Pharmaceuticals and Medical Devices Safety Information

No. 256 March 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. 256 March 2009

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

[Outline of Information]

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1	**Skin necrosis/ulcer following injection of hydroxyzine hydrochloride**	*P* *C*	MHLW has alerted healthcare providers regarding skin necrosis/ulcer following injection of hydroxyzine hydrochloride by describing injection site skin necrosis/ulcer in the "Other Adverse Reactions" and "Precautions in Use" sections of package inserts. Recently, as a result of review of injection site reactions, on February 13, 2009, MHLW requested relevant pharmaceutical companies to revise PRECAUTIONS of the package inserts to provide additional alert about skin necrosis/ulcer following injection. The content of these safety measures is described hereinafter.	3
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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.

1

Skin necrosis/ulcer following injection of hydroxyzine hydrochloride

Active ingredient Brand name (name of company)	Active ingredient	Brand name (name of company)
	Hydroxyzine hydrochloride (injectable dosage form)	Atarax-P Parenteral Solution (25 mg/ml and 50 mg/ml) (Pfizer Japan Inc.)
Therapeutic Category	Psychotropics	
Indications	Anxiety, tension, depressed mood in neurosis Anaesthetic premedication Prevention of preoperative or postoperative nausea/vomiting	

1. Introduction

Hydroxyzine hydrochloride (injectable dosage form) is psychotropics with the indications for "anxiety, tension, depressed mood in neurosis", "anaesthetic premedication", and "prevention of preoperative or postoperative nausea/vomiting", which has been marketed since March1966. The number of patients treated with this commonly-used drug per year is approximately 4 millions (December 2007 to November 2008, estimated by relevant pharmaceutical companies).

MHLW has alerted healthcare providers about skin necrosis/ulcer following injection of this drug by describing "swelling, induration, ulcer, phlebitis and pain" of the injection site in the "Other Adverse Reactions" section of the package inserts. In addition, MHLW has alerted about the following precautions for preventing effects on tissues or nerves in the case of intramuscular injection in "Precautions in Use" section of the package inserts.

1) This drug should be administered cautiously to the area other than nerves.
2) When repeatedly administered, injecting the same site should be avoided, for example, by alternately injected from left to right. Successive administration is not recommended for infants and children.
3) If complaints of megalgia from patients or a regurgitation of blood was found when inserting the needle, immediately remove an injection needle and use another injection site.
4) Do not knead strongly but gently apply pressure to the injection site [Intradermal or subcutaneous extravasation of fluid may lead to local pain and local disorder].

Recently, as a result of review of the injection sites reactions, on February 13, 2009, MHLW requested relevant pharmaceutical companies to revise PRECAUTIONS of the package inserts to provide additional alert about skin necrosis/ulcer following injection and precautions for intramuscular injection. The content of these safety measures is described hereinafter.

2. Reports of skin necrosis/ulcer following injection

From April 1994 to September 2008, 45 cases were reported including adverse reactions such as "swelling, induration, ulcer, phlebitis and pain" caused by this drug. However some cases were not fully evaluated the causality between the drug and the adverse reactions due to the lack of information, etc. As a result of review of the reports of these adverse reactions, 9 serious cases of skin necrosis/ulcer following injection that required necrectomy or skin graft were identified.

Therefore, MHLW requested relevant companies to add a description of "injection site skin necrosis/ ulcer" in the "Clinically significant adverse reactions" section of package inserts to provide additional alert from the view of an expert review.

Since this drug has high acidity, intradermal or subcutaneous extravasation of fluid may lead to local pain and local disorder as described above. Therefore, MHLW has called for reminding healthcare professionals not to knead strongly but to apply pressure gently to the injection site after intramuscular injection. As a result of the review of abovementioned 45 cases of adverse reactions, 9 cases described the situations of intramuscular injection and kneading of the injection site. Those who kneaded injection sites include 3 healthcare professionals and 1 patient (include 5 unknown cases). [Refer to **Table** below]

Table Number of adverse reactions from skin necrosis/ulcer following injection of hydroxyzine hydrochloride

Number of adverse reaction (number of cases)	Number of reports include kneading of the injection site	Number of people who kneaded the injection site
45	9	Healthcare professional: 3 Patient: 1 Unknown: 5

Based on these results, MHLW requested relevant companies to describe not to knead strongly but gently apply pressure to the injection site after intramuscular injection to provide additional alert from the view of an expert review.

Healthcare providers should take further cares to ensure closely monitoring of injection site reactions and not to knead strongly the injection site. Healthcare providers should also be encouraged to adequately advise patients to refrain from kneading strongly the injection site.

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

[Important Precautions]

Intradermal or subcutaneous extravasation of fluid may occur and lead to injection site reaction such as skin necrosis/ulcer, pain, etc. after kneading injection sites when intramuscular injecting of this drug. **Do not knead strongly but gently apply pressure to the injection site.**

[Adverse Reactions (clinically significant adverse reactions)]

Injection site skin necrosis/ulcer: Injection site skin necrosis/ulcer may occur and lead to scar formation. If the skin necrosis/ulcer is severe, necrectomy or skin graft may be needed. If pain, swelling, or induration of injection site is observed, appropriate measures, such as discontinuation of administration, should be taken.

[Adverse Reactions (other adverse reactions)]

Injection site: swelling, induration, phlebitis, numbness, paraesthesia, muscle atrophy, muscle contracture, pain

[Precautions in use]

Intramuscular injection: Skin necrosis/ulcer, pain, induration, numbness, paraesthesia or muscular disorder such as muscle atrophy or muscle contracture at the injection site may occur following intramuscular injection. The following precautions should be observed for preventing effects on tissues or nerves before intramuscular injection.

1) This drug should be administered cautiously to **the area other than nerves**.
2) **If complaints of megalgia from patients or a regurgitation of blood was found** when inserting the needle, **immediately remove an injection needle** and use another injection site..
3) **Do not knead strongly but gently apply pressure** to the injection site. [Intradermal or subcutaneous extravasation of fluid may lead to injection site reactions such as skin necrosis/ulcer, and pain, etc.].
4) When repeatedly administered, **injecting the same site should be avoided,** for example**,** by alternately injected from left to right.
Successive administration is not recommended for infants and children.

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Preoperative administration (none)	50 mg Once	**Skin necrosis at the injection site** Underlying disease: right cholesteatoma Before administration: The patient was hospitalized in the department of otolaryngology for right cholesteatoma. Day of administration: In the afternoon, the patient was given an intramuscular injection of this drug as preoperative administration of right cholesteatoma. Immediately after the administration, skin red and skin induration were developed at the injection site, the nurse massaged the site. 1 day after administration: In the morning, the skin turned slightly green and vascular insufficiency was observed, gentamicin sulfate ointment and fradiomycin sulfate were applied. 2 days after administration: The patient was applied dimethyl isopropylazulene ointment at the department of dermatology and she was followed up. 10 days after administration: The patient was discharged from the department of otolaryngology. 40 days after administration: The patient visited the department of plastic surgery and skin necrosis was excised. 83 days after administration: The excised site became scarred and recovered.
	Concomitant medications: pethidine hydrochloride·levallorphan tartrate			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Rest at testing (Parkinson's disease, hypertension, constipation, gastritis, peripheral neuropathy)	50 mg Once	**Skin necrosis at the injection site, skin ulcer at the injection site** Approx. 20 years before administration: The patient developed Parkinson's disease. Unknown: The patient was hospitalized for controlling oral drug for Parkinson's disease. Day of administration: The patient was given an intramuscular injection of 50 mg of this drug in the lateralis of the right upper arm as pretreatment for head MRI. 2 days after administration: His family members noticed skin eruption, skin red on the lateralis of his right upper arm while taking a bath. 5 days after administration: Skin eruption and skin red turned into 15-mm-sized black necrosis was found during examination. The patient complained of pain. The redness, swelling and induration of 40 mm in diameter were found around the lesion. The lesion was covered with gauze after washing with physiological saline solution. Purulent discharge was not observed. 6 days after administration: A 15 mm in diameter x 3 to 4 mm necrosis including skin and subcutaneous tissues was excised. The lesion was covered with a saline wet gauze after washing with physiological saline solution every day. 9 days after administration: The remaining necrosis tissues were excised. 12 days after administration: Application of a coating material to the lesion was started. 30 days after administration: The patient had no pain. 34 days after administration: The symptom improved, and the patient was discharged from the hospital for his own reasons.
	Concomitant medications: magnesium oxide, clonazepam, levodopa/carbidopa, spironolactone, bromocriptine mesilate, nizatidine, nicardipine hydrochloride, selegiline hydrochloride, mecobalamin, amantadine hydrochloride			

2

Important Safety Information

This section presents contents of revisions and 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 Notifications dated February 13, 2009.

1 Tocilizumab (Genetical recombination)

Brand Name (name of company)	ACTEMRA 80 mg, 200 mg, and 400 mg for Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Biological preparations-Miscellaneous
Indications	○ The diseases which are not adequately responsive to conventional therapies Rheumatoid arthritis (including prevention for structural damage of joints), polyarticular-course juvenile idiopathic arthritis, and systemic-onset juvenile idiopathic arthritis ○ Improvement of symptoms and laboratory findings of Castleman's disease (increased C-reactive protein, fibrinogen, or erythrocyte sedimentation rate, decreased hemoglobin or albumin, and general malaise). This drug is only indicated for patients who are not indicated for lymphadenectomy.

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

[Careful Administration] Patients with a history of interstitial pneumonia

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia: Interstitial pneumonia may occur in patients with rheumatoid arthritis. Patients should be carefully monitored for respiratory symptoms of pyrexia, cough, and dyspnoea, etc. If any abnormalities are observed, examinations such as a chest X-ray, CT, and blood gas testing should be immediately conducted, and in addition to discontinuing administration of this drug, differential diagnosis of pneumocystis pneumonia (β-D glucan measurement, etc.) should be considered, and appropriate measures should be taken. In addition, when administering the drug to patients with a history of interstitial pneumonia, caution should be exercised by conducting periodic interviews, etc.

<Reference Information>

The number of the reported adverse reaction cases in about the last 3 years (June 13, 2005 to January 13, 2009) (events for which a causality to the drug could not be denied)

- Interstitial pneumonia: 7 cases (of which 1 had a fatal case: female in 70s)

The number of patients treated with Tocilizumab for a year estimated by MAH (Marketing Authorization Holder): approximately 5000 (February 2008 to January 2009)

Marketed in Japan in: June 2005
(ACTEMRA 200 mg for Intravenous Infusion)
June 2008
(ACTEMRA 80 mg and 400 mg for Intravenous Infusion)

Date of approval of an additional indication for rheumatoid arthritis: April 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Rheumatoid arthritis (interstitial pneumonia)	400 mg/ 4 weeks Twice	**Aggravation of interstitial pneumonia** Approx. 15 months before administration: The patient developed rheumatoid arthritis (RA). [Past treatments] Bucillamine Tablets at 100 mg/day (from more than 3 months to 25 days before administration of this drug) Salazosulfapyridine enteric tablets at 1000 mg/day (from more than 3 months before administration of this drug until day 1 of administration of this drug) Prednisolone at 5 mg/day (continued since more than 3 months before administration of this drug) Methotrexate could not be used due to concomitant interstitial pneumonia. 104 days before administration: Chest X-ray was conducted, and no findings of tuberculosis were confirmed. 81 days before administration: Laparoscopic cholecystectomy was conducted (for a treatment of gallbladder polyp). 11 days before administration: Electrocardiogram was performed, and abnormal findings were observed (ventricular extrasystoles). 9 days before administration: Tuberculin test: negative 6 days before administration: ESR (erythrocyte sedimentation rate): 110 mm/hr; TJC (tender joints count): 6; SJC (swollen joints count) : 6. On day 1 of administration: The patient received the first administration of this drug (400 mg/4 weeks). 30 days after administration (day of last administration): The patient received the second administration of this drug (the last administration). ESR: 11 mm/hr, VAS (visual analog scale) : 20 mm. 12 days after the last administration: Dyspnoea exertional had continued for a week. The patient had no pyrexia, cough, and sputum. She had an appetite. Rales were heard over the middle and lower lung field. KL-6: 617 U/mL; SPA: 26.9 ng/mL; SPO_2: 98%; CRP: 0.03 mg/dL. No changes were found in CHI (contrast harmonic imaging) of lung as same as CT conducted the previous day. No new change of lung was observed. CT findings: Similar to the result of CT conducted 10 days before administration, honeycomb shadows dominant on (lung field) peripheral and ground-glass opacity were observed. (Mediastinum) Dominant size LN swelling was not confirmed. 28 days after the last administration: Cough and shortness of breath developed. The patient had significant cough and no arthralgia. Rales were heard over the lung field. LDH: 318 IU/L; KL-6: 637 U/mL; SPO_2: 98%, and almost no change was observed in chest X-ray film.

				35 days after the last administration: The patient developed dry cough and exertional dyspnoea. She had an appetite and no arthralgia. Body temperature was 37.0°C. The rales were heard over the entire lung field. SPO_2: 96%; LDH: 369 IU/L; KL-6: 857 U/mL; SP-A: 52.2 ng/mL; CRP: 0.04 mg/dL. Lung CT showed pale shadows randomly distributed over the lung field compared to the findings from 12 days after the last administration. Interstitial pneumonia was tend to aggravated. Prednisolone 20 mg/day (4 days) and tacrolimus hydrate 1 mg/day were concomitantly used. CT findings: Widespread honeycomb-like changes were confirmed mainly over the apical portion of the lung. CT showed ground-glass opacity randomly distributed over the upper and middle lung field compared to the findings from 12 days after the last administration. Aggravation of interstitial pneumonia was suspected. Calcification was confirmed in a portion of the coronary artery. Pleural effusion (−). Diagnosis: RA-IP. A follow-up observation was conducted. 36 days after the last administration: Interstitial pneumonia was aggravated. Methylprednisolone sodium succinate for injection at 500 mg/day (3 days) was administered. Tazobactam sodium/piperacillin sodium for injection at 5 g/day (5 days) was administered. Initial symptom: cough Transbronchial lung biopsy, pulmonary function test, and BAL were not performed. 39 days after the last administration: The patient had no pyrexia, cough, and sputum. Exertional shortness of breath was confirmed. She had an appetite. SPO_2 was 96%. Decreased inspiration and mild wheezing was confirmed. Prednisolone at 40 mg/day (11 days) was administered. 40 days after the last administration: CT showed improvement of randomly distributed diffuse reticular shadows. CT findings: Based on honeycomb shadows and ground-glass opacity dominant on peripheral (lung field), pneumopathy in RA was considered. The cause of the symptom was suspected to be the acute aggravation. Macular ground-grass opacity was slightly improved compared to the findings from CT conducted 35 days after the last administration. 49 days after the last administration: CT showed slight improvement. CT findings: Based on honeycomb shadows and ground-glass opacity dominant on peripheral (lung field), pneumopathy in RA was considered. Ground-glass opacity in right upper lobe was slightly improved compared to the findings from CT conducted 40 days after the last administration. Pleural effusion was not confirmed. 50 days after the last administration: Prednisolone at 35 mg/day (8 days) was administered. 58 days after the last administration: Improvement trendency. Prednisolone at 30 mg/day (7 days) was administered. 65 days after the last administration: Chest X-ray film showed no aggravation. Prednisolone at 25 mg/day (continuous administration) was administered.

				69 days after the last administration: Cough, shortness of breath, and aggravation of interstitial pneumonia were improved. CT findings: Based on honeycomb shadows and ground-glass opacity dominant on peripheral (lung field), pneumopathy in RA was considered. There was nearly no change from the previous examination. Pleural effusion was not confirmed. 70 days after the last administration: No aggravation was confirmed in chest X-ray film and CT. Some improvement was observed in crepitations.
	Concomitant medications: prednisolone, salazosulfapyridine, zaltoprofen, loxoprofen sodium hydrate, diclofenac sodium			

Clinical Laboratory Values

	6 days before administration	12 days after the last administration	28 days after the last administration	35 days after the last administration	48 days after the last administration	69 days after the last administration
WBC (/mm^3)	6800	8000	6700	8000	12000	7200
Neutrophils (%)	52.1	60.1	37.6	44.8	68.7	66.2
Lymphocytes (%)	34.1	30.2	47.2	42.4	21.6	24.7
PLT ($\times10^4$/mm^3)	46.1	28.2	25.8	28.6	30.3	16.6
Albumin (g/dL)	—	4.2	4.1	4.1	—	—
LDH (IU/L)	—	269	318	369	322	348
ESR (mm/hr)	110	11	7	7	—	—
CRP (mg/dL)	6.03	0.03	0.02	0.04	0.09	0.59

WBC: White Blood Cell
PLT: Platelet
LDH: Lactate Dehydrogenase
ESR: Erythrocyte Sedimentation Rate
CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Rheumatoid arthritis (interstitial pneumonia, hyperlipidemia)	400 mg/ 4 weeks Once	**Aggravation of interstitial pneumonia** Approx. 4 years before administration: The patient developed rheumatoid arthritis. [Past treatments] Methotrexate at 8 mg/week was administered (until 76 days prior to the day of administration of this drug, for approximately 1 year and 5 months long). Prednisolone at 10mg/day (continued since more than 3 months before administration of this drug). 200 days before administration: Tuberculin test was negative. 7 days before administration: CT findings: Nothing special of note Day of administration: Chest X-ray was conducted before administration, and no findings of tuberculosis was confirmed. Electrocardiogram was conducted, and no abnormal findings were observed. No symptom was observed. As XP and CT showed no problem, first administration of this drug was conducted (400 mg/4 weeks, last administration). The other drugs were continuously administered without any change. ESR: 70 mm/hr, TJC: 21, SJC: 13, VAS: 67 mm 7 days after administration: Follow-up CT confirmed bacterial pneumonia in the right middle lung field. Drip infusion of meropenem hydrate at 0.5 g x 2 times/day was started on the same day. CT findings: consolidation (infiltrative shadow) in S5 and S6 of the right lung. Diagnosis: pneumonia bacterial Sputum gram stain: only oral indigenous bacteria were found. Identification by sputum culture: only oral indigenous bacteria were identified. Sputum cytology, transbronchial lung biopsy, pulmonary function test, and BAL were not performed. 11 days after administration: No symptom was observed. Although improvement in bacterial pneumonia was confirmed, follow-up CT showed pneumonia, follow-up CT conducted after the administration of antibiotics showed interstitial image and ground-glass opacity in hilum of both lung. Interstitial pneumonia developed. β-D-glucan and cytomegalovirus antigen were both negative. Although the adverse reactions due to meropenem hydrate was suspected, meropenem hydrate was thought to be negative because the similar symptoms were not observed following the use of the drug in the past. CT findings: Ground-glass opacity in the right upper and middle lung field. Diagnosis: interstitial pneumonia 12 days after administration: No symptom was observed. KL-6: 221U/mL. 16 days after administration: Mini-pulse therapy (methylprednisolone 500 mg/day) was conducted (3 days). Follow-up CT showed gradual improvement.

				18 days after administration: Follow-up CT showed that ground-glass opacity disappeared. Interstitial pneumonia was improved. 30 days after administration: CT conducted after pulse therapy showed that images of pneumonia and interstitial images were completely disappeared. ESR: 52 mm/hr, TJC: 11, SJC: 4, VAS: 26 mm 51 days after administration: KL-6 was 288 U/mL. 121 days after administration: No symptom was observed.
	Concomitant medications: prednisolone, irsogladine maleate, rebamipide, indometacin, lansoprazole, sodium ferrous citrate, clarithromycin, carbocisteine, sodium risedronate hydrate			

Clinical Laboratory Values

	Day of administration	9 day after administration	11 days after administration	30 days after administration	51 days after administration
WBC (/mm^3)	11420	7550	6060	—	11170
Neutrophils (%)	92	—	—	—	76
Lymphocytes (%)	7	—	—	—	15
PLT ($\times10^4$/mm^3)	30.2	24.8	21.3	—	26.4
TP (g/dL)	6.1	—	—	6.9	7.0
Albumin (%)	54.0	—	—	63.1	64.1
LDH (IU/L)	246	265	231	389	359
ESR (mm/hr)	70	—	—	52	23
CRP (mg/dL)	7.11	0.11	0.06	2.13	0.07

WBC: White Blood Cell
PLT: Platelet
TP: Total Protein
LDH: Lactate Dehydrogenase
ESR: Erythrocyte Sedimentation rate
CRP: C-Reactive Protein

3

List of products subject to Early Post-marketing Phase Vigilance

(As of March 1, 2009)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Estradiol / Julina 0.5 mg	Bayer Yakuhin, Ltd.	September 16, 2008
Mometasone Furoate Hydrate / Nasonex Nasal Solution 50 μg 56 metered spray	Schering-Plough K.K.	September 16, 2008
Cetuximab (genetical recombination) / Erbitux Injection 100 mg	Merck Serono Co., Ltd.	September 19, 2008
Tazobactam·Piperacillin Hydrate / ZOSYN	Taiho Pharmaceutical Co., Ltd.	October 1, 2008
Neostigmine Methylsulfate·Atropine Sulfate Hydrate / Atvago Reverse Intravenous Injection Syringe 3 mL and 6 mL	Terumo Corporation	October 1, 2008
Ramosetron Hydrochloride / Irribow Tablets 2.5 μg and 5 μg	Astellas Pharma Inc.	October 7, 2008
Rifabutin / MYCOBUTIN Capsules 150 mg	Pfizer Japan Inc.	October 7, 2008
Pegaptanib Sodium / MACUGEN IVT Inj. KIT 0.3 mg	Pfizer Japan Inc.	October 14, 2008
Interferon Alfa (NAMALWA) / Sumiferon 300 and 600, Sumiferon DS 300 and 600[*1]	Dainippon Sumitomo Pharma Co., Ltd.	October 16, 2008
Estradiol / Julina Tablets 0.5 mg[*2]	Bayer Yakuhin, Ltd.	October 16, 2008
Freeze -dried Polyethylene Glycol Treated Human Normal Immunoglobulin / kenketu glovenin-I-NICHIYAKU[*3]	Nihon Pharmaceutical Co., Ltd.	October 16, 2008
Ciclosporin / Neoral Oral Solution, Neoral Capsules 10 mg, 25 mg, and 50 mg[*4]	Novartis Pharma K.K.	October 16, 2008
Somatropin (genetical recombination) / Genotropin 5.3 mg, Genotropin MiniQuick s.c. inj. 0.6 mg, 1.0 mg, 1.4 mg, Genotropin Inj. 12 mg[*5]	Pfizer Japan Inc.	October 16, 2008
Bepridil Hydrochloride Hydrate / Bepricor Tablets 50 mg and 100 mg[*6]	Schering-Plough K.K.	October 16, 2008
Adapalene / Differin Gel 0.1%	Galderma Pharma S.A.	October 21, 2008
Tacrolimus Hydrate / Graceptor Capsules 0.5 mg, 1 mg, and 5 mg	Astellas Pharma Inc.	October 28, 2008
Anti-human Thymocyte Immunoglobulin, Rabbit / Thymoglobuline for Intravenous Infusion 25 mg	Genzyme Japan K.K.	November 28, 2008

Pirfenidone Pirespa Tablets 200 mg	Shionogi & Co., Ltd.	December 12, 2008
Lamotrigine Lamictal Tablets 2 mg, 5 mg, 25 mg, and 100 mg	GlaxoSmithKline K.K.	December 12, 2008
Tafluprost TAPROS ophthalmic solution 0.0015%	Santen Pharmaceutical Co., Ltd.	December 16, 2008
Phenobarbital Sodium NOBELBAR 250 mg for Injection	Nobelpharma Co., Ltd.	December 16, 2008
Haemophilus influenzae type b conjugate vaccine ActHIB	Sanofi Pasteur-Daiichi Sankyo Vaccine Co., Ltd.	December 19, 2008
Thyrotropin Human Alfa (genetical recombination) THYROGEN IM Injection 0.9 mg	Sato Pharmaceutical Co., Ltd.	January 13, 2009
Etravirine INTELENCE Tablets 100 mg	Janssen Pharmaceutical K.K.	January 19, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 100 Diskus *7	GlaxoSmithKline K.K.	January 21, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 250 Diskus *8	GlaxoSmithKline K.K.	January 21, 2009
Ganirelix Acetate Ganirest Subcutaneous 0.25mg Syringe	Schering-Plough K.K.	January 22, 2009
Maraviroc CELSENTRI Tablets 150 mg	Pfizer Japan Inc.	January 22, 2009
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

*1: An additional indication for "the improvement of viremia in compensated cirrhosis type C (except in the patients with HCV serogroup 1 and high blood HCV-RNA level)"

*2: An additional indication for "osteoporosis postmenopausal"

*3: An additional indication for "pemphigus (only for cases not adequately responsive to corticosteroids)"

*4: An additional indication for "dermatitis atopic (patients who are not adequately responsive to conventional therapies)"

*5: An additional indication for "SGA (Small-for-Gestational Age) dwarfism without epiphyseal closure"

*6: An additional indication for "sustained arterial fibrillation when other antiarrhythmic agents cannot be used or are ineffective"

*7: An additional administration for "pediatrics"

*8: 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)"