# Pharmaceuticals and Medical Devices Safety Information

## No. 255 February 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. 255 February 2009

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

## [Outline of Information]



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

**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

# 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 December 19, 2008 and January 9, 2009.

## 1 Sorafenib Tosilate

| | |
|---|---|
| **Brand Name (name of company)** | Nexavar 200 mg (Bayer Yakuhin, Ltd.) |
| **Therapeutic Category** | Antineoplastics-Miscellaneous |
| **Indications** | Radically non-resectable or metastatic renal cell carcinoma |

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

**[Important Precautions]**

Acute lung disorder and interstitial pneumonia may occur. Before administration, patients should be carefully monitored for clinical symptoms such as dyspnoea, pyrexia, and cough, etc. If any abnormalities are observed, examinations such as a chest X-ray should be immediately conducted. If acute lung disorder or interstitial pneumonia is suspected, administration should be discontinued and appropriate measures such as administration of adrenal corticosteroids should be taken. Patients should be instructed to contact their physicians immediately if symptoms such as dyspnoea, pyrexia, and cough, etc. occur.

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

**Acute lung disorder, interstitial pneumonia:** Acute lung disorder or interstitial pneumonia may occur. Patients should be carefully monitored for clinical symptoms such as dyspnoea, pyrexia, and cough etc. If any abnormalities are observed, examinations such as a chest X-ray should be immediately conducted. If acute lung disorder or interstitial pneumonia is suspected, administration should be discontinued and appropriate measures such as administration of adrenal corticosteroids should be taken.

**<Reference Information>**

The number of reported adverse reaction cases in about the last 10 months (February 25, 2008 to December 17, 2008) (events for which a causality to the drug could not be denied)

- Acute lung disorder, interstitial pneumonia: 4 cases (of which 2 had fatal cases)

The number of patients treated with Sorafenib estimated by MAH (Marketing Authorisation Holder): approximately 2000 (February 25, 2008 to December 17, 2008)

Marketed in Japan in: April 2008 (compassionate use February 25, 2008)

## Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male<br>50s | Stage IV renal cell carcinoma (cancer pain, diverticulitis intestinal, metastases to bone, metastases to lung) | 400 mg (alternate-day)<br>217 days<br>↓<br>800 mg<br>45 days<br>↓<br>(60 day drug withdrawal)<br>↓<br>800 mg<br>56 days | **Interstitial pneumonia**<br>14 days before administration:<br>The patient was reexamined due to metastatic bone tumor. CT findings: Nothing special of note other than metastases to lung.<br>On day 1 of administration:<br>The drug was initiated (400 mg/alternate-day) after import by the individual.<br>On day 218 of administration:<br>The dose was increased to 800 mg/day.<br>On day 253 of administration:<br>Chest CT confirmed metastases to lung (the size and number of metastases to lung increased; other than this nothing special of note).<br>On day 263 of administration:<br>The drug was withdrawn. Treatment with teceleukin (genetical recombination) was started (700000 units, 3 times a week).<br>On day 33 of withdrawal:<br>CT findings: Nothing special of note other than progression of metastases to lung.<br>On day 61 of withdrawal (On day 1 of readministration):<br>The administration of this drug was recommenced with the patient's and his families strong wishes.<br>On day 26 to 35 of readministration:<br>The patient was readministered blood transfusions of 2 units concentrated human red blood cells on day 26, 27, 34, and 35 of readministration.<br>On day 54 of readministration:<br>Dyspnoea began to be observed.<br>On day 57 of readministration<br>(day of discontinuation of readministration):<br>The patient was hospitalized due to dyspnoea. CT revealed ground-glass opacity in right lung, and prominent left pleural effusion. Pleural puncture revealed effusion pleural bloody (the cause of pleural effusion according to the reporting physician was bleeding from metastases to lung). Condition of the primary disease: diagnostic imaging found no other metastases than to the bone and lung, and no local recurrence. The drug was discontinued after interstitial pneumonia was diagnosed.<br>SP-D (standard value: 0–109.9 ng/mL): 70.4 ng/mL<br>KL-6 (standard value: 0–409 U/mL): 565 U/mL<br>4 days after discontinuation:<br>A trocar was placed into the left thoracic cavity. Cytodiagnosis: class 4<br>10 days after discontinuation:<br>Chest X-ray findings worsened.<br>11 days after discontinuation:<br>Corticosteroid therapy of dexamethasone sodium phosphate 4 mg was started.<br>Although respiratory symptoms improved, chest X-ray findings worsened.<br>SP-D: 229.2 ng/mL; KL-6: 625 U/mL; DLST: 7.6% (+)<br>19 days after discontinuation:<br>The patient died of respiratory failure. Autopsy: no information |

| | |
|---|---|
| | Concomitant medications: oxycodone hydrochloride hydrate, etodolac, milnacipran hydrochloride, zolpidem tartrate, flunitrazepam, interferon alpha (NAMALWA), zoledronic acid hydrate, metoclopramide, prochlorperazine maleate, sennoside, magnesium oxide |

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Male 70s | Stage IV renal cell carcinoma (Metastases to lymph nodes) | 800 mg 39 days | **Interstitial pneumonia**<br>Medical history: interstitial pneumonia, chronic renal failure, rheumatoid arthritis<br>On day 1 of administration:<br>This drug was initiated at 800 mg/day.<br>On day 40 of administration (day of discontinuation):<br>The patient experienced anorexia from around this time. This drug was discontinued.<br>3 days after discontinuation:<br>The patient died at home in the morning.<br>Postmortem CT confirmed pleural effusion. Aggravation of interstitial pneumonia was suspected.<br>Cause of death: respiratory failure; autopsy: not performed |
| | Concomitant medications: rebamipide, teprenone, actarit, famotidine, prednisolone, acetaminophen | | | |

## 2 Etanercept (genetical recombination)

| | |
|---|---|
| **Brand Name (name of company)** | ENBREL 25 mg for S.C. Injection, ENBREL 25 mg Syringe 0.5 mL for S.C. Injection (Wyeth K.K.) |
| **Therapeutic Category** | Miscellaneous metabolism agents |
| **Indications** | Rheumatoid arthritis (only in cases which are not adequately responsive to conventional therapies) |

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

**[Warning]**

**WARNING**

Infectious disease

Tuberculosis: Tuberculosis including disseminated tuberculosis (miliary tuberculosis) and extrapulmonary tuberculosis leading to death (e.g. pleural, lymph node) has been reported in patients receiving this drug. Since symptoms may become manifest or aggravated in patients infected with tuberculosis, patients should be tested for latent tuberculosis infection prior to initiating this drug and complete interview regarding tuberculosis, chest X-ray and tuberculin test, and chest CT test as necessary should be performed. Treatment of latent tuberculisis should be initiated prior to therapy with this drug. <u>There have also been reports of cases in which active tuberculosis was confirmed after administration of this drug in patients who tested negative for latent tuberculosis infection.</u>

**[Important Precautions]**

Since symptoms may emerge and worsen in patients infected with tuberculosis, patients should be tested for latent tuberculosis infection prior to initiating this drug and complete interview regarding tuberculosis, chest X-ray and tuberculin test, and chest CT test as necessary should be performed. Particularly for patients who are suspected to be infected with tuberculosis, the presence or absence of tuberculosis infection should be appropriately confirmed by multiple tests. The patient should consult a physician who has clinical experience with tuberculosis. Patients with tuberculosis or those suspected of tuberculosis through tests should be initiated an antitubercular agent prior to this drug. As active tuberculosis was confirmed after administration of this drug in patients who tested negative for latent tuberculosis infection, the patient should be closely monitored for the onset of tuberculosis symptoms during the administration of this drug. Patients should be instructed to contact their physician immediately if symptoms of tuberculosis (e.g. persistent cough, pyrexia) are suspected.

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

**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythema multiforme:** Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), and erythema multiforme may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

**Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis:** Antineutrophilic cytoplasmic antibody (ANCA) positive vasculitis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

**Acute renal failure, nephrotic syndrome:** Acute renal failure or nephrotic syndrome 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, 2005 to October 7, 2008) (events for which a causality to the drug could not be denied)

- Acute renal failure, nephrotic syndrome: 16 cases (of which 1 had a fatal case)

The number of patients treated with Etanercept for a year estimated by MAH: approximately 27000 (December 2007 to November 2008)

Marketed in Japan in: March 2005 (ENBREL 25 mg for S.C. Injection)
June 2008 (ENBREL 25 mg Syringe 0.5 mL for S.C. Injection)

## Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 60s | Rheumatoid arthritis (Pneumoconiosis, diabetes mellitus, interstitial lung disease) | 25 mg (twice a week) 3 days | **Acute renal failure, pneumonia bacterial**<br>217 days before administration:<br>Although the patient was being treated for rheumatoid arthritis at another hospital, the condition was poorly controlled. Administration of prednisolone, sodium risedronate hydrate, mizoribin, salazosulfapyridine, etodolac, and sodium rabeprazole was started. Even after this, there was no improvement of symptoms with high CRP and MMP-3 values, and the condition was poorly controlled.<br>159 days before administration:<br>Tacrolimus hydrate 10 mg was added. After this, symptoms improved slightly.<br>21 days before administration:<br>Symptoms worsened again. CRP and MMP-3 levels were high at 4.93 mg/dL and 568 ng/mL, respectively.<br>Unknown:<br>Tuberculin test (−), chest CT inflammation images (−), Gaffky (−), MTD (−), and common bacteria (−).<br>On day 1 of administration:<br>Administration of this drug was started.<br>On day 2 of administration:<br>Improvement of arthralgia was confirmed.<br>On day 3 of administration (day of discontinuation):<br>The second administration of this drug was performed.. The pyrexia occurred from the evening.<br>General malaise continued thereafter, and dyspnoea was exacerbated. Administration of this drug was discontinued.<br>5 days after discontinuation (day of onset):<br>Onset of acute renal failure, bacterial pneumonia. Chest X-ray and CT confirmed pneumonia and bacterial pneumonia was diagnosed. CRP levels increased to 42.61 mg/dL, $O_2$ and antibiotics were administered. Levels of BUN was 72.7 mg/dL, creatinine was 3.41 mg/dL.<br>«Bacteria test»<br>Sample: sputum, culture; bacterial strain: *E.coli*<br>On day 2 of onset:<br>$SpO_2$ levels decreased, an artificial respirator was attached, and endotoxin adsorption therapy was started.<br>On day 14 of onset:<br>The patient died of pneumonia and acute renal failure. |
| | Concomitant medications: mizoribin, salazosulfapyridine, tacrolimus hydrate, prednisolone, etodolac | | | |

## Clinical Laboratory Values

| | On day 1 of administration | 5 days after discontinuation (day of onset) | On day 3 of onset | On day 10 of onset |
|---|---|---|---|---|
| WBC (/$mm^3$) | 11000 | 5300 | 28000 | 19600 |
| BUN (mg/dL) | 21.8 | 72.7 | 125.2 | 250 |
| Creatinine (mg/dL) | 0.48 | 3.41 | 4.52 | 6.49 |
| CRP (mg/dL) | 1.84 | 42.61 | — | — |

WBC: White Blood Cell CRP: C-Reactive Protein
BUN: Blood Urea Nitrogen

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Female 60s | Rheumatoid arthritis (none) | 25 mg (twice a week) 44 days | **Nephrotic syndrome**<br>Approx. 8 months before administration:<br>Systemic arthralgia was confirmed.<br>On day 1 of administration:<br>Administration of this drug was started.<br>On day 34 of administration:<br>Onset of nephrotic syndrome. Protein urine was confirmed.<br>On day 48 of administration (day of discontinuation):<br>Lower leg oedema, hypoalbuminaemia, protein urine were confirmed. Administration of this drug was discontinued.<br>15 days after discontinuation:<br>Oral administration of furosemide 20 mg/day was started.<br>28 days after discontinuation:<br>Uric protein was 10 g/g・Cre (adjusted creatinine value).<br>32 days after discontinuation:<br>The patient was hospitalized at the department of nephrology.<br>35 days after discontinuation:<br>Renal biopsy was conducted. Proliferation of mesangial cells and increased mesangial matrix were confirmed through HE staining and showed a membranoproliferative glomerulonephritis (MPGN) -like pattern. PAS and PAM staining showed double contour (−) and spike (−), and all antibodies including κ and λ were negative by the fluorescence antibody technique. While electron microscopy revealed double contour in some tissue, deposits were (−). Although adhesion to the visceral layer of Bowman's capsule and obstruction of the lumen were observed in a portion of the glomerulus, the condition had not developed to the point of focal glomerulosclerosis (FGS).<br>42 days after discontinuation:<br>Oral administration of prednisolone 40 mg/day was started. Protein urine was 2.1 g/g Cre (1.4 g/day) and showed a decreasing tendency.<br>Approx. 1.5 months after discontinuation:<br>Nephrotic syndrome improved.<br>49 days after discontinuation:<br>Prednisolone was decreased to 30 mg/day. |
| | Concomitant medications: isoniazid, diclofenac sodium (oral dosage form, suppository), misoprostol | | | |

## Clinical Laboratory Values

| | On day 15 of administration | On day 34 of administration | 14 days after discontinuation | 32 days after discontinuation | 49 days after discontinuation | 113 days after discontinuation |
|---|---|---|---|---|---|---|
| TP (g/dL) | 8.2 | 7.6 | 6.3 | 5.0 | 5.2 | 5.7 |
| Albumin (g/dL) | 4.3 | 4.1 | 2.9 | 2.3 | 2.3 | 3.3 |
| BUN (mg/dL) | 10.8 | 13.1 | 18.3 | 31.4 | 38.1 | 27.1 |
| Creatinine (mg/dL) | 0.6 | 0.6 | 0.8 | 0.9 | 1.0 | 1.0 |
| CRP (mg/dL) | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 |

TP: Total Protein CRP: C-Reactive Protein
BUN: Blood Urea Nitrogen

## 3 Temozolomide

| | |
|---|---|
| **Brand Name (name of company)** | Temodal Capsules 20 mg and 100 mg (Schering-Plough K.K.) |
| **Therapeutic Category** | Alkylating agents |
| **Indications** | Malignant glioma |

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

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

**Interstitial pneumonia**: Interstitial pneumonia may occur. Patients should be carefully monitored for clinical symptoms of pyrexia, cough, and dyspnoea etc. If any abnormalities are observed, examinations such as a chest X-ray, etc. should be immediately conducted, and in addition to discontinuing administration of this drug, differential diagnosis of pneumocystis pneumonia (e.g. β-D glucan measurement) should be considered, and appropriate measures should be taken.

**<Reference Information>**

The number of reported adverse reaction cases in about the last 2 years (September 15, 2006 to November 30, 2008) (events for which a causality to the drug could not be denied)

- Interstitial pneumonia: 2 cases (no fatal cases)

The number of patients treated with Temozolomide for a year estimated by MAH: approximately 3800 (January 2008 to December 2008)
Marketed in Japan in: September 2006

### Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 50s | Anaplastic oligoastrocytoma [new-onset] (none) | 75 mg/m$^2$<br>38 days<br>150 mg/m$^2$<br>5 days<br>(3 courses) | **Interstitial lung disease**<br>Alcohol consumption (social drinking), smoking (20 cigarettes/day for 39 years).<br>Allergic history: none<br>Complications: none<br>Medical history: appendicitis<br>Before administration of this drug, lung CT showed no lesions.<br>On day 1 of administration:<br>Administration of this drug was started. Administration of sulfamethoxazole/trimethoprim was started.<br>Approx. in the 6th mouth of administration:<br>The patient started coughing.<br>Thinking it was pollinosis, ketotifen fumarate was orally administered, but the condition did not improve.<br>On day 207 of administration<br>(27 days after the last administration):<br>There was respiratory failure with $SpO_2$ at 84%, and the patient was hospitalized to undergo detailed examination. The findings characteristic for interstitial pneumonia were observed through hematological assessment, X-ray and CT.<br>Unknown:<br>It was decided to discontinue administration of this drug.<br>Symptoms and X-ray findings slightly improved through only the discontinuation of this drug. |

| | | | | |
|---|---|---|---|---|
| | | | | Nonspecific interstitial pneumonia (NSIP pattern) was diagnosed through bronchoalveolar lavage and transbronchial lung biopsy.<br>38 days after the last administration:<br>Oral administration of prednisolone (25 mg/day) was started.<br>63 days after the last administration:<br>Interstitial pneumonia, coughing improved. After administration of prednisolone, subjective symptoms improved markedly, and interstitial shadows gradually improved. |
| | Concomitant medications: sulfamethoxazole/trimethoprim, phenytoin, magnesium oxide, ramosetron hydrochloride | | | |

### Clinical Laboratory Values

| | 28 days after the last administration | 42 days after the last administration | 46 days after the last administration | 52 days after the last administration | 63 days after the last administration |
|---|---|---|---|---|---|
| LDH (IU/L) | 236 | 200 | 211 | — | 167 |
| KL-6 (U/mL) | 2562 | — | — | 3137 | — |
| SP-A (ng/mL) | 88.6 | — | — | 47.5 | — |
| SP-D (ng/mL) | 295.0 | — | — | 197.0 | — |
| CRP (mg/dL) | 2.00 | 1.63 | 0.96 | — | 0.09 |

LDH: Lactate Dehydrogenase
SP-A: Pulmonary Surfactant Protein-A
SP-D: Pulmonary Surfactant Protein-D
CRP: C-Reactive Protein

## 4 Rituximab (genetical recombination)

| | |
|---|---|
| **Brand Name (name of company)** | Rituxan Injection 10 mg/mL (Zenyaku Kogyo Co., Ltd.) |
| **Therapeutic Category** | Antineoplastics-Miscellaneous |
| **Indications** | 1. CD20 positive B-cell non-Hodgkin's lymphoma<br>2. Premedication for indium ($^{111}$In) ibritumomab tiuxetan (genetical recombination) injection and yttrium ($^{90}$Y) ibritumomab tiuxetan (genetical recombination) injection |

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

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

**Pancytopenia, leukopenia, neutropenia, thrombocytopenia**: Severe cytopenias may occur. As cases of neutropenia have been reported more than 4 weeks after the last administration of this drug, patients should be carefully monitored such as by conducting periodic blood tests during and after the treatment period with this drug. If any abnormalities are observed, appropriate measures such as by discontinuing administration of this drug, etc. should be taken.

**Infectious diseases**: Serious infectious diseases from bacteria, fungi, or viruses (e.g. sepsis, pneumonia) may occur. Patients should be carefully monitored during and after the treatment period with this drug, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

**Progressive multifocal leucoencephalopathy (PML)**: Progressive multifocal leucoencephalopathy (PML) may occur. Patients should be carefully monitored during and after the treatment period with this drug, and if symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia, quadriplegia), and language disorders etc. are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, 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, 2005 to November 30, 2008) (events for which a causality with the drug could not be denied)

- PML: 2 cases (of which 1 had a fatal case)

The number of patients treated with Rituximab for a year estimated by MAH: approximately 19000 (December 2007 to November 2008)
Marketed in Japan in: September 2001

## Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 40s | Non-Hodgkin's lymphoma [Histological type: Diffuse large B-cell lymphoma] (none) | 500 mg 50 days (5 times) | **Progressive multifocal leucoencephalopathy (PML), pneumocystis carinii pneumonia**<br>Before administration<br>Extranodal disease: bulky disease on left ilium.<br>Approx. 3 months before administration:<br>The patient was diagnosed with non-Hodgkin's lymphoma.<br>28 days before administration:<br>The first course of CHOP therapy was started (vincristine sulfate, doxorubicin hydrochloride, cyclophosphamide, prednisolone).<br>7 days before administration:<br>The second course of CHOP therapy was conducted.<br>On day 1 of administration:<br>The patient received the first administration of this drug (500 mg). d-chlorpheniramine maleate and acetaminophen were administered as premedication. The same drugs were given as premedication prior to the administration of this drug thereafter.<br>On day 13 of administration:<br>The patient received the second administration of this drug (500 mg). Thereafter, the patient experienced diplopia and lightheadedness.<br>On day 15 of administration:<br>The third course of CHOP therapy was conducted.<br>On day 28 of administration:<br>The patient received the third administration of this drug (500 mg).<br>On day 34 of administration:<br>The patient received the fourth administration of this drug (500 mg).<br>On day 36 of administration:<br>The fourth course of CHOP therapy was conducted.<br>On day 50 of administration (last day of administration):<br>The patient received the fifth administration of this drug (500 mg).<br>5 days after completion:<br>The fifth course of CHOP therapy was conducted.<br>24 days after completion:<br>The patient was immediately hospitalized due to pyrexia and gradually worsening lightheadedness. MRI was performed and lesions were confirmed in the cerebellum and brain stem. The lightheadedness was due to cerebellar ataxia.<br>30 days after completion:<br>Although the patient was initially being treated for encephalitis, as respiratory status rapidly worsened, carinii pneumonia was diagnosed by CT and bronchoscopy [bronchoscopy with lavage (BAL)]. Carinii pneumonia was the cause of pyrexia. Although administration of sulfamethoxazole/trimethoprim was started, the patient was eventually put on an artificial respirator. |

| | | | | |
|---|---|---|---|---|
| | | | | 38 days after completion:<br>The treatment was effective and the patient was taken off the artificial respirator.<br>48 days after completion:<br>After administration of sulfamethoxazole/trimethoprim was completed, CT did not confirm active lesions, and it was determined that the patient had recovered from carinii pneumonia.<br>82 days after completion:<br>Even after recovery from carinii pneumonia, there was aggravation not only of cerebellar ataxia, but paralysis of the right recurrent nerve, facial palsy, bulbar palsy, and pyramidal disorder. There were findings of demyelination from MRI, and PML was suspected. JC virus was detected from spinal fluid, and PML was diagnosed.<br>83 days after completion:<br>Administration of cytarabine at 2 mg/kg was started (for 5 days). However, progression of PML did not stop, and nervous symptoms aggravated. Bulbar palsy progressed to recurrent pneumonia aspiration.<br>112 days after completion:<br>As pneumonia subsided, intraspinal injection of cytarabine 20 mg was conducted.<br>114 days after completion:<br>The disease progressed, respiratory status worsened, and the patient died. |
| | Concomitant medications: vincristine sulfate, doxorubicin hydrochloride, cyclophosphamide, prednisolone, oxethazaine, ranitidine hydrochloride, d-chlorpheniramine maleate, acetaminophen | | | |

## Clinical Laboratory Values

| | 39 days before administration | 1 day before administration | On day 28 of administration | On day 34 of administration | On day 50 of admin. (last day of admin.) | 24 days after completion | 30 days after completion | 48 days after completion | 82 days after completion | 91 days after completion |
|---|---|---|---|---|---|---|---|---|---|---|
| WBC ($/mm^3$) | 7300 | 6400 | 3800 | 7000 | 1900 | 9200 | 9900 | 5100 | 3300 | 2200 |
| Neutrophils (%) | 89.0 | 95.0 | 85.0 | 86.0 | 67.0 | 91.0 | — | 81.0 | 70.0 | 60.0 |
| Lymphocytes (%) | 5.0 | 5.0 | 9.0 | 5.0 | 18.0 | 5.0 | — | 7.0 | 18.0 | 23.0 |
| PLT ($\times 10^4/mm^3$) | 38.2 | 42.4 | 33.6 | 40.9 | 30.0 | 37.5 | 41.2 | 28.8 | 34.0 | 15.4 |
| CRP (mg/dL) | 1.7 | <0.1 | 1.3 | 1.6 | 1.7 | 16.5 | 23.4 | 0.1 | <0.1 | 0.2 |

WBC: White Blood Cell CRP: C-Reactive Protein
PLT: Platelet

# 2

# Revision of PRECAUTIONS

# (No. 204)

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 January 9, 2009 (excluding those presented in "1. Important Safety Information" of this Bulletin).

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<Psychotropics>

## 1 Aripiprazole

**[Brand Name]** Abilify Powder 1%, Abilify Tablets 3 mg, 6 mg, and 12 mg (Otsuka Pharmaceutical Co., Ltd.)

**[Other Precautions]** Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs including this drug revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious disease (e.g., pneumonia) in nature. Higher incidence of death and cerebrovascular disorder (e.g., stroke, transient ischaemic attack) was reported in 3 studies of this drug (n = 938; mean age: 82.4 years; range: 56-99 years) compared to placebo. It has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

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<Psychotropics>

## 2 Oxypertine<br>Pipamperone Hydrochloride

**[Brand Name]** FORIT POWDER 10%, FORIT TABLETS 20 mg and 40 mg (DAIICHI SANKYO COMPANY, LIMITED)
Propitan Powder 10%, Propitan Tablets 50 mg (Sannova Co. Ltd.)

**[Other Precautions]** Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

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<Psychotropics>

## 3 Olanzapine

**[Brand Name]** Zyprexa Fine Granules 1%, Zyprexa Tablets 2.5 mg, 5 mg, and 10 mg, Zyprexa Zydis Tablets 5 mg and 10 mg (Eli Lilly Japan K.K.)

**[Adverse Reactions (clinically significant adverse reactions)]** **Ileus paralytic**: Since paralysis intestinal (including symptoms such as anorexia, nausea/vomiting, significant constipation, abdominal distension or abdominal flaccidity, and stagnation of intestinal contents) may lead to ileus paralytic. If ileus paralytic is observed,.appropriate measures such as discontinuation of the drug should be taken.

**[Other Precautions]**

Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs including this drug revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In 5 placebo-controlled studies of olanzapine, higher incidence of death and cerebrovascular disorder (e.g., stroke, transient ischaemic attack) was reported in olanzapine-treated patients compared to placebo-treated patients. As for the risk factors for death, age (aged 80 and older), sedation, concomitant benzodiazepine drugs, and respiratory diseases have been reported. It has been reported that the patients with cerebrovascular disorder had risk factors such as a history of cerebrovascular disorder, transient ischaemic attack, or hypertension, or complication with such diseases, and smoking. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

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**4** <Psychotropics>

1. **Carpipramine Hydrochloride**
2. **Carpipramine Maleate**
3. **Clocapramine Hydrochloride**
4. **Chlorpromazine Hydrochloride**
5. **Chlorpromazine Hydrochloride/Promethazine Hydrochloride/Phenobarbital**
6. **Chlorpromazine Hibenzate**
7. **Chlorpromazine Phenolphthalinate**
8. **Spiperone**
9. **Sultopride Hydrochloride**
10. **Sulpiride**
11. **Zotepine**
12. **Timiperone**
13. **Trifluoperazine Maleate**
14. **Nemonapride**
15. **Haloperidol**
16. **Pimozide**
17. **Fluphenazine Decanoate**
18. **Fluphenazine Maleate**
19. **Prochlorperazine Maleate**
20. **Prochlorperazine Mesilate**
21. **Propericiazine**
22. **Bromperidol**
23. **Perphenazine**
24. **Perphenazine Hydrochloride**
25. **Perphenazine Fendizoate**
26. **Perphenazine Maleate**
27. **Mosapramine Hydrochloride**
28. **Moperone Hydrochloride**
29. **Levomepromazine Hydrochloride**
30. **Levomepromazine Maleate**

**[Brand Name]**

1. DEFEKTON SUGAR-COATED TABLETS 25 mg and 50 mg (Mitsubishi Tanabe Pharma Corporation)
3. DEFEKTON POWDER 10% (Mitsubishi Tanabe Pharma Corporation)
4. CLOFEKTON GRANULES 10% (Mitsubishi Tanabe Pharma Corporation), and others
5. Wintermin Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg (Shionogi & Co., Ltd.), and others
5. Vegetamin-A and -B (Shionogi & Co., Ltd.)
6. CONTOMIN POWDER 10%, CONTOMIN GRANULES 10% (Mitsubishi Tanabe Pharma Corporation)
7. Wintermin Fine Granules (10%) (Shionogi & Co., Ltd.)
8. Spiropitan Powder 0.3%, Spiropitan Tablets 0.25 mg and 1 mg (Sannova Co. Ltd.)
9. Barnetil Fine granule 50%, Barnetil Tab. 50, 100, and 200 (Bayer Yakuhin, Ltd.), and others
10. Abilit Fine Granules 10% and 50%, Abilit Tablets 50 mg, 100 mg, and 200 mg, Abilit Capsules 50 mg (Dainippon Sumitomo Pharma Co., Ltd.), and others
11. Lodopin Fine Granules 10% and 50%, Lodopin Tablets 25 mg, 50 mg, and 100 mg (Astellas Pharma Inc.), and others
12. Tolopelon Fine Glanules 1%, Tolopelon Tablets 0.5 mg, 1 mg, 3 mg, Tolopelon Injection 4 mg (DAIICHI SANKYO COMPANY, LIMITED), and others
13. TRIFLUOPERAZINE POWDER 1% “MITSUBISHI”, TRIFLUOPERAZINE SUGAR-COATED TABLETS “YOSHITOMI” (2.5) and (5) (Mitsubishi Tanabe Pharma Corporation)
14. Emilace Fine Granules 2%, Emilace Tablets 3 mg and 10 mg (Astellas Pharma Inc.)
15. Serenace Fine Granules 1%, Serenace Tablets 0.75 mg, 1 mg, 1.5 mg, and 3 mg, Serenace for Internal Use 0.2%, Serenace Injection 5 mg (Dainippon Sumitomo Pharma Co., Ltd.), and others
16. Orap Fine Granules 1%, Orap Tablets 1 mg and 3 mg (Astellas Pharma Inc.)
17. Fludecasin INTRAMUSCULAR INJECTION 25 mg, Fludecasin Kit INTRAMUSCULAR INJECTION 25 mg (Mitsubishi Tanabe Pharma Corporation)
18. FLUMEZIN POWDER 0.2%, FLUMEZIN SUGAR-COATED TABLETS (0.25), (0.5), and (1) (Mitsubishi Tanabe Pharma Corporation)
19. Novamin Tablets 5 mg (Shionogi & Co., Ltd.)
20. Novamin Intramuscular Injection 5 mg (Shionogi & Co., Ltd.)
21. Neuleptil Fine Granules 10%, Neuleptil Tablets 5 mg, 10 mg, and 25 mg, Neuleptil for Internal Use 1% (Shionogi & Co., Ltd.), and others
22. Impromen Fine Granules 1%, Impromen Tablets 1 mg, 3 mg, and 6 mg (Janssen Pharmaceutical K.K.), and others
23. TRILAFON Powder 1%, TRILAFON Tab. 2 mg, 4 mg, and 8 mg (Kyowa Pharmaceutical Industry Co., Ltd.)
24. PZC INTRAMUSCULAR INJECTION 2 mg (Mitsubishi Tanabe Pharma Corporation)
25. PZC POWDER 1% (Mitsubishi Tanabe Pharma Corporation)
26. PZC SUGAR-COATED TABLETS 2 mg, 4 mg, and 8 mg (Mitsubishi Tanabe Pharma Corporation)
27. Cremin Granules 10%, Cremin Tablets 10 mg, 25 mg, and 50 mg (Mitsubishi Tanabe Pharma Corporation)
28. Luvatren Powder, Luvatren Tablets (Astellas Pharma Inc.)
29. Hirnamin Intramuscular Injection 25 mg (Shionogi & Co., Ltd.), and others
30. Hirnamin Powder 50%, Hirnamin Fine Granules 10%, Hirnamin Tablets (5 mg), (25 mg), and (50 mg) (Shionogi & Co., Ltd.), and others

**[Other Precautions]**

Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

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## 5 <Psychotropics> Quetiapine Fumarate

**[Brand Name]**

Seroquel Fine Granules 50%, Seroquel 25 mg and 100 mg Tablets
(Astellas Pharma Inc.)

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

**Ileus paralytic**: Since paralysis intestinal (including symptoms such as anorexia, nausea/vomiting, significant constipation, abdominal distension or abdominal flaccidity, and stagnation of intestinal contents) may lead to ileus paralytic. If ileus paralytic is observed, appropriate measures such as discontinuation of the drug should be taken.

**Rhabdomyolysis**: Rhabdomyolysis may occur. If symptoms such as myalgia, feelings of weakness, CK (CPK) increased, and blood or urine myoglobin increased are observed, administration should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

**[Other Precautions]**

Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs including this drug revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

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## 6 <Psychotropics> Haloperidol Decanoate

**[Brand Name]**

NEOPERIDOL Injection 50 and 100 (Johnson & Johnson K.K.), HALOMONTH Injection 50 mg and 100 mg (Janssen Pharmaceutical K.K.)

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

**Rhabdomyolysis**: Rhabdomyolysis may occur. If symptoms such as myalgia, feelings of weakness, CK (CPK) increased, and blood or urine myoglobin increased are observed, administration should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

**[Other Precautions]**

Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

## 7 <Psychotropics> Blonanserin

**[Brand Name]**

LONASEN Powder 2%, LONASEN Tablets 2 mg and 4 mg (Dainippon Sumitomo Pharma Co., Ltd.)

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

**Ileus paralytic**: Since paralysis intestinal (including symptoms such as anorexia, nausea/vomiting, significant constipation, abdominal distension or abdominal flaccidity, and stagnation of intestinal contents) may lead to ileus paralytic. If ileus paralytic is observed,.appropriate measures such as discontinuation of the drug should be taken.. In addition, antiemetic effect was confirmed in animal studies (dogs). Caution should be exercised as emergence of nausea/vomiting of this drug may be inapparent.

**Rhabdomyolysis**: Rhabdomyolysis may occur. If symptoms such as myalgia, feelings of weakness, CK (CPK) increased, and blood or urine myoglobin increased are observed, administration should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

**[Other Precautions]**

Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs of similar drugs revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In addition, a causal relationship with this drug is not fully understood, as it is not assessed. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

## 8 <Psychotropics> Perospirone Hydrochloride

**[Brand Name]**

Lullan Tablets 4 mg, 8 mg, and 16 mg (Dainippon Sumitomo Pharma Co., Ltd.)

**[Other Precautions]**

Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs of similar drugs revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

## 9 <Psychotropics> Risperidone

**[Brand Name]**

Risperdal Fine Granules 1%, Risperdal Tablets 1 mg, 2 mg, and 3 mg, Risperdal OD Tablets 1 mg and 2 mg, Risperdal Oral Solution 1 mg/mL (Janssen Pharmaceutical K.K.), and others

**[Other Precautions]**

Analyses of 17 overseas placebo-controlled trials in elderly patients with dementia-related psychosis (non-approved indications) treated with atypical antipsychotic drugs including this drug revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. In addition, it has been reported from an overseas epidemiological study that typical antipsychotic drugs are also associated with increased risk of death similar to atypical antipsychotic drugs.

## 10 <Digestive organ agents-Miscellaneous> Infliximab (Genetical recombination)

**[Brand Name]** Remicade for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corporation)

**[Warning]**

**WARNING**

Infectious disease
Tuberculosis: Tuberculosis including disseminated tuberculosis (miliary tuberculosis) and extrapulmonary tuberculosis leading to death (e.g. pleural, lymph node) has been observed in patients receiving this drug. Since symptoms may become manifest or aggravated in patients infected with tuberculosis, patients should be tested for latent tuberculosis infection prior to initiating this drug and complete interview regarding tuberculosis, chest X-ray and tuberculin test, and chest CT test as necessary should be performed. Treatment of latent tuberculisis should be initiated prior to therapy with this drug There have also been reports of cases in which active tuberculosis was confirmed after administration of this drug, in patients who tested negative for latent tuberculosis infection..

**[Important Precautions]** Since symptoms may emerge and worsen in patients infected with tuberculosis, patients should be tested for latent tuberculosis infection prior to initiating this drug and complete interview regarding tuberculosis, chest X-ray and tuberculin test, and chest CT test as necessary should be performed. Particularly for patients who are suspected to be infected with tuberculosis, the presence or absence of tuberculosis infection should be appropriately confirmed by multiple tests. The patient should consult a physician who has clinical experience with tuberculosis. Patients with tuberculosis or those suspected of tuberculosis through tests should be initiated an antitubercular agent prior to this drug. As active tuberculosis was confirmed after administration of this drug in patients who tested negative for latent tuberculosis infection, the patient should be closely monitored for the onset of tuberculosis symptoms during the administration of this drug. Patients should be instructed to contact their physician immediately if symptoms of tuberculosis (e.g. persistent cough, pyrexia) are suspected.

## 11 <Hormones-Miscellaneous> Dienogest

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

**[Careful Administration]** Patients with uterine myoma or adenomyosis uteri

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

**Metrorrhagia, anaemia**: Metrorrhagia leading to severe anaemia may occur after the administration of this drug. If massive haemorrhage over the long-term is observed, patients should be carefully monitored and physicians should conduct a blood test as necessary. If severe anaemia is observed, appropriate measures such as drug discontinuation should be taken.

## 12 <Synthetic antibacterials> Garenoxacin Mesilate Hydrate

**[Brand Name]** Geninax Tablets 200 mg (Toyama Chemical Co., Ltd.)

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

**Oculomucocutaneous syndrome (Stevens-Johnson syndrome)**: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

**Hepatic function disorder**: Hepatic function disorder with significant elevations of AST (GOT) or ALT (GPT) etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

## 13 <Antivirals> Efavirenz

**[Brand Name]** STOCRIN Capsules 200, STOCRIN Tablets-600 mg (Banyu Pharmaceutical Co., Ltd.)

**[Adverse Reactions (clinically significant adverse reactions)]** Since foetal malformations have been observed in animal species, women should use appropriate contraceptive measures during therapy with this drug and for 12 weeks after discontinuation of this drug. Women should be advised to notify their physician if they become pregnant.

## 14 Over the counter drug Magnesium Oxide

**[Brand Name]** Slaria Laxative (ROHTO Pharmaceutical Co., Ltd.), and others

**[Consultation]** In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.

The following symptoms are observed after taking this drug

**Cardiovascular system**: Dizziness on standing up, pulse become slow
**Psychoneuropathy**: Excessive sleepiness, consciousness decreased
**Others**: Respiratory discomfort, muscular weakness, dry mouth

# 3

# List of products subject to Early Post-marketing Phase Vigilance

(As of February 1, 2009)

| Nonproprietary name / Brand name | Name of the marketing authorisation holder | Date of EPPV initiation |
|---|---|---|
| Yttrium ($^{90}$Y) Ibritumomab Tiuxetan (Genetical recombination) / Zevalin yttrium ($^{90}$Y) injection | Bayer Yakuhin, Ltd. | August 4, 2008 |
| Indium ($^{111}$In) Ibritumomab Tiuxetan (Genetical recombination) / Zevalin indium ($^{111}$In) injection | Bayer Yakuhin, Ltd. | August 4, 2008 |
| Levobupivacaine Hydrochloride / POPSCAINE 0.75% inj. 75 mg/10 mL, POPSCAINE 0.75% inj. 150 mg/20 mL, POPSCAINE 0.25% inj. 25 mg/10 mL, POPSCAINE 0.25% inj. bag 250 mg/100 mL, POPSCAINE 0.75% inj. syringe 75 mg/10 mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL | Maruishi Pharmaceutical Co., Ltd. | August 5, 2008 |
| Estradiol / Julina 0.5mg | 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 100mg | 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)<br>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<br>Bepricor Tablets 50 mg and 100 mg[*6] | Schering-Plough K.K. | October 16, 2008 |
| Adapalene<br>Differin Gel 0.1% | Galderma Pharma S .A. | October 21, 2008 |
| Tacrolimus Hydrate<br>Graceptor Capsules 0.5 mg, 1 mg, and 5 mg | Astellas Pharma Inc. | October 28, 2008 |
| Anti-human Thymocyte Immunoglobulin, Rabbit<br>Thymoglobuline for Intravenous Infusion 25 mg | Genzyme Japan K.K. | November 28, 2008 |
| Pirfenidone<br>Pirespa Tablets 200 mg | Shionogi & Co., Ltd. | December 12, 2008 |
| Lamotrigine<br>Lamictal Tablets 2 mg, 5 mg, 25 mg, and 100 mg | GlaxoSmithKline K.K. | December 12, 2008 |
| Tafluprost<br>TAPROS ophthalmic solution 0.0015% | Santen Pharmaceutical Co., Ltd. | December 16, 2008 |
| Phenobarbital Sodium<br>NOBELBAR 250 mg for Injection | Nobelpharma Co., Ltd. | December 16, 2008 |
| Haemophilus influenzae type b conjugate vaccine<br>ActHIB | Sanofi Pasteur-Daiichi Sankyo Vaccine Co., Ltd. | December 19, 2008 |
| Thyrotropin Human Alfa (Genetical recombination)<br>THYROGEN IM Injection 0.9 mg | Sato Pharmaceutical Co., Ltd. | January 13, 2009 |
| Etravirine<br>INTELENCE Tablets 100 mg | Janssen Pharmaceutical K.K. | January 19, 2009 |
| Salmeterol Xinafoate/Fluticasone Propionate<br>Adoair 100 Diskus[*7] | GlaxoSmithKline K.K. | January 21, 2009 |
| Salmeterol Xinafoate/Fluticasone Propionate<br>Adoair 250 Diskus[*8] | GlaxoSmithKline K.K. | January 21, 2009 |
| Ganirelix Acetate<br>Ganirest Subcutaneous 0.25mg Syringe | Schering-Plough K.K. | January 22, 2009 |
| Maraviroc<br>CELSENTRI Tablets 150 mg | Pfizer Japan Inc. | January 22, 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)"

Reference

# Precautions regarding abnormal behaviour when infected with influenza

MHLW has been conducting dissemination and education of activities information relating to the prevention of influenza, such as by distributing posters ("Do you know about influenza?") to each medical institution in January 2008, and by placing the following "Basic knowledge on influenza" on its website.

- Materials for dissemination and education of basic knowledge on the prevention of influenza (complete edition)
  [http://www.mhlw.go.jp/bunya/iyakuhin/file/dl/File01.pdf (in Japanese)]
- Materials for dissemination and education of basic knowledge on the prevention of influenza (abridged edition)
  [http://www.mhlw.go.jp/bunya/iyakuhin/file/dl/File02.pdf (in Japanese)]
- Poster [http://www.mhlw.go.jp/bunya/iyakuhin/poster/A2_poster.html (in Japanese)]

On January 29, 2009, MHLW notified each related MAH regarding the "Reminder: PRECAUTIONS in the package inserts of anti influenza virus drugs" and instructed them to implement thorough measures to alert healthcare providers on this matter.