropenem hydrate to tazobactam sodium/piperacillin sodium. Minocycline hydrochloride was discontinued. Endotracheal intubation was performed to treat poor respiratory status and mechanically- assisted respiratory management was initiated. PaO₂ was 68.3 mmHg and SaO₂ was 93.8%, under FiO₂ 100%. Blood pressure dropped and administration of dopamine hydrochloride was initiated.</p> <p>11 days after discontinuation: The methylprednisolone sodium succinate dose was changed to 80 mg.</p> <p>21 days after discontinuation: Methicillin-resistant <i>S. epidermidis</i> was detected in the sputum. Administration of teicoplanin was initiated.</p> <p>24 days after discontinuation: Medication was switched from tazobactam sodium/piperacillin sodium to panipenem/betamipron. The methylprednisolone sodium succinate dose was changed to 40 mg.</p> <p>29 days after discontinuation: Administration of micafungin sodium 100 mg was initiated to prevent fungal infection.</p> <p>34 days after discontinuation: Medication was switched from teicoplanin to vancomycin hydrochloride.</p> <p>36 days after discontinuation: SaO₂ remained in the 70-80% range, under FiO₂ 100%.</p> <p>37 days after discontinuation: Respiratory failure progressed and the patient died.</p>
Concomitant medications: mefruside, amlodipine besylate, enalapril maleate, and tipepidine hibenazate				

Clinical Laboratory Values

	On day 20 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	4 days after discontinuation	5 days after discontinuation	21 days after discontinuation	26 days after discontinuation
LDH (IU/L)	386	416	484	622	697	503	480
KL-6 (U/mL)	—	1810	—	—	—	—	4160
SP-D (ng/mL)	—	342	—	—	—	—	372
CRP (mg/dL)	12.16	—	8.64	—	—	—	—

Phenytoin, Phenytoin/Phenobarbital, Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate, Phenytoin Sodium

Brand Name (name of company)	Phenytoin Aleviatin Powder 10%, Aleviatin Tablets 25 mg and 100 mg (Dainippon Sumitomo Pharma Co., Ltd.) Hydantol Powder 10%, Hydantol Tablets 25 mg and 100 mg (Fujinaga Pharm Co., Ltd.) Phenytoin Powder 10% “Kyowa Iryo” (Kyowa Iryo Kaihatsu Co., Ltd.) Phenytoin/Phenobarbital Aleviatin with Phenobarbital Tablets (Dainippon Sumitomo Pharma Co., Ltd.) Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate Hydantol D, E, and F (Fujinaga Pharm Co., Ltd.) Phenytoin Sodium Aleviatin Injection 250 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Antiepileptics
Indications	Phenytoin, Phenytoin/Phenobarbital, Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate Convulsive epileptic seizures Tonic-clonic seizures (generalized convulsive seizures and grand mal) Focal convulsion (including Jacksonian seizure) Autonomic seizures Psychomotor seizures Phenytoin Sodium 1. Prolonged epileptiform convulsive seizures (status epilepticus) 2. Oral administration is not possible and it is suspected that there is a high probability of a convulsive seizure occurring (particularly in cases of impaired consciousness, and in preoperative, and postoperative cases) 3. Immediate control of epileptiform convulsive seizures is required.

《PRECAUTIONS (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored, and if myalgia, feelings of weakness, elevated CK (CPK), increased blood myoglobin, or increased urine myoglobin are observed, administration should be discontinued and appropriate measures should be taken. Due attention should be paid to the development of acute renal failure associated with rhabdomyolysis.

Acute renal failure, interstitial nephritis: Acute renal failure or interstitial nephritis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2006 to May 25, 2009) (events for which a causality to the drug could not be denied):

- Rhabdomyolysis: 2 cases (no fatal case)

The number of patients treated with these drugs for a year, estimated by MAH: approximately 220,000 (April 2008 to March 2009)

Marketed in Japan in: October 1940 (phenytoin)

December 1953 (phenytoin/phenobarbital)

August 1959 (phenytoin/phenobarbital/caffeine and sodium benzoate)

July 1963 (phenytoin sodium)

Case Summary

< Phenytoin (oral dosage form) and phenytoin sodium (injectable dosage form)>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 40s	Traumatic convulsion (None)	Injection 500 mg for 2 days Oral 250 mg for 3 day	<p>Rhabdomyolysis</p> <p>On day 1 of administration: The patient seen due to a convulsive seizure, was admitted to the hospital, and intravenously received 500 mg of phenytoin sodium. He had no noteworthy past history, and this was his first convulsive seizure.</p> <p>On day 2 of administration: Administration of intravenous phenytoin sodium 500 mg and oral phenytoin 250 mg was initiated. The patient was discharged from the hospital</p> <p>On day 4 of administration: Administration of oral phenytoin 250 mg was continued. The patient had myalgia.</p> <p>On day 5 of administration (day of discontinuation): The patient had an elevated CK value at an outpatient examination, and was diagnosed with rhabdomyolysis (onset of rhabdomyolysis). Mild muscle tenderness was noted. Phenytoin were discontinued and a transfusion was performed (over 2 days).</p> <p>4 days after discontinuation: CK values decreased and the patient was discharged (rhabdomyolysis remitted).</p>
Concomitant medications: none				

Clinical Laboratory Values

	On day 1 of administration	On day 2 of administration	On day 5 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	4 days after discontinuation
WBC (/mm ³)	10900	5700	3430	3920	3260	4260
CRP (mg/dL)	0.2	1.7	1.8	1.2	0.7	0.4
AST (GOT) (IU/L)	31	42	273	229	147	77
ALT (GPT) (IU/L)	41	30	105	171	171	151
LDH (IU/L)	248	247	1354	425	231	178
CK (CPK) (IU/L)	419	2523	52900	20630	9780	3195
BUN (mg/dL)	12	10	6	6	6	10
Serum creatinine (mg/dL)	1.44	1.30	1.16	1.14	1.14	1.21
Urine myoglobin (ng/mL)	—	—	560	—	—	180

< Phenytoin (oral dosage form) and phenytoin sodium (injectable dosage form)>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 20s	Symptomatic epilepsy (adrenoleukody strophy)	Injection 500 mg for 10 days Oral 600 mg for 9 days	<p>Rhabdomyolysis</p> <p>Before administration: The patient was receiving treatment for adrenoleukodystrophy as an outpatient when aspiration pneumonia developed. He was hospitalized and treated with antibiotics, and the symptoms improved. During hospitalization, a petit mal convulsion occurred and antiepileptics were partly added.</p> <p>1 day before administration: Status epilepticus was noted.</p> <p>On day 1 of administration: Intravenous administration of phenytoin sodium 500 mg was initiated.</p> <p>On day 2 of administration: Administration of oral phenytoin 600 mg was initiated. The sodium valproate dose was increased.</p> <p>On day 4 of administration: Blood tests showed a slight elevation of CK (319 IU/L) (onset of rhabdomyolysis)</p> <p>On day 6 of administration: The patient had a pyrexia.</p> <p>On day 7 of administration: Aspiration pneumonia relapsed. Administration of sulbactam sodium/ampicillin sodium 6 g was initiated (administered for 12 days).</p> <p>On day 8 of administration: CK values further elevated. Fluid replacement was increased to facilitate excretion.</p> <p>On day 9 of administration: Intravenous administration of dantrolene sodium hydrate was initiated to treat possible malignant syndrome.</p> <p>On day 10 of administration (day of discontinuation): CK values exceeded 10,000 IU/L. Oral phenytoin and phenytoin sodium injection were discontinued.</p> <p>1 day after discontinuation: CK values peaked out and fell to the 9,000-10,000 IU/L range. Fluid replacement was continued. Administration of clobazam 10 mg was initiated.</p> <p>13 days after discontinuation: CK values gradually decreased to 328 IU/L. Fluid replacement for high CK levels was discontinued.</p> <p>26 days after discontinuation: Follow-up blood tests confirmed normal CK values (recovery from rhabdomyolysis). Antiepileptic medication was switched to sodium valproate, clobazam, and carbamazepine, which can control the disease</p> <p>41 days after discontinuation: The patient was discharged from the hospital.</p>
Concomitant medications: carbamazepine, sodium valproate				

Clinical Laboratory Values

	On day 1 of administration	On day 4 of administration	On day 7 of administration	On day 8 of administration	On day 9 of administration	On day 10 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	5 days after discontinuation	9 days after discontinuation	13 days after discontinuation	26 days after discontinuation
WBC (/mm ³)	7000	6400	11800	8900	—	9100	—	9500	10900	8200	9200	6900
AST (GOT) (IU/L)	17	—	48	—	212	224	—	111	35	35	29	19
ALT (GPT) (IU/L)	13	—	22	—	74	87	—	72	37	28	25	13
LDH (IU/L)	190	—	416	—	470	533	—	380	268	246	269	195
γ-GPT (IU/L)	—	—	82	—	51	58	—	59	114	141	116	66
CK (CPK) (IU/L)	186	319	1244	6105	9175	11180	9271	4418	846	655	328	200
Serum creatinine (mg/dL)	0.32	—	1.04	—	0.31	0.35	—	0.36	0.32	0.31	0.34	0.35
BUN (mg/dL)	4.5	—	29.1	—	4.5	2.4	—	1.8	1.5	8.5	6.6	5.8
Na (mEq/L)	139	136	147	140	137	139	—	139	145	142	139	139
K (mEq/L)	3.9	4.3	4.0	3.4	3.4	3.7	—	4.0	3.8	4.1	4.4	4.6
Cl (mEq/L)	100	95	104	101	104	103	—	103	103	107	101	98
CRP (mg/dL)	0.29	1.00	10.07	19.17	—	9.43	—	12.93	6.26	1.42	0.46	0.81

Revision of PRECAUTIONS

(No. 208)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated July 3, 2009 (excluding those presented in “1. Tricyclic, tetracyclic antidepressants, etc. and aggression” and “2. Important Safety Information” of this Bulletin).

1 <Antiepileptics> Lamotrigine

[Brand Name] Lamictal Tablets 2 mg for Children, 5 mg for Children, 25 mg, and 100 mg (GlaxoSmithKline K.K.)

[Other Precautions] A review of 199 overseas placebo-controlled clinical studies of antiepileptics including this drug in patients with epilepsy, psychiatric disorders, etc. indicated that the risk of suicidal ideation and suicide attempts in patients receiving antiepileptics was double that in those receiving placebo (0.43% vs. 0.24%) and the number of patients receiving antiepileptics who were at risk of suicidal ideation or a suicide attempt was calculated to be higher by 1.9 per 1,000 patients than that of those receiving placebo (95% confidence interval: 0.6-3.9). Further, the number of patients with epilepsy who had such risk was calculated to be higher by 2.4 per 1,000 patients than that of those receiving placebo.

2 <Antiepileptics> Topiramate, Sodium Valproate

[Brand Name] Topina Tablets 50 mg and 100 mg (Kyowa Hakko Kirin Co., Ltd.)
Selenica-R Granules 40%, Selenica-R Tablets 200 mg and 400 mg (Kowa Co., Ltd.),
Depakene Fine Granules 20% and 40%, Depakene Tablets 100 and 200, Depakene-R
Tablets 100 and 200, Depakene Syrup 5% (Kyowa Hakko Kirin Co., Ltd.) and others

[Other Precautions] A review of 199 overseas placebo-controlled clinical studies of antiepileptics including this drug in patients with epilepsy, psychiatric disorders, etc. indicated that the risk of suicidal ideation and suicide attempts in patients receiving antiepileptics was doubled that in those receiving placebo (0.43% vs. 0.24%) and the number of patients receiving antiepileptics who were at a risk of suicidal ideation or a suicide attempt was calculated to be higher by 1.9 per 1,000 patients than that of those receiving placebo (95% confidence interval: 0.6-3.9). Further, the number of patients with epilepsy who had such risk was calculated to be higher by 2.4 per 1,000 patients than that of those receiving placebo.

<Antiepileptics> 3 Gabapentin, Carbamazepine, Zonisamide (preparations with the indication for epilepsy)

[Brand Name] Gabapen Tablets 200 mg, 300 mg, and 400 mg (Pfizer Japan Inc.)

Tegretol Fine Granules 50%, Tegretol Tablets 100 mg and 200 mg (Novartis Pharma K.K.) and others
Excegran Powder 20%, Excegran Tablets 100 mg (Dainippon Sumitomo Pharma Co., Ltd.)

[Other Precautions] A review of 199 overseas placebo-controlled clinical studies of antiepileptics including this drug in patients with epilepsy, psychiatric disorder, etc. indicated that the risk of suicidal ideation and suicide attempts in patients receiving antiepileptics was double that in those receiving placebo (0.43% vs. 0.24%), and the number of patients receiving antiepileptics who were at risk of suicidal ideation or a suicide attempt was calculated to be higher by 1.9 per 1,000 patients than that of those receiving placebo (95% confidence interval: 0.6-3.9). Further, the number of patients with epilepsy who had such risk was calculated to be higher by 2.4 per 1,000 patients than that of those receiving placebo.

<Hypnotic and sedatives, anxiolytics, antiepileptics, kampo medicines>

4 Potassium Bromide, Calcium Bromide, Sodium Bromide, Acetylpheneturide, Ethosuximide, Ethotoin, Sulthiame, Trimethadione, Saiko-ka-ryukotsu-borei-to (Chai hu jia long gu mu li tang) [Kampo medicine] (Preparations with the indication for epilepsy)

[Brand Name] Potassium Bromide “Yamazen” (Yamazen Corporation)
Brocal Injection 2% (Otsuka Pharmaceutical Co., Ltd.)
Sodium Bromide “Yamazen” (Yamazen Corporation)
Powdered Crampol and Crampol Tablets 200 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Epileo petit mal 50% (Eisai Co., Ltd.), Zarontin Syrup 5% (Daiichi Sankyo Co., Ltd.)
Powdered Accenon (Dainippon Sumitomo Pharma Co., Ltd.)
Ospolot Tablets 50 mg and 200 mg (Kyowa Pharmaceutical Industry)
Minoale Powder 66.7% (Dainippon Sumitomo Pharma Co., Ltd.)
Tsumura Saiko-ka-ryukotsu-borei-to Extract Granules (for prescription) (Tsumura & Co.) and others

[Other Precautions] A review of 199 overseas placebo-controlled clinical studies of antiepileptics in patients with epilepsy, psychiatric disorder, etc. indicated that the risk of suicidal ideation and suicide attempt in patients receiving antiepileptics was double that in those receiving placebo (0.43% vs. 0.24%) and the number of patients receiving antiepileptics who were at risk of suicidal ideation or suicide attempt was calculated to be higher by 1.9 per 1,000 patients than that of those receiving placebo (95% confidence interval: 0.6-3.9). The number of patients with epilepsy who had such risk was calculated to be higher by 2.4 per 1,000 patients than that of those receiving placebo.

<Hypnotics and sedatives, anxiolytics, antiepileptics, diuretics>

5 Nitrazepam, Phenobarbital, Phenobarbital Sodium (subcutaneous/intramuscular injection), Clonazepam, Clobazam, Phenytoin, Phenytoin/Phenobarbital, Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate, Phenytoin Sodium, Primidone, Acetazolamide, Acetazolamide Sodium

[Brand Name] Nelbon Powder 1%, Nelbon Tablets 5 mg and 10 mg (Daiichi Sankyo Co., Ltd.), Benzalin Fine Granules 1%, Benzalin Tablets 2, 5, and 10 (Shionogi & Co., Ltd.) and others
Powdered Phenobal, Phenobal Powder 10%, Phenobal Tablets 30 mg, Phenobal Elixir 0.4%, Phenobal Injection 100 mg (Fujinaga Pharm Co., Ltd.) and others
10% Phenobarbital Injection “Nobel” (Nobelpharma Co., Ltd.)
Landsen Fine Granules 0.1% and 0.5%, Landsen Tablets 0.5 mg, 1 mg, and 2 mg (Dainippon Sumitomo Pharma Co., Ltd.), Rivotril Fine Granules 0.1% and 0.5%, Rivotril Tablets 0.5 mg, 1 mg, and 2 mg (Chugai Pharmaceutical Co., Ltd.)
Mystan Fine Granules 1%, Mystan Tablets 5 mg and 10 mg (Dainippon Sumitomo

Pharma Co., Ltd.)
Aleviatin Powder 10%, Aleviatin Tablets 25 mg and 100 mg (Dainippon Sumitomo Pharma Co., Ltd.), Hydantol Powder 10%, Hydantol Tablets 25 mg and 100 mg (Fujinaga Pharm Co., Ltd.), Phenytoin Powder 10% “Kyowa Iryo” (Kyowa Iryo Kaihatsu Co., Ltd.)
Aleviatin with Phenobarbital Tablets (Dainippon Sumitomo Pharma Co., Ltd.)
Hydantol D, E, and F (Fujinaga Pharm Co., Ltd.)
Aleviatin Injection 250 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Primidone fine granules 99.5%, Primidone Tablets 250 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Powdered Diamox, Diamox Tablets 250 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
Diamox Injection 500 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)

[Other Precautions] A review of 199 overseas placebo-controlled clinical studies of antiepileptics in patients with epilepsy, psychiatric disorder, etc. indicated that the risk of suicidal ideation and suicide attempt in patients receiving antiepileptics was double that in those receiving placebo (0.43% vs. 0.24%) and the number of patients receiving antiepileptics who were at risk of suicidal ideation or suicide attempt was calculated to be higher by 1.9 per 1,000 patients than that of those receiving placebo (95% confidence interval: 0.6-3.9). The number of patients with epilepsy who had such risk was calculated to be higher by 2.4 per 1,000 patients than that of those receiving placebo.

6 < Ophthalmic agents >

6 Tosufloxacin Tosilate Hydrate (ophthalmic solution)

[Brand Name] OZEX ophthalmic solution 0.3% (Toyama Chemical Co.,Ltd.),
TOSUFLO Ophthalmic Solution 0.3% (Nidek Co.,Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored and if symptoms such as erythema rash, dyspnoea, decreased blood pressure, or eyelid oedema are observed, administration of this drug should be discontinued and appropriate measures should be taken.

7 <Antihypertensives >

7 Azelnidipine

[Brand Name] CALBLOCK TABLETS 8 mg, 16mg (Daiichi Sankyo Company, Limited.)

[Adverse Reactions (clinically significant adverse reactions)] **Atrioventricular block, sinus arrest, bradycardia:** Atrioventricular block, sinus arrest or bradycardia may occur. If abnormalities such as dizziness or light-headed feeling are observed, administration of this drug should be discontinued and appropriate measures should be taken.

8 <Contraceptives>

8 Levonorgestrel

[Brand Name] Mirena 52 mg (Bayer Yakuhin, Ltd.)

[Important Precautions] Precautions on removal:
Check of the profile of the outside of this product after removal
Accidents have been reported wherein the cylindrical part of the product was came off and wrapped itself around the horizontal arm, and other cases have also been reported where the cylindrical part was left behind when the product was removed from the uterus. After removal, the product should be checked for any abnormalities or defects of its outside.

9 <Anticoagulants>
Dalteparin Sodium

[Brand Name] Fragmin IV 5000 (Pfizer Japan Inc.) and others

[Relative Contraindications] Patients with a history of hypersensitivity to any of the ingredients of this product, heparin, or other low-molecular-weight heparins

10 <Synthetic antibacterials>
Moxifloxacin Hydrochloride (oral dosage form)

[Brand Name] Avelox Tablets 400 mg (Bayer Yakuhin, Ltd.)

[Careful Administration] Patients with myasthenia gravis (Symptoms may be exacerbated.)

[Adverse Reactions (clinically significant adverse reactions)] **Oculomucocutaneous syndrome (Steven-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome):** Oculomucocutaneous syndrome (Steven-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures 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 should be discontinued and appropriate measures should be taken.

4

List of products subject to Early Post-marketing Phase Vigilance

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

(As of August 1, 2009)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Dasatinib Hydrate ----- SPRYCEL Tablets 20 mg and 50 mg	Bristol Myers K.K.	February 2, 2009
Estradiol-Norethisterone Acetate ----- MENOAID COMBIPATCH	ASKA Pharmaceutical Co., Ltd.	February 5, 2009
Thalidomide ----- THALED capsule 100	Fujimoto Pharmaceutical Corporation	February 6, 2009
Nilotinib Hydrochloride Hydrate ----- TASIGNA Capsules 200 mg	Novartis Pharma K.K.	February 16, 2009
Estradiol-Levonorgestrel ----- Wellnara	Bayer Yakuhin, Ltd.	February 17, 2009
Botulinum toxin type A ----- BOTOX Vista Injection 50 Units	GlaxoSmithKline K.K.	February 23, 2009
Enoxaparin Sodium ----- Clexane for Subcutaneous Injection Kit 2000 IU *3	Sanofi-Aventis K.K.	February 23, 2009
Lanthanum Carbonate Hydrate ----- Fosrenol Chewable Tablets 250mg and 500mg	Bayer Yakuhin, Ltd.	March 11, 2009
Omalizumab (Genetical Recombination) ----- Xolair for s.c. injection	Novartis Pharma K.K.	March 13, 2009
Candesartan Cilexetil / Hydrochlorothiazide ----- ECARD Combination Tablets LD, ECARD Combination Tablets HD	Takeda Pharmaceutical Company Limited	March 13, 2009
Zonisamide ----- TRERIEF Tablets 25mg	Dainippon Sumitomo Pharma Co., Ltd.	March 13, 2009
Valsartan/Hydrochlorothiazide ----- Co-DIO Combination Tablets MD, Co-DIO Combination Tablets EX	Novartis Pharma K.K.	March 13, 2009
Ranibizumab (Genetical Recombination) ----- LUCENTIS solution for intravitreal injection 2.3mg/0.23mL	Novartis Pharma K.K.	March 13, 2009

Nalfurafine Hydrochloride REMITCH CAPSULES 2.5µg	Toray Industries, Inc.	March 24, 2009
Azithromycin Hydrate ZITHROMAC SR Dry Syrup 2g for Adults	Pfizer Japan Inc.	April 6, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adair 50 Air 120 puffs	GlaxoSmithKline K.K.	April 6, 2009
Minodronic Acid Hydrate Bonoteo Tablets 1mg	Astellas Pharma Inc.	April 7, 2009
Minodronic Acid Hydrate RECALBON Tablets 1mg	Ono Pharmaceutical Co., Ltd.	April 7, 2009
Cetirizine Hydrochloride Zyrtec Dry Syrup 1.25%, Zyrtec tablets 5mg *1	UCB Japan Co. Ltd	April 22, 2009
Somatropin (genetical recombination) NORDITROPIN S injection 5mg and 10mg, Norditropin NordiFlex injection 5mg, 10mg and 15mg *4	Novo Nordisk Pharma Ltd.	April 22, 2009
Doxorubicin Hydrochloride DOXIL Injection 20mg *5	Janssen Pharmaceutical K.K.	April 22, 2009
Sodium Chloride/Potassium Chloride/Sodium Bicarbonate/Anhydrous Sodium Sulfate Niflec for internal use *6	Ajinomoto Pharma Co., Ltd.	April 22, 2009
Mosapride Citrate Gasmotin Tablets 2.5 mg and 5 mg, Gasmotin Powder *7	Dainippon Sumitomo Pharma Co., Ltd.	April 22, 2009
Sorafenib Tosilate Nexavar Tablets 200mg	Bayer Yakuhin, Ltd.	May 20, 2009
Valganciclovir Hydrochloride VALIXA Tablets 450mg	Mitsubishi Tanabe Pharma Corporation	May 20, 2009
Pemetrexed Sodium Hydrate Alimta Injection 500mg	Eli Lilly Japan K.K.	May 20, 2009
Freeze-dried cell culture derived Japanese encephalitis vaccine Jebik V	The Research Foundation for Microbial diseases of Osaka University	June 2, 2009
Atomoxetine Hydrochloride Strattera capsule 5mg, 10mg, and 25mg	Eli Lilly Japan K.K.	June 19, 2009
Fluticasone Furoate Allermist 27.5µg 56metered Nasal Spray	GlaxoSmithKline K.K.	June 19, 2009
Lapatinib Tosilate Hydrate Tykerb Tablets 250mg	GlaxoSmithKline K.K.	June 19, 2009
Telmisartan, Hydrochlorothiazide Micombi Combination Tablets AP and BP	Nippon Boehringer Ingelheim Co., Ltd.	June 23, 2009
Risperidone RISPERDAL Consta Intramuscular Injection 25mg, 37.5mg, and 50mg	Janssen Pharmaceutical K.K.	June 23, 2009
Insulin Glulisine (Genetical Recombination) APIDRA Inj. Cart, Inj. SoloStar, Inj. 100 units/mL	Sanofi-Aventis K.K	June 24, 2009
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion100 *10	Mitsubishi Tanabe Pharma Corporation	July 7, 2009
Etanercept (Genetical Recombination) ENBREL 25mg Syringe for S.C. Injection *11	Wyeth K.K.	July 7, 2009

Somatropin (Genetical Recombination) Growject injection 1.33mg, 8mg, BC 8mg ^{*3}	JCR Pharmaceuticals Co., Ltd.	July 7, 2009
Levofloxacin Hydrate CRAVIT TABLETS 250mg, 500mg, Fine Granules 10%	Daiichi Sankyo Company, Limited.	July 7, 2009
Clozapine CLOZARIL Tablets 25mg, 100mg	Novartis Pharma K.K.	July 29, 2009

*1: An additional administration for “pediatrics”

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

*3: An additional indication for “prophylaxis of venous thromboembolisms in patients undergoing abdominal surgery who are at risk for thromboembolic complications”

*4: An additional indication for “replacement of endogenous growth hormone in adults with growth hormone hyposecretion (restricted to serious cases)”

*5: An additional indication for “treatment of patients with ovarian cancer whose disease has progressed after chemotherapy”

*6: An additional indication for “cleansing of the colon as a preparation prior to radiographic contrast barium enema”

*7: An additional indication for “adjunction with colonic cleansing agent for a preparation prior to radiographic contrast barium enema”

*8: An additional indication for “treatment of patients with unresectable hepatocellular carcinoma”

*9: An additional indication for “treatment of patients with cytomegalovirus infections associated with Acquired immunodeficiency syndrome, organ transplants (including haemopoietic stem cell transplants), or Malignant tumour”

*10: Rheumatoid arthritis which is not adequately responsive to conventional therapies (including prevention for structural damage of joints).

*11: Polyarticular-course juvenile idiopathic arthritis (only for cases which are not adequately responsive to conventional therapies).