Pharmaceuticals and Medical Devices Safety Information

No. 268 April 2010

Table of Contents

1. **Manuals for Management of Individual Serious Adverse Drug Reactions** 4
2. **Project of Japan Drug Information Institute in Pregnancy** 9
3. **Important Safety Information** 11
   - 1 Atorvastatin Calcium Hydrate, Simbastatin, Pitavastatin Calcium, Pravastatin Sodium, Fluvastatin Sodium, Rosuvastatin Calcium, Amlodipine Besilate/Atorvastatin Calcium Hydrate 11
   - 2 Cetuximab (Genetical Recombination) 16
4. **Revision of PRECAUTIONS (No. 215)**
   Aripiprazole (and 6 others) 22
5. **List of products subject to Early Post-marketing Phase Vigilance** 25

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/, only available in Japanese language).

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Pharmaceuticals and Medical Devices Safety Information

No. 268 April 2010

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	**Manuals for Management of Individual Serious Adverse Drug Reactions**		Ministry of Health, Labour and Welfare (MHLW) has been developing "Manuals for Management of Individual Serious Adverse Drug Reactions" with cooperation of experts from relevant academic societies since FY2005 as part of the "Initiative of Comprehensive Actions for Serious Adverse Drug Reactions". The manuals for management of adverse drug reactions including "Thrombotic Thrombocytopenic Purpura (TTP)" have been completed and are available on the MHLW website (http://www.mhlw.go.jp/). This section presents the aim of its initiative, as well as information about the Manuals.	4
2	**Project of Japan Drug Information Institute in Pregnancy**		MHLW established "Japan Drug Information Institute in Pregnancy**"** in the National Center for Child Health and Development on October 2005 to provide consultation services and perform research activities. Two hospitals that joined the project in FY2010 are introduced together with the summary and current status of the project.	9
3	**Atorvastatin Calcium Hydrate (and 1 other)**	*P* *C*	This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated March 23, 2010.	11
4	**Aripiprazole (and 6 others)**		Revision of PRECAUTIONS (No.215)	22
5	**Products subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of April 1, 2010	25

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

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

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

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

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

1

Manuals for Management of Individual Serious Adverse Drug Reactions

1. Introduction

MHLW has been developing "Manuals for Management of Individual Serious Adverse Drug Reactions" (hereinafter referred to as "the Manuals") with the cooperation of experts from relevant academic societies since FY2005[1)]. The Manuals are targeting adverse drug reactions which are to be crucial in order to ensure early recognition and treatments of them. The Manuals include comprehensively relevant initial symptoms, typical clinical cases and diagnostics of the serious adverse drug reactions. So far the Manuals are available for 49 adverse drug reactions.

2. The Manuals

The current safety measures have been drug-oriented. Reports of adverse drug reactions have been collected and reviewed for each drug, and relevant package inserts have been revised accordingly to alert healthcare providers. However, adverse drug reactions may occur in unaffected organs, and serious adverse drug reactions are infrequent generally and may be unfamiliar to healthcare providers. Therefore, the recognition of adverse drug reactions may be delayed, and related symptoms may be aggravated.

In addition to existing drug-oriented safety measures, MHLW launched to develop the Manuals to implement the safety management that focuses on drug-induced adverse reactions.

The Manuals are developed for both patients and healthcare providers. The manuals for patients include the summary of the adverse drug reaction which patients and their family members should know, the initial symptoms, and key points for early recognition and treatments as much as possible in plain words. The manuals for healthcare include the key points for early recognition and treatments, the summary of the adverse drug reaction, diagnostics, general treatment and typical clinical cases.

The Manuals are available on the MHLW and Pharmaceuticals and Medical Devices Agency websites. Additional Manuals will be posted on the websites in the future.

MHLW http://www.mhlw.go.jp/topics/2006/11/tp1122-1.html
PMDA http://www.info.pmda.go.jp/juutoku/juutoku_index.html

3. Newly available Manuals

The Manuals for 14 adverse drug reactions were completed in March 2010 and are now available on the MHLW and PMDA websites.

Titles of the newly available Manuals and common initial symptoms are shown in **Table 1**. The existing Manuals and those currently under development are listed in **Table 2**.

New Manuals will be developed in FY2010, and the existing Manuals will be updated as necessary.

4. Requests to healthcare providers

The Manuals are prepared for the patients and healthcare providers separately. Healthcare providers such as physicians, dentists and pharmacists are encouraged to use the Manuals for in-house communication and medication instruction for the patients as well as for actual management of adverse drug reactions to ensure early recognition and treatments of serious adverse drug reactions. In addition, it would be appreciated that the Manuals are introduced to the patients.

<Reference>

1) Pharmaceuticals and Medical Devices Safety Information No. 230 (November 2006)

Table 1 Manuals for Management of Individual Serious Adverse Drug Reactions released in March 2010

Manual title (adverse drug reaction)	Common initial symptoms
Thrombotic thrombocytopenic purpura (TTP)	"Fever", "Malaise", "Feeling of weakness", "Nausea", "Anorexia", "Bruising", "Bleeding from nose or gum", "Decrease of urine output", "Skin and white of the eye turn yellow", "Short-term symptoms such as mild headache, dizziness, convulsion, sudden disorientation about place and one's name, and drowsiness"
Heparin-induced thrombocytopenia (HIT)	"Sudden dyspnea", "Disturbance in consciousness, convulsion, and movement/sensory disturbance", "Swelling, pain, and skin discoloration in extremities", "Redness and/or tender lump in injection site occurring several days after injection"
Nephrotic syndrome	"Swollen leg", "Decrease of urine output", "Sluggishness", "Foaming urine", "Difficulty in breathing", "Red urine"
Acute eosinophilic pneumonia	"Dry cough", "Shortness of breath or difficulty in breathing when climbing the stairs or on light exertion", "Fever"
Pulmonary alveolar hemorrhage (pulmonary hemorrhage, diffuse pulmonary alveolar hemorrhage)	"Bleeding when coughing", "Bloody sputum", "Black sputum", "Shortness of breath/difficulty in breathing", "Cough"
Severe diarrhea	"Muddy or watery stool," "Urge to defecate or tenesmus," "Stabbing pain in the abdomen," "Diarrhea too frequent to leave the bathroom," "Mucoid stool," "Bloody stool"
Hand and foot syndrome	"Abnormal sensation" such as "Numbness" and "Pain", in hands and feet, "Redness (erythema) ", "Swelling", "Pigmentation", "Keratosis (skin surface turning hard, thick, and coarse) ", "Chapped skin", "Blisters", on the skin of hands and feet, "Deformity" and "Pigmentation" of nails
Neonatal drug withdrawal syndrome	"Becoming limp", "Shaky hands and feet", "Convulsion", and "Temporary apnea" in newborns
Serotonin syndrome	"Anxiety", "Confusion", "Irritation", "Agitation", "Moving about", "Involuntary movement of hands and feet", "Involuntary movement of eyes", "Shaking", "Rigidity", "Sweating", "Fever", "Diarrhea", "Increased pulse rate"
Akathisia	"Body or feet feeling restless or irritated and unable to sit or lie still, having an urge to move", "Unable to be still, having an urge to walk", "Having an urge to move one's body or feet", "Restless feet", "Unable to stand still, having an urge to step"
Ataxia	"Jerky movement of hands and feet", "Unable to use chopsticks well", "Slurred speech", "Feeling wobbly", "Unable to walk straight"
Headache	"Headache"
Hearing loss (associated with aminoglycoside antibacterial drugs, platinum-containing drugs, salicylic acid preparations or loop diuretics)	"Difficulty in hearing", "Ringing or beeping in the ears", "Feeling of ears being bunged up", "Feeling wobbly"
Drug-induced contact dermatitis	"Soreness", "Redness", or "Itchiness with rash" immediately after drug usage, "Sudden itchiness, redness, rash or exudate" at some point after drug usage.

Table 2 List of the Manuals for Management of Individual Serious Adverse Drug Reactions (including those at drafting stage)

(As of April 2010)

Field	Name of cooperating society	Covered adverse drug reaction
Dermatologicals	The Japanese Dermatological Association	○ Stevens-Johnson syndrome (Oculomucocutaneous syndrome) ○ Toxic epidermal necrosis (Toxic epidermal necrolysis) (Lyell syndrome, Drug eruption Lyell syndrome type) ○ Drug-induced hypersensitivity syndrome ○ Acute generalized exanthematous pustulosis ☆ Drug-induced contact dermatitis
Hepatic	The Japan Society of Hepatology	○ Drug-induced hepatic disorder (hepatocellular-type drug-induced liver disorder, Cholestasis-type drug-induced liver disorder, Mixed-type drug-induced liver disorder, Acute hepatic failure, other drug-induced liver disease)
Renal	The Japanese Society of Nephrology	○ Acute renal failure ○ Interstitial nephritis (Tubulointerstitial nephritis) ☆ Nephrotic syndrome Pyelonephritis Nephrogenic diabetes insipidus Tumour lysis syndrome
Blood	The Japanese Society of Hematology	○ Aplastic anaemia (Pancytopenia) ○ Bleeding tendency ○ Drug-induced anaemia (Haemolytic anaemia, Methaemoglobinaemia, pure red cell aplasia, Sideroblastic anaemia, Megaloblastic anaemia) ○ Agranulocytosis (Granulocytopenia ,Neutropenia) ○ Thrombocytopenia ○ Thrombosis (Thromboembolism, Embolism, Infarction) ○ Disseminated intravascular coagulation (Systemic hypercoagulative disorder, Consumption coagulopathy) ☆ Thrombotic thrombocytopenic purpura (TTP) ☆ Heparin-induced thrombocytopenia (HIT)
Respiratory system	The Japanese Respiratory Society	○ Interstitial pneumonia (Pneumonitis, Alveolitis, Pulmonary fibrosis) ○ Asthmatic attack due to nonsteroidal anti-inflammatory drug (Aspirin asthma, analgesics-induced asthma, aspirin intolerant asthma, Analgesic asthma syndrome) ○ Acute lung injury/Acute respiratory distress syndrome (Acute respiratory distress syndrome), (Adult respiratory distress syndrome [Adult respiratory distress syndrome]) ○ Pulmonary oedema ○ Pleurisy, Pleural effusion ☆ Acute eosinophilic pneumonia ☆ Pulmonary alveolar haemorrhage (pulmonary haemorrhage, diffuse pulmonary alveolar haemorrhage)

Field	Name of cooperating society	Covered adverse drug reaction
Alimentary tract	The Japanese Society of Gastroenterology	○ Paralytic ileus ○ Peptic ulcer (Gastric ulcer, Duodenal ulcer, Acute gastric mucosal lesion, NSAIDs-induced ulcer) ○ Pseudomembranous colitis ○ Pancreatitis acute (Drug-induced pancreatitis) ☆ Severe diarrhoea
Cardiovascular system	The Japanese Circulation Society	○ Ventricular tachycardia ○ Congestive cardiac failure
Nervous and musculo-skeletal system	The Japanese Society of Neurology	○ Drug-induced parkinsonism ○ Rhabdomyolysis ○ Leukoencephalopathy ○ Peripheral neuropathy ○ Guillain-Barre syndrome (Acute inflammatory demyelinating polyradiculoneuropathy, Acute inflammatory demyelinating polyneuropathy) ○ Dyskinesia ○ Convulsion/Epilepsy ☆ Ataxia ☆ Headache Aseptic meningitis Acute disseminated encephalomyelitis
Psychiatric	The Japanese Society of Clinical Neuropsychopharmacology	○ Neuroleptic malignant syndrome ○ Drug-induced depression ☆ Akathisia ☆ Serotonin syndrome
	The Japan Pediatric Society	☆ Neonatal drug withdrawal syndrome
	The Japanese Society of Child Neurology	Acute encephalopathy in children
Metabolism and endocrine	The Japan Endocrine Society	○ Pseudoaldosteronism ○ Thyrotoxicosis ○ Hypothyroidism
	The Japan Diabetes Society	○ Hyperglycaemia Hypoglycaemia
Hypersensitivity	The Japanese Society of Allergology	○ Anaphylaxis ○ Angioedema (Angioneurotic edema) ○ Laryngeal oedema ○ Urticaria/Angiooedema due to nonsteroidal anti-inflammatory drug
Sensory organs (visual)	The Japanese Ophthalmological Society	○ Retinal disorder/Visual field defects ○ Glaucomas Corneal opacity
Sensory organs (auditory)	The Oto-Rhino-Laryngological Society of Japan, Inc.	☆ Deafness (associated with aminoglycoside antibacterial agents, platinating agents, salicylic acid preparations or loop diuretics)
Sensory organs (mouth)	The Japanese Stomatological Society	Taste disorders
Oral cavity	The Japanese Society of Oral and Maxillofacial Surgeons	○ Osteonecrosis of jaw due to bisphosphonates ○ Drug-induced stomatitis ○ Stomatitis due to anticancer agents
Bones	The Japanese Orthopaedic Association	○ Osteoporosis Femoral head avascular necrosis
Urinary organs	The Japanese Urological Association	○ Urinary retention /dysuria Haemorrhagic cystitis
Ovary	The Japan Society of Obstetrics and Gynecology	Ovarian hyperstimulation syndrome
Carcinoma	The Japan Society of Clinical Oncology	☆ Hand and foot syndrome

Note) Manuals with "○" have already published before, and those with "☆" have newly published recently.

2

Project of Japan Drug Information Institute in Pregnancy

1. Project of Japan Drug Information Institute in Pregnancy

When using drugs during pregnancy, sufficient attention should be paid to their influence, on the fetus as well as the mother.

On the other hand, because of excessive anxiety about drug-related risks, some physicians withhold necessary drug therapies or some patients stop taking medications on their own judgment, although few drugs have been confirmed to have teratogenic effects on humans. Not using necessary medication may result in aggravation of the mother's condition and adversely affect the fetus. Some patients even give up childbearing because they are on medication for treatment of chronic diseases.

"Japan Drug Information Institute in Pregnancy (JDIIP)" (http://www.ncchd.go.jp/kusuri/index.html) was established in the National Center for Child Health and Development (NCCHD) on October 2005 to collect and evaluate the latest evidence of effects of drugs on fetuses and provide consultation services for women who wish to become pregnant and those who are already pregnant, based on the collected information.

In addition, delivery and post-delivery information is collected and evaluated from women who have received consultation in the project for future pregnancy consultation services.[1)]

2. Current activities

Other than the consultation services provided by physicians affiliated with NCCHD and cooperating hospitals and consulters' physicians, the JDIIP started the telephone consultation services in July 2007 for users of popular OTC drugs such as cold remedies, painkillers, antiallergics and gastrointestinal drugs about which inquiries are frequently made. Number of consultations (including telephone consultations) provided have been increasing year after year: 111 in FY2005, 335 in FY2006, 673 in FY2007, 960 in FY2008, and 1016 in FY2009.

In December 2007, the JDIIP added a section of "Drugs and breastfeeding" in "Drug information for mothers" on the website, which includes information of "Drugs that nursing mothers may use" and "Drugs that nursing mothers should avoid".

In response to H1N1 influenza epidemic, the basic concept of influenza treatment and vaccination during pregnancy has been introduced in the section of "Influenza Update Information" since September 2009. Thus, the latest information about drugs and pregnancy is provided on the website. We hope the website will be useful for pregnant women and nursing mothers.

3. Cooperating hospitals

The JDIIP project has been carried out with the cooperation of 14 hospitals nationwide. Moreover, in wider collaboration with two new hospitals in FY2010, the JDIIP will enhance the system for consultation service and information collection regarding pregnancy and drugs, for user's further convenience. See below for details of the 16 cooperating hospitals.

<Reference>

1) Pharmaceuticals and Medical Devices Safety Information No.235 (April 2007)

[Information on "Japan Drug Information Institute in Pregnancy" and cooperating hospitals]

"Japan Drug Information Institute in Pregnancy" − Setagaya-ku, Tokyo
in National Center for Child Medical Health and Development (NCCHD)
URL: http://www.ncchd.go.jp/kusuri/index.html

(Cooperating hospitals) ⊙ Joined since 2010

Hokkaido University Hospital − Sapporo-city, Hokkaido

Iwate Medical University Hospital−Morioka-city, Iwate

National Hospital Organization Sendai Medical Center − Sendai-city, Miyagi
URL: http://www.snh.go.jp/Medicine/index.html

Tsukuba University Hospital − Tsukuba-city, Ibaraki

Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital − Minato-ku, Tokyo

St. Luke's International Hospital − Chuo-ku, Tokyo

⊙Shinsyu University Hospital – Matsumoto-city, Nagano (to be opened in May 2010)

Japanese Red Cross Nagoya First Hospital − Nagoya-city, Aichi

National Hospital Organization Nagara Medical Center −Gifu-city, Gifu

National Hospital Organization Kanazawa Medical Center − Kanazawa-city, Ishikawa

Nara Medical University Hospital − Kashihara-city, Nara

Osaka Medical Center and Research Institute for Maternal and Child Health − Izumi-city, Osaka
URL: http://www.mch.pref.osaka.jp/osirase/ninshin/index.html

National Hospital Organization Kagawa Children's Hospital− Zentsuji-city, Kagawa

Hiroshima University Hospital − Hiroshima-city, Hiroshima

Kyushu University Hospital − Fukuoka-city, Fukuoka

⊙Kagoshima City Hospital – Kagoshima-city, Kagoshima

3

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 March 23, 2010.

1 Atorvastatin Calcium Hydrate, Simvastatin, Pitavastatin Calcium, Pravastatin Sodium, Fluvastatin Sodium, Rosuvastatin Calcium, Amlodipine Besilate/Atorvastatin Calcium Hydrate

❶ Atorvastatin Calcium Hydrate, Simvastatin, Pitavastatin Calcium, Pravastatin Sodium, Fluvastatin Sodium, Rosuvastatin Calcium

Brand Name (name of company)	**Atorvastatin Calcium Hydrate** Lipitor Tablets 5 mg, 10 mg (Astellas Pharma Inc.) **Simvastatin** LIPOVAS Tablets 5, 10, 20 (Banyu Pharmaceutical Co., Ltd.) and the others **Pitavastatin Calcium** LIVALO Tablet 1 mg, 2 mg (Kowa Company, Ltd.) **Pravastatin Sodium** MEVALOTIN FINE GRANULES 0.5%, 1%, MEVALOTIN TABLETS 5, 10 (Daiichi Sankyo Company Limited) and the others **Fluvastatin Sodium** LOCHOL Tablets 10 mg, 20 mg, 30 mg (Novartis Pharma K.K.) and the others **Rosuvastatin Calcium** CRESTOR Tablets 2.5 mg, 5 mg (AstraZeneca K.K.)
Therapeutic Category	Hyperlipidaemia agents
Indications	Hypercholesterolemia, familial hypercholeseterolemia

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

[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia:** Interstitial pneumonia may occur. If pyrexia, cough, dyspnoea or chest x-ray abnormal occurs, administration should be discontinued even though the patient has been administered this drug for long term, and appropriate measures such as administration of corticosteroid should be taken.

❷ Amlodipine Besilate/Atorvastatin Calcium Hydrate

Brand Name (name of company)	Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban (Pfizer Japan Inc.)
Therapeutic Category	Cardiovascular agents-Miscellaneous
Indications	Use this drug (amlodipine/atorvastatin combination) in the following patients for whom treatment with both amlodipine and atorvastatin is appropriate: Patients with hypertension or angina, concurrently with hypercholesterolemia or familial hypercholesterolemia Each amlodipine and atorvastatin are indicated for treatment of the following disorders: Amlodipine • Hypertension • Angina Atorvastatin • Hypercholesterolemia • Familial hypercholesterolemia

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

[Adverse Reactions (clinically significant adverse reactions)]

(Atorvastatin)
Interstitial pneumonia: Interstitial pneumonia may occur. If pyrexia, cough, dyspnoea or chest x-ray abnormal occurs, administration should be discontinued even though the patient has been administered this drug for long term, and appropriate measures such as administration of corticosteroid should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2006 to November 25, 2009):
- Interstitial pneumonia: 7 cases (no fatalities)

The number of patients treated with this drug per year estimated by marketing authorization holder (MAH): approximately 8.12million patients (January to December 2009)

Marketed in Japan in: October 1989 (Pravastatin Sodium)
December 1991 (Simvastatin)
May 2000 (Atorvastatin Calcium Hydrate)
June 2003 (Fluvastatin Sodium)
September 2003 (Pitavastatin Calcium)
April 2005 (Rosuvastatin Calcium)
December 2009 (Amlodipine Besilate/Atorvastatin Calcium Hydrate)

Case Summary
<Pravastatin Sodium>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Hyperlipidemia (None)	5 mg About 8 months	**Interstitial pneumonia** Day 1 of administration: The patient started receiving pravastatin sodium and loratadine for hyperlipidemia. Month 7 of administration: The patient became aware of exertional dyspnoea. Month 7.5 of administration: The patient started receiving diazepam, betahistine mesilate for anxiety and dizziness. Month 8 of administration (day of discontinuation): All

				medications other than pravastatin sodium were discontinued due to dyspnoea possibly associated with the concomitant drugs. Even after discontinuation of the drugs, dyspnoea did not improve. Chest x-ray showed abnormal findings. Pravastatin sodium was discontinued. 1 day after discontinuation: The patient was referred to our hospital and hospitalized for interstitial pneumonia. 6 days after discontinuation: Bronchoscopy was performed based on suspicion of hypersensitivity pneumonia or drug-induced pneumonia. Number of lymphocytes in bronchoalveolar lavage (BAL) fluid increased. 24 days after discontinuation: The patient showed no pneumonia symptoms so stayed at home on a trial basis. Hypersensitivity pneumonia was considered to be ruled out because the patient's condition was not aggravated. Trichosporon antibody was negative. The DLST was positive for pravastatin sodium. 37 days after discontinuation: The chest x-ray showed opacity had decreased. The patient was discharged from the hospital. Since then, her condition has not worsened.
	Concomitant medications: diazepam, betahistine mesilate, loratadine			

Clinical Laboratory Values

	1 day after discontinuation	22 days after discontinuation	35 days after discontinuation
RBC ($\times 10^4$/mm^3)	483	469	–
Hemoglobin (g/dL)	15.1	14.1	–
Hematocrit (%)	43.9	42.7	–
PLT ($\times 10^4$/mm^3)	36.3	26.7	–
WBC (/mm^3)	7720	6870	–
Basophils (%)	0.5	0.5	–
Eosinophils (%)	4.8	2.9	–
Neutrophils (%)	63.1	58.9	–
Lymphocytes (%)	25.1	32.4	–
Monocytes (%)	6.5	5.3	–
ESR (mm/h)	28	15	–
CRP (mg/dL)	0.7	0.1	0.1
AST (GOT) (IU/L)	22	21	17
ALT (GPT) (IU/L)	14	21	17
ALP (IU/L)	213	221	176
LDH (IU/L)	400	274	203
Total bilirubin (mg/dL)	0.5	–	–
BUN (mg/dL)	16.4	12.4	13.1
Serum creatinine (mg/dL)	0.65	0.64	0.59
$PaCO_2$ (mmHg)	41.1	–	–
PaO_2 (mmHg)	103.8	–	–
KL-6 (U/mL)	2520	1780	–

RBC: Red blood cell count
PLT: Platelet
WBC: White blood cell count
CRP: C-reactive protein

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)
ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)
ALP: Alkaline phosphatase
LDH: Lactate dehydrogenase
BUN: Blood urea nitrogen

<Pitavastatin Calcium>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Hypercholesterolemia (Type 2 diabetes, hypertension, fatty liver)	2 mg 10 days	**Drug-induced lung disorder** Day 1 of administration: The patient had been treated for hypercholesterolemia, type 2 diabetes (HbA_{1c} 8.0%), hypertension and fatty liver. Oral administration of pravastatin sodium 10 mg was switched to pitavastatin calcium 2 mg. Day 10 of administration (day of discontinuation): The patient experienced malaise, anorexia, dyspnoea on exertion (DOE) and chills in the back. Pitavastatin calcium was discontinued. 5 days after discontinuation: The patient visited the hospital. Crepitation was heard in the bilateral lower back. SpO_2 was 95%. The patient had DOE. Chest x-ray showed a patchy, particulate opacity in the bilateral lower lung field. Oral administration of prednisolone 20 mg was started. 7 days after discontinuation: The patient visited our hospital again. The dose of prednisolone was decreased to 10 mg. The symptoms improved. 12 days after discontinuation: Prednisolone was temporarily discontinued. KL-6 was 960 U/mL 23 days after discontinuation: The patient visited our hospital again. The symptoms had been resolved but crepitation in the back was still present. SpO_2 increased to 96%. KL-6 increased to 1920 U/mL. A chest x-ray showed that opacity tended to be decreased. Prednisolone 10 mg was prescribed. 30 days after discontinuation: The patient was referred to the respiratory department in another hospital, although her respiratory condition had improved. An imaging test was performed by chest CT scan. PaO_2, $PaCO_2$, and pH were 68 torr, 39.0 torr, 7.43, respectively. The CT scan showed reticular and linear opacities and lower-lobe traction bronchiectasis in the bilateral peripheral lung fields, and non-segmental ground-glass opacities in both lung fields. 32 days after discontinuation: Prednisolone 15 mg × 10 days was prescribed. The patient had no DOE. 42 days after discontinuation: Prednisolone 10 mg × 12 days was prescribed. SpO_2 was 96%. The patient had no DOE. 54 days after discontinuation: Prednisolone 5 mg (dose decrease) × 14 days was prescribed. SpO_2 was 96%. The patient had no symptoms including DOE. KL-6 was 2050 U/mL. 68 days after discontinuation: Prednisolone 5 mg was continued. 84 days after discontinuation: The dose of prednisolone was

				decreased to 2.5 mg. SpO_2 was 96%. The patient had no symptoms. KL-6 decreased to 1520 U/mL. 100 days after discontinuation: Prednisolone was discontinued. Crepitation in the lower back decreased. The patient had no symptoms. 166 days after discontinuation: Drug-induced lung disorder was resolved.
	Concomitant medications: amlodipine besilate, metformin hydrochloride, glimepiride			

Clinical Laboratory Values

	31 days before administration	21 days after discontinuation	23 days after discontinuation	54 days after discontinuation	84 days after discontinuation	157 days after discontinuation
WBC (/mm^3)	8900	8200	8200	10600	10100	–
KL-6 (U/mL)	–	960	1920	2050	1520	1220
CRP (mg/dL)	–	2.49	0.29	–	–	–

WBC: White blood cell count
CRP: C-reactive protein

2 Cetuximab (Genetical Recombination)

Brand Name (name of company)	ERBITUX Injection 100 mg (Merck Serono Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	EGFR-positive, incurable, unresectable, advanced/recurrent colorectal cancer

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

[Precautions of Indications]

Screen the patient for KRAS mutation before using this drug.

[Adverse Reactions (clinically significant adverse reactions)]

Cardiac failure: Cardiac failure may occur. Patients should be carefully monitored and if any abnormality occurs, appropriate measures, such as discontinuing treatment, should be taken.

Severe diarrhoea: Severe diarrhoea and dehydration may occur, resulting in renal failure in some cases. Patients should be carefully monitored. If diarrhoea or dehydration occurs, appropriate measures, such as administration of an antidiarrhoeal (Loperamide etc.) and fluid replacement, should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 1 year (September 19, 2008 to February 15, 2010):

- Cardiac failure: 2 cases (fatality)
- Severe diarrhoea: 5 cases (no fatalities)

The number of patients treated with this drug per year estimated by MAH: approximately 6,500 patients (Year 2009)
Marketed in Japan in: September 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Colon cancer (Lung metastasis, peritoneal metastasis, diabetes, hypertension, valvular disease, arrhythmia)	670 mg 1 day	**Cardiac failure** History of prior treatment: UFT/LV (about 4 years to about 3 years and 4 months before cetuximab administration), IFL (about 3 years to about 2 years and 7 months before cetuximab administration), TS1 (about 2 years and 5 months to about 1 year and 9 months before cetuximab administration), FOLFOX (about 1 year and 7 months to about 1 year before cetuximab administration), bevacizumab (genetical recombination; about 10 months to about 4 months before cetuximab administration) Surgery: anterior resection (about 4 years and 1 month before cetuximab administration,) Hartmann's pouch procedure (about 1 year and 8 months before cetuximab administration) Day 1 of administration (Day of discontinuation): The patient received cetuximab 670 mg and irinotecan hydrochloride hydrate 250 mg. 7 days after discontinuation: Intestinal obstruction (Grade 3) occurred. 11 days after discontinuation: Dyspnoea, which is considered to be caused by cardiac failure occurred. Pneumonia (Grad

				e 1) occured. Dyspnoea was aggravated. X-ray showed an enlarged cardiac outline. Echocardiogram showed decreased wall motion. The patient was unresponsive to diuretic. Administration of catecholamine was started. 12 days after discontinuation: Dyspnoea was followed by shock sympton. Epinephrine was given. The patient was unresponsive to dopamine hydrochloride, dobutamine hydrochloride, and noradrenaline. Blood pressure continued to decrease despite volume load. The patient died.
	Concomitant medications: irinotecan hydrochloride hydrate, diphenhydramine hydrochloride, dexamethasone sodium phosphate, filgrastim (genetical recombination), granisetron hydrochloride			

Clinical Laboratory Values

	Day of administration (Day of discontinuation)	2 days after discontinuation	7 days after discontinuation	9 days after discontinuation	10 days after discontinuation	11 days after discontinuation	12 days after discontinuation
WBC (/mm^3)	106.8	154.6	5.4	7.2	–	10.9	30.8
PLT(×10^4/mm^3)	21	18.6	10.1	9.6	–	7.3	6.6
Hemoglobin (g/dL)	11.7	10.0	8.2	6.9	–	7.1	6.2
Hematocrit (%)	35.4	30.6	24.5	20.5	–	21.8	19.0
Total bilirubin (mg/dL)	1.4	1.8	3.5	2.8	–	3.3	3.3
Direct bilirubin (mg/dL)	0.4	0.7	2.0	1.3	–	2.4	2.7
AST (GOT) (IU/L)	34	43	25	12	–	12	35
ALT (GPT) (IU/L)	24	29	21	13	–	13	14
LDH (IU/L)	468	428	321	229	–	222	269
BUN (mg/dL)	16.4	26.7	22.9	26.3	40.3	58.7	81.1

WBC: White blood cell count
PLT: Platelet
AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)
ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)
LDH: Lactate dehydrogenase
BUN: Blood urea nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Rectal cancer (Liver and lung metastases)	600 mg Once a week 1 day ↓ 400 mg Once a week 70 days	**Right ventricular failure** History of prior treatment: FOLFOX (about 4 months before cetuximab administration), bevacizumab (genetical recombination; about 3 months before cetuximab administration) Surgery: Hartmann's pouch procedure (about 4 months before cetuximab administration) Day 1 of administration: The patient started receiving combination therapy with cetuximab 600 mg and FOLFIRI. 62 days after administration: Forth cycle of FOLFIRI combination therapy completed. 76 days after administration (Day of discontinuation): Last treatment with cetuximab 400 mg was performed. 1 day after discontinuation: The patient was urgently admitted to the hospital for respiratory discomfort. Chest CT showed right pleural effusion and right heart failure. CT scan: Overall metastatic lesions in both lungs shrunk (max 17 × 16 mm to 14 × 10 mm). Enlarged lymph node was not noted. Right pleural effusion occurred. Lung field opacity increased slightly. Marked (right) cardiomegaly was observed compared with that of the last examination. Oedema associated with cardiac failure was suspected. Multiple liver metastases and hepatomegaly were noted. 2 days after discontinuation: Clinical laboratory values: AST (GOT) 95 IU/L, LDH 508 IU/L, total bilirubin 1.2 mg/dL, BUN 35.9 mg/dL, serum creatinine 2.09 mg/dL, BS 13 mg/dL, Hemoglobin 12.5 g/dL, WBC 17200/mm^3. Despite treatment with aminophylline hydrate, dopamine hydrochloride, and oxygen, the patient's condition was not improved. The patient died.
	Concomitant medications: irinotecan hydrochloride hydrate, fluorouracil, calcium folinate, *d*-chlorpheniramine maleate, dexamethasone sodium phosphate, azasetron hydrochloride			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Rectal cancer (Lung metastasis, hypertension, aortic aneurysm)	660 mg Once a week 1 day ↓ 400 mg Once a week Continued (including rest period in a week)	**Diarrhoea** History of prior treatment: FOLFOX (period of administration unknown), FOLFIRI (period of administration unknown), UFT/LV (period of administration unknown) Surgery: anterior resection of the rectum (about 3 years and 2 months before cetuximab administration), hepatectomy (about 1 year before cetuximab administration), hepatectomy (about 7 months before cetuximab administration), hepatectomy (about 3 months before cetuximab administration), partial lung lobectomy (about 6 months before cetuximab administration) Day 1 of administration: The patient started receiving cetuximab 660 mg and irinotecan hydrochloride hydrate 240 mg. 49 days after administration: Cetuximab 400 mg and irinotecan hydrochloride hydrate 240 mg were given. Diarrhoea occurred 4 to 6 times a day. Anorexia occurred. 56 days after administration: During a routine visit, it was considered that the patient had dehydration due to diarrhoea. He was admitted to the hospital to receive fluid replacement. Fluid replacement 1000 mL was started. 57 days after administration: Fluid replacement 1000 mL continued. Diarrhoea occurred 5 times/day. The patient regained his appetite. 58 days after administration: Fluid replacement 1000 mL continued. Diarrhoea occurred 6 times/day. 59 days after administration: Fluid replacement 1000 mL continued. Diarrhoea occurred 2 times/day. 60 days after administration: Diarrhoea occurred 2 times/day. 61 days after administration: Diarrhoea resolved. 63 days after administration: Cetuximab 400 mg was administrated. 64 days after administration: The patient was discharged from the hospital. 285 days after administration: Cetuximab 400 mg and irinotecan hydrochloride hydrate 200 mg were administrated. 287days after administration: Diarrhoea occurred 5 times/day 291 days after administration: The patient had frequent watery stool. 292 days after administration: During a routine visit, watery stool occurred every 10 minutes. He was urgently admitted to the hospital to receive fluid replacement. He was in the fasted state, and started given fluid replacement 1000 mL. 293 days after administration: Fluid replacement 1000 mL continued. Diarrhoea became milder. 294 days after administration: Fluid replacement 1000 mL continued. Diarrhoea occurred 2 times/day. The patient started to eat porridge. 295 days after administration: Fluid replacement 1000 mL continued. Diarrhoea occurred 5 to 6 times/day. 296 days after administration: Fluid replacement 1000 mL

				continued. Diarrhoea resolved. 297 days after administration: Fluid replacement 1000 mL completed. 298 days after administration: The patient ate up all his porridge. Gastrointestinal symptoms improved. 301 days after administration: Cetuximab 400 mg was administrated. 305 days after administration: The patient was discharged from the hospital.
	Concomitant medications: irinotecan hydrochloride hydrate, chlorpheniramine maleate, dexamethasone sodium phosphate, granisetron hydrochloride, lactomin			

Clinical Laboratory Values

	Day 1 of administration	49 days after administration	56 days after administration	59 days after administration	61 days after administration	62 days after administration	292 days after administration	294 days after administration	295 days after administration
Serum creatinine (mg/dL)	0.88	0.78	2.17	0.64	0.65	0.65	1.08	0.76	0.64
BUN (mg/dL)	–	–	38	8	13	–	–	–	8

BUN: Blood urea nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 50s	Colon cancer (Liver metastasis, hypertension)	575 mg Once a week 1 day ↓ 360 mg Once a week 32 days	**Diarrhoea** History of prior treatment: FOLFOX (about 2 years and 3 months to 1 year and 9 months before cetuximab administration), FOLFIRI (about 1 year and 9 months to 1 year before cetuximab administration), bevacizumab (genetical recombination; about 1 year 6 months to 7 days before cetuximab administration) Surgery: Transverse colectomy (about 2 years and 4 months before cetuximab administration) Day 1 of administration: The patient started receiving cetuximab 575 mg/week and irinotecan hydrochloride hydrate 216 mg/week. 32 days after administration (Day of discontinuation): The patient had abdominal bloating without passage of gas. Moderate nausea and vomiting occurred. He was unable to eat. Watery stool was frequently noted. His body weight decreased by 2 kg. Fluid replacement was given for diarrhoea and vomiting (Grade 3). Treatment with cetuximab and irinotecan hydrochloride hydrate was discontinued. 3 days after discontinuation: The patient visited the outpatient department and was immediately admitted to the hospital because he had decreased kidney function (Grade 3) due to dehydration caused by diarrhoea and vomiting. Fluid replacement 1500 to 2000 mL and cefazolin sodium hydrate 1 g were started. 4 days after discontinuation: Diarrhoea and vomiting resolved. Fluid replacement 1500 to 2000 mL and cefazolin sodium hydrate 2 g continued. Diarrhoea stopped. Urination was normal. He was able to eat a small amount of food. 5 days after discontinuation: Fluid replacement 1000 mL was given. The patient's kidney function improved by fluid replacement. 6 days after discontinuation: Fluid replacement 1000 mL was given. He regained appetite and weight. 8 days after discontinuation: Kidney function returned to normal. The patient was discharged from the hospital.
	Concomitant medications: irinotecan hydrochloride hydrate, chlorpheniramine maleate, dexamethasone sodium phosphate, granisetron hydrochloride, amlodipine besilate			

Clinical Laboratory Values

	Day 1 of administration	3 days after discontinuation	5 days after discontinuation	8 days after discontinuation
BUN (mg/dL)	8	43	55	7
Serum creatinine (mg/dL)	0.62	3.66	1.85	0.78

BUN: Blood urea nitrogen

4

Revision of PRECAUTIONS

(No.215)

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 March 23, 2010 (excluding those presented in "3. Important Safety Information" of this Bulletin).

1

<Psychotropics>

Aripiprazol
Oxypertine
Olanzapine
Carpipramine Hydrochloride Hydrate
Carpipramine Maleate
Quetiapine Fumarate
Clocapramine Hydrochloride Hydrate
Chlorpromazine Hydrochloride
Chlorpromazine Hydrochloride/Promethazine Hydrochloride/Phenobarbital
Chlorpromazine Hibenzate
Chlorpromazine Phenolphthalinate
Spiperone
Sultopride Hydrochloride
Sulpiride
Zotepine
Timiperone
Trifluoperazine Maleate
Nemonapride
Haloperidol
Haloperidol Decanoate
Pipamperone Hydrochloride
Pimozide
Fluphenazine Decanoate
Fluphenazine Maleate
Prochlorperazine Maleate
Prochlorperazine Mesilate
Blonanserin
Propericiazine
Bromperidol
Perphenazine
Perphenazine Hydrochloride
Perphenazine Fendizoate
Perphenazine Maleate
Perospirone Hydrochloride Hydrate
Mosapramine Hydrochloride
Moperone Hydrochloride
Levomepromazine Hydrochloride
Levomepromazine Maleate

[Brand Name]	ABILIFY powder 1% (Otsuka Pharmaceutical Co., Ltd.) and the others
[Important Precautions]	Some cases of thromboembolism (e.g. pulmonary embolism, venous thrombosis) are reported in association with antipsychotics. Caution should be taken when using antipsychotics in patients with risk factors such as immobility, prolonged bed rest, obesity, dehydration.
[Adverse Reactions (clinically significant adverse reactions)]	**Pulmonary embolism, deep vein thrombosis**: Some cases of thromboembolism including pulmonary embolism and venous thrombosis are reported in association with antipsychotics. Patients should be carefully monitored. If symptoms such as shortness of breath, chest pain, pain in the extremities and oedema are observed, appropriate measures, such as discontinuing administration, should be taken..

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2 <Psychotropics >

Clozapine

[Brand Name] Clozaril Tablets 25 mg, 100 mg (Novartis Pharma K.K.)

[Important Precautions] Some cases of thromboembolism including pulmonary embolism and venous thrombosis are reported in association with antipsychotics. Caution should be taken when using antipsychotics in patients with risk factors such as immobility, prolonged bed rest, obesity, and dehydration.

3 <Psychotropics >

Risperidone

[Brand Name] RISPERDAL Fine Granules 1% (Janssen Pharmaceutical K.K.) and the others

[Important Precautions] Some cases of thromboembolism including pulmonary embolism and venous thrombosis are reported in association with antipsychotics. Caution should be taken when using antipsychotics in patients with risk factors such as immobility, prolonged bed rest, obesity, and dehydration.

[Adverse reactions (clinically significant adverse reactions)]

Pulmonary embolism, deep vein thrombosis : Some cases of thromboembolism including pulmonary embolism and venous thrombosis are reported in association with antipsychotics. Patients should be carefully monitored. If symptoms such as shortness of breath, chest pain, pain in the extremities and oedema are observed, appropriate measures, such as discontinuing treatment, should be taken.

Paralytic ileus: Paralytic ileus may occur followed by paralysis intestinal (e.g. anorexia, nausea/vomiting, severe constipation, abdominal distension or flaccidity, and stagnation of intestinal contents). If intestinal paresis occurs, appropriate measures, such as discontinuing treatment, should be taken. This drug is antiemetic in animals (dogs). Nausea/vomiting may therefore be inapparent.

4 <Allergic agents-Miscellaneous>

Zafirlukast

[Brand Name] ACCOLATE Tablets 20 mg, 40 mg (AstraZeneca K.K.)

[Important Precautions] Psychiatric symptoms including depression have been reported in overseas patients treated with this drug. Psychiatric symptoms such as suicidal ideation, suicide and aggressive behavior occurred in patients treated with other leukotriene antagonist, although the causality was unclear. Patients should be carefully monitored when using this drug.

5 <Allergic agents-Miscellaneous>

Pranlukast hydrate

[Brand Name] ONON drysyrup 10% (Ono Pharmaceutical Co., Ltd.) and the others

[Important Precautions] Psychiatric symptoms such as depression, suicidal ideation, suicide and aggressive behavior have been reported in patients treated with other leukotriene antagonist, although the causality was unclear. Patients should be carefully monitored when using this drug.

6 **<Allergic agents-Miscellaneous>**

Montelukast sodium

[Brand Name] KIPRES Fine Granules 4 mg (Kyorin Pharmaceutical Co., Ltd.) and the others

[Important Precautions] Psychiatric symptoms such as depression, suicidal ideation, suicide and aggressive behavior have been reported in patients treated with this drug, although the causal relationship was unclear. Patients should be carefully monitored when using this drug.

[Other Precautions] The result of a meta- analysis of 41 placebo-controlled clinical trials studies showed that1 of 9929 patients treated with this drug had suicidal ideation, while none of 7780 placebo patients did. The result of another meta- analysis of 46 placebo-controlled clinical trials showed that adverse events related to behavioral changes (e.g. insomnia and irritability) occurred in 319 of 11673 patients (2.73%) treated with this drug and in 200 of 8827 placebo patients (2.27%); however, there was no statistically significant difference.

7 **<Antineoplastics-Miscellaneous>**

Thalidomide

[Brand Name] THALED CAPSULE 100 (Fujimoto Pharmaceutical Corporation)

[Important Precautions] This drug is teratogenic (thalidomide embryopathy; see "WARNINGS"). When administering this drug to women with potentially pregnant, it should be started only after a negative pregnancy test is confirmed at four weeks, two weeks and immediately prior to the scheduled treatment. Periodic pregnancy tests must be given at intervals of not longer than four weeks to confirm that the patient is not pregnant.
The duration of one prescription should be at most 12 weeks.

5

List of products subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder 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 April 1, 2010)

Nonproprietary name Brand name on	Name of the marketing authorisation holder	Date of EPPV initiate
Bimatoprost LUMIGAN OPHTHALMIC SOLUTION 0.03%	Senju Pharmaceutical Co., Ltd.	October 5, 2009
Paroxetine Hydrochloride Hydrate PAXIL Tablets 10 mg, 20 mg*1	GlaxoSmithKline K.K.	October 16, 2009
Interferon Beta FERON Injections 1 (106 IU, 3 (106 IU, 6 (106 IU*2	Toray Industries, Inc.	October 16, 2009
Ribavirin REBETOL Capsules 200 mg*3	Schering-Plough K.K.	October 16, 2009
Voglibose BASEN Tablets 0.2, BASEN OD Tablets 0.2*4	Takeda Pharmaceutical Company Limited	October 19, 2009
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL, 400 mg/16 mL Intravenous Infusion*5	Chugai Pharmaceutical Co., Ltd.	November 6, 2009
Amlodipine Besilate/Atorvastatin Calcium Hydrate Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban	Pfizer Japan Inc.	December 2, 2009
Aprepitant EMEND Capsules 80 mg, 125 mg, EMEND Capsule Set	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate GLACTIV Tablets 25 mg, 50 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate JANUVIA Tablets 25mg, 50 mg, 100 mg	Banyu Pharmaceutical Co., Ltd.	December 11, 2009
Tadalafil Adcirca Tablets 20 mg	Eli Lilly Japan K.K.	December 11, 2009
Dexamethasone Cipecilate Erizas Capsule for Nasal Spray 400 μg	Nippon Shinyaku Co., Ltd.	December 11, 2009
Mesalazine ASACOL Tablets 400 mg	Zeria Pharmaceutical Co., Ltd.	December 16, 2009
Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cells) Cervarix	GlaxoSmithKline K.K.	December 22, 2009
Vancomycin Hydrochloride Vancomycin Ophthalmic Ointment 1%	Toa Pharmaceutical Co., Ltd.	December 28, 2009

Nitric Oxide INOflo for Inhalation 800 ppm	Air Water Inc.	January 1, 2010
Tosufloxacin Tosilate Hydrate OZEX fine granules 15% for pediatric	Toyama Chemical Co., Ltd.	January 12, 2010
Budesonide/Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses	AstraZeneca K.K.	January 13, 2010
Adalimumab (Genetical Recombination) HUMIRA SC Injection 40 mg Syringe 0.8 mL*6	Abbott Japan Co., Ltd.	January 20, 2010
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion 100*7	Mitsubishi Tanabe Pharma Corp.	January 20, 2010
Nonacog Alfa (Genetical Recombination) BeneFIX Intravenous 500, 1000, 2000	Wyeth K.K.	January 20, 2010
Fentanyl Durotep MT Patch 2.1 mg, 4.2 mg, 8.4 mg, 12.6 mg, 16.8 mg*8	Janssen Pharmaceutical K.K.	January 20, 2010
Pramipexole Hydrochloride Hydrate BI•Sifrol Tablets 0.125 mg, 0.5 mg*9	Nippon Boehringer Ingelheim Co., Ltd.	January 20, 2010
Miriplatin Hydrate MIRIPLA for Intra-arterial Injection 70 mg	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Meropenem Hydrate Meropen Vial for IV Drip Infusion 0.25 g, 0.5g, Meropen Kit for Intravenous Drip Infusion 0.5 g*10	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Peramivir Hydrate RAPIACTA Vial for IV Drip Infusion 150 mg, RAPIACTA Bag for IV Drip Infusion 300 mg	Shionogi & Co., Ltd.	January 27, 2010
Pneumococcal polysaccharide conjugate vaccine (adsorbed) Prevenar Suspension Liquid for S.C. Injection	Wyeth K.K.	February 24, 2010
Everolimus AFINITOR tablets 5mg	Novartis Pharma K.K.	March 8, 2010

*1: An additional indication for “treatment of patients with social anxiety disorder”
*2: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with ribavirin in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy”
*3: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with interferon beta in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy”
*4: An additional indication for “inhibition of the development of type II diabetes mellitus in patients with abnormal glucose tolerance (only when diet and exercise therapies failed to improve the condition)”
*5: An additional indication for “treatment of patients with advanced or recurrent, inoperable non-squamous non-small cell lung cancer except for squamous cell carcinoma”
*6: An additional indication for “treatment of patients with psoriasis vulgaris or psoriasis arthropathica, which is not adequately responsive to conventional therapies”
*7: An additional indication for “treatment of patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis, which is not adequately responsive to conventional therapies”
*8: An additional indication for “analgesia of moderate to severe chronic pain cannot be managed by treatments with non-opioid analgesics and weak opioid analgesics (only in patients who switch from an opioid analgesic)”
*9: An additional indication for “treatment of patients with moderate to severe idiopathic restless leg syndrome”
*10: An additional indication for “treatment of patients with febrile neutropenia”