# Table of Contents

1. **Manuals for Management of Individual Serious Adverse Drug Reactions** .................................................. 3

2. **Important Safety Information** .................................................. 6
   - Amantadine Hydrochloride .................................................. 6
   - Ceftriaxone Sodium .................................................. 12

3. **Revision of PRECAUTIONS (No. 181)**
   - Sulindac (and 11 others) .................................................. 16

4. **List of products subject to Early Post-marketing Phase Vigilance** .................................................. 20

---

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 also available on the Pharmaceuticals and Medical Devices information Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

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

**Translated by**
Pharmaceuticals and Medical Devices Agency

**Published by**
Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

**Translated by**
Office of Safety, Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

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

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>Measures</th>
<th>Outline of information</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Manuals for Management of Individual Serious Adverse Drug Reactions</td>
<td>Ministry of Health, Labour and Welfare (MHLW) has been preparing “Manuals for Management of Individual Serious Adverse Drug Reactions” with cooperation of experts etc. from relevant medical societies since FY2005 as a 4-year “Project of Comprehensive Measures for Serious Adverse Reactions”. The first series of manuals of adverse drug reactions, including “Stevens-Johnson syndrome” and “interstitial pneumonia”, have been finalized and are available on MHLW website. This section presents the objective and process of this project, as well as information about the manuals.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Amantadine Hydrochloride (and 1 other)</td>
<td>Presents contents of revisions, 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 after the issue before previous bulletin (Pharmaceuticals and Medical Devices Safety Information No.228), together with reference materials.</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sulindac (and 11 others)</td>
<td>Revision of PRECAUTIONS (No. 181)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Products subject to Early Post-marketing Phase Vigilance</td>
<td>Lists products subject to Early Post-marketing Phase Vigilance as of November 1, 2006.</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

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

---

### 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. Introduction

Ministry of Health, Labour and Welfare (MHLW) has been preparing “Manuals for Management of Individual Serious Adverse Drug Reactions” (hereinafter referred to as “the Manuals”) with cooperation of experts etc. from relevant medical societies since FY2005 as a 4-year “Project of Comprehensive Measures for Serious Adverse Reactions”. The first series of manuals of adverse drug reactions, including “Stevens-Johnson syndrome” and “interstitial pneumonia”, have been finalized and are available on the MHLW website (http://www.mhlw.go.jp/) and the Pharmaceutical and Medical Devices Information website (http://www.info.pmda.go.jp/). This section presents the objective and process of this project, as well as information about the Manuals.

2. Project of Comprehensive Measures for Serious Adverse Reactions

(1) Objective

The current safety measures are drug-oriented and mainly “alert-release” and “post-event response” types, i.e., information of adverse reactions were collected and evaluated for each drug and notified to physicians and healthcare providers as revisions of the package insert etc. However, these types of measures may delay recognition of adverse reactions and cause serious conditions due to the following reasons.

① Adverse reactions may occur in the organs in which the attending physicians are not specialized.
② Incidence of serious adverse reactions is generally low and physicians and healthcare providers may have a little experience with such events. Therefore, in some cases, detection of adverse reactions may delay, leading to the increased severity.

The objective of this project is to modernize safety measures that “predict” and “prevent” adverse drug reactions by preparing adverse-reaction oriented, not drug-oriented, safety measures in addition to current safety measures and by promoting researches which elucidate mechanism of adverse reactions.

(2) Process

This project will proceed in the following three steps starting in FY2005.

1st step: “Preparation for early recognition of and prompt response to adverse reactions”

We will promote early recognition of and prompt response to adverse reactions in clinical practice by preparing and publishing manuals. The manuals summarize comprehensively information of adverse reactions that are considered to be highly necessary based on the severity of the adverse reactions, including recognition and treatment methods useful for patients and clinicians such as physicians and pharmacists. We plan to complete and publish those manuals in four years.

2nd step: “Preparation for prediction of adverse reactions”

The Manuals will be revised based on the findings in high-risk patient group, which are obtained by collecting and analyzing adverse reaction cases.

3rd step: “Preparation for prevention of adverse reactions”
Investigation of risk factors and researches on mechanism of adverse reactions should be promoted. The drug use in high-risk patient group should be prevented in clinical practice, and in pharmaceutical industries, new drugs that cause less adverse reactions should be developed.

3. Information about the Manuals

Preparation of Manuals for Management of Individual Serious Adverse Drug Reactions was discussed in the first Review Meeting on Comprehensive Measures for Serious Adverse Reactions (Chairman: Kazunori Matsumoto, Professor at International University of Health and Welfare) on July 19, 2005. The adverse drug reactions for which Manuals should be prepared (Table 1) and items described in the Manuals (Table 2) were decided.

The important points regarding the items include ① to clearly summarize the keys to early recognition of and prompt response to adverse reactions for both patients and healthcare providers, ② to describe the distinction and treatment methods for adverse drug reactions, bearing in mind that healthcare providers may have a little experience with such cases, and ③ to present typical cases.

MHLW has been drafting Manuals based on the discussion results with cooperation of relevant medical societies. In the second Review Meeting on Comprehensive Measures for Serious Adverse Reactions on October 19, 2006, the evaluation and discussion were completed for Stevens-Johnson syndrome, toxic epidermal necrosis, interstitial pneumonia, acute lung injury, acute respiratory distress syndrome, asthmatic attack due to nonsteroidal anti-inflammatory drug, drug-induced Parkinsonism, rhabdomyolysis, leukoencephalopathy, and pseudohypaldosteronism.

Table 1. List of subject adverse drug reactions included in the Manuals

<table>
<thead>
<tr>
<th>Field</th>
<th>Names of cooperating society</th>
<th>Subject adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stevens-Johnson syndrome*</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>The Japanese Dermatological Association</td>
<td>Toxic epidermal necrosis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug-induced hypersensitivity syndrome</td>
</tr>
<tr>
<td>Hepatic</td>
<td>The Japan Society of Hepatology</td>
<td>Drug-induced liver disorder</td>
</tr>
<tr>
<td>Renal</td>
<td>The Japanese Society of Nephrology</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephritis interstitial</td>
</tr>
<tr>
<td>Blood</td>
<td>The Japanese Society of Hematology</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aplastic anaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaemia</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>The Japanese Respiratory Society</td>
<td>Interstitial pneumonia*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthmatic attack due to nonsteroidal anti-inflammatory drug*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute lung injury/Acute respiratory distress syndrome*</td>
</tr>
<tr>
<td>Alimentary tract</td>
<td>The Japanese Society of Gastroenterology</td>
<td>Ileus paralytic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peptic ulcer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>The Japanese Circulation Society</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac failure congestive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac function disturbance</td>
</tr>
<tr>
<td>Nervous and musculo-skeletal system</td>
<td>The Japanese Society of Neurology</td>
<td>Drug-induced Parkinsonism*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhabdomyolysis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukoencephalopathy*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral nerve disorder</td>
</tr>
</tbody>
</table>
The second Review Meeting on Comprehensive Measures for Serious adverse reactions selected additional adverse reactions including nephrotic syndrome, pulmonary oedema, and movements involuntary for the conventional fields of renal, respiratory system, and nervous and musculo-skeletal system and metabolism and endocrine systems as well as new fields of sensory organs (e.g., visual disturbance), pancreas (pancreatitis), oral cavity (stomatitis), bones (e.g., osteonecrosis), and urinary organs (e.g., urinary retention).

* The adverse reactions for which the Manuals were published this time.

### Table 2. Items described in the Manuals

<table>
<thead>
<tr>
<th>Items</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Name of the adverse reaction</td>
<td>Descriptions of the name including synonyms</td>
</tr>
<tr>
<td>2 Summary of the adverse reaction</td>
<td>The keys to early recognition of and prompt response to the adverse reaction for patients and their families</td>
</tr>
<tr>
<td>3 The keys to early recognition and prompt response</td>
<td>The points to which healthcare providers should pay attention.</td>
</tr>
<tr>
<td>4 Summary of the adverse reaction</td>
<td>Summary of the adverse drug reaction, including symptoms</td>
</tr>
<tr>
<td>5 Distinction criteria for the adverse reaction (distinction method)</td>
<td>Summary of criteria for distinction between the adverse reaction and primary or other diseases</td>
</tr>
<tr>
<td>6 Diseases that should be distinguished and distinction method</td>
<td>Summary of methods to distinguish between the adverse reaction and other diseases</td>
</tr>
<tr>
<td>7 Treatment methods</td>
<td>Treatments that may be performed when the adverse reaction occurs.</td>
</tr>
<tr>
<td>8 Case summaries of typical adverse reactions</td>
<td>Case summaries that can serve as a reference of typical adverse reaction</td>
</tr>
<tr>
<td>9 Cited literatures/References</td>
<td>A list of cited literatures and relevant materials in the Manual</td>
</tr>
</tbody>
</table>

### 4. Closing comments

The manuals prepared this time were notified to the prefectural and city governments, the Japan Medical Association, the Japan Pharmaceutical Association, the Japanese Society of Hospital Pharmacists, and other relevant parties and are available on the websites of MHLW and the Pharmaceutical and Medical Devices Information.

Preparation of draft manuals will be continued with cooperation of relevant medical societies and Japanese Society of Hospital Pharmacists. The final manuals will be published after evaluation and discussion in the Review Meeting on Comprehensive Measures for Serious adverse reactions.

It is hoped that these manuals will be used by healthcare providers including physicians, dentists, and pharmacists as well as patients for achieving early recognition of and prompt response to serious adverse reactions.
**Important Safety Information**

This section presents contents of revisions, reference materials 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 after the issue before previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 228).

### 1. Amantadine Hydrochloride

<table>
<thead>
<tr>
<th>Brand Name (name of company)</th>
<th>Therauptic Category</th>
<th>Indications</th>
</tr>
</thead>
</table>
| Atenegine Fine Granules, Atenegine 50 and 100 (Tsuruhara pharmaceutical Co., Ltd.) | Antiparkinsonian agents | ■ Improvement of decreased motivation and initiative associated with late effects of cerebral infarction  
■ Parkinson syndrome  
■ Influenza A virus infection |
| Amazolon Fine Granules, Amazolon Tablets 50 and 100 (Sawai Pharmaceutical Co., Ltd.) | | |
| Amantadine HCl Tablets 50 “Nichiko” (Nichi-iko Pharmaceutical Co., Ltd.) | | |
| Shikitan (Zensei Pharmaceutical Industries Co., Ltd.) | | |
| Symmetrel Fine Granules, Symmetrel Tablets 50 mg and 100 mg (Novartis Pharma K.K.) | | |
| Topharmin Fine Granules, Topharmin Tablets 50 and 100 (Toyo Pharmar Co., Ltd.) | | |
| Boidan Powder, Boidan Tablets 50 mg and 100 mg (ISEI Co., Inc.) | | |
| Lusyton Fine Granules, Lusyton Tablets (Tatsumi Kagaku Co., Ltd.) | | |
| Rotifamin Tablets 50 and 100 (Yaiyo Yakuhin Co., Ltd.) | | |

**<Reference Information>**

Company report
The number of reported adverse reaction cases in about the last 3 years (April 1,
2003 to July 31, 2006) (events for which a causality to the drug could not be denied)
- Myoclonus: 9 cases (no fatal case)
The number of patients treated with Amantadine estimated by MAH (Marketing Authorisation Holder): approximately 0.4 million (FY2005)
Marketed in Japan in: 1975

### Case Summary

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Daily dose/ Treatment duration</th>
<th>Adverse reactions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex/Age</td>
<td>Reason for use (complications)</td>
<td>Clinical course and therapeutic measures</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
<td>60s</td>
<td>Vascular parkinsonism (chronic renal failure, diabetic nephropathy, and diabetes mellitus)</td>
<td>Gait disturbance, hallucination, and movements involuntary</td>
</tr>
</tbody>
</table>

#### Company report

**Approx. 26 years before administration:**
The patient had diabetes mellitus and had been treated by a local doctor.

**Approx. 3 years before administration:**
The patient developed cerebral infarction and hospitalized to the neurosurgery department at the local hospital. During the follow-up visits after discharge, he had aphasia and dysphagia.

**Approx. 2 years before administration:**
Creatinine (Cr) 1.7 mg/dL, proteinuria (3+).

**Approx. 8 months before administration:**
Renal failure due to diabetic nephropathy was observed with Cr of 4.7 mg/dL.

**Approx. 3 months before administration:**
The renal failure progressed with Cr of 6.3 mg/dL.

**On day 1 of administration:**
Amantadine hydrochloride at 150 mg was started for the treatment of symptoms of cerebrovascular parkinsonism.

**On day 36 of administration:**
Gait disturbance, hallucination, and movements involuntary developed.

**On day 53 of administration (day of discontinuation):**
The patient had an outpatient visit at our hospital. He was emergently hospitalized with BUN 101 mg/dL, Cr 8.9 mg/dL, and K 7.2 mEq/L.

**[Physical findings on admission]**
Body temperature 36.3°C, blood pressure 205/80 mmHg, pulse rate 60 beats/min (regular). The patient had a JCSII-3 level of consciousness. Neurological observations were rigidity of limbs, masked face, and movements involuntary such as pill-rolling tremor.

Abasia developed. Tendon reflexes were symmetrical.

**[Laboratory findings on admission]**
Normochromic normocytic anaemia was observed with haemoglobin 7.2 g/dL and haematocrit 22.5%.
Proteinuria was (3+). Head CT revealed old cerebral infarction lesions in the white matter of the cerebral hemisphere, bilateral basal ganglia, and left thalamus, but no new infarction or haemorrhagic lesions were observed.

[Clinical course after admission] Ultrasound revealed the renal atrophy, indicating chronic renal failure due to diabetic nephropathy. Since the patient also had hyperkalaemia, he started haemodialysis on the day of admission. The patient also received hemoperfusion therapy because of possible amantadine intoxication. Blood amantadine concentration was 2800 ng/mL. The drug was discontinued.

1 day after discontinuation:
The patient received hemoperfusion therapy (2 hours) and hemofiltration dialysis. Hemofiltration dialysis was performed three times a week thereafter. Blood amantadine concentration was 3500 ng/mL.

3 days after discontinuation:
The movements involuntary were resolved. The orientation was improved. Blood amantadine concentration was 2200 ng/mL.

8 days after discontinuation:
Blood amantadine concentration was 1200 ng/mL.

11 days after discontinuation:
The patient opened his eyes to calling, but was unable to speak. Head CT revealed suggested multiple penetrating artery infarctions.

27 days after discontinuation:
Since the blood amantadine concentration was 64 ng/mL, the patient switched to haemodialysis.

40 days after discontinuation:
Because of disuse muscle atrophy after hospitalization, the patient had delayed gait recovery, but eventually became able to walk after rehabilitation.

Concomitant medications: candesartan cilexetil, nifedipine, calcium polystyrene sulfonate, oxybutynin hydrochloride, aspirin/dialuminate, magnesium oxide, insulin human (Genetical recombination)
<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Daily dose/ Treatment duration</th>
<th>Adverse reactions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex/Age</td>
<td>Reason for use (complications)</td>
<td>Clinical course and therapeutic measures</td>
<td></td>
</tr>
</tbody>
</table>
| 2   | Male 60s| Multiple cerebral infarction [short-stepped gait] (hypertension, chronic renal failure, uraemic encephalopathy) | 150 mg 18 days | Cognitive disorder, movement disorder, and generalised convulsion  
Approx. 17 years before administration: The patient started haemodialysis due to chronic renal failure.  
Approx. 5 years before administration: Cerebral infarction (left thalamus to posterior limb of internal capsule) developed.  
38 days before administration: The patient was hospitalized because of pyrexia (pneumonia).  
On day 1 of administration: Amantadin hydrochloride at 150 mg was started for the treatment of right hemiparesis and short-stepped limping.  
On day 8 of administration: At midnight, the patient fell on the floor when he got out of his bed with a basin, stating “I was going to take a bath”. In the evening, he almost fell on his back while eating. Increased unsteady gait was observed. He was also lisping.  
On day 9 of administration: The patient sat down by his bedside and could not move while trying to go to the bathroom. He had slurred speech.  
On day 13 of administration: The patient was fed by a helper because he could not use his hands well. He choked on liquids.  
On day 14 of administration: Truncal ataxia and disorientation to time were observed. Uraemic encephalopathy was considered. Intramuscular dexamethasone sodium phosphate was started. The patient was unable to hold arms extended.  
On day 15 of administration: Head MRI revealed punctate infarction lesions in the deep white matter near the frontal horn of lateral ventricle. The patient was able to hold arms extended.  
On day 16 of administration: Hallucination, dyslalia, and unrest (abnormal behaviour) were observed.  
On day 17 of administration: One-minute generalised tonic convulsion, hallucination, and abnormal behaviours such as trying to catch something in the air were observed.  
On day 18 of administration (day of discontinuation): Generalised convulsion, dyslalia, and dysphagia were observed. Approximately 1 hour later, the patient had jitteriness and unrest. It was considered to be a result of increased blood amantadine concentration. Thus, amantadine hydrochloride was discontinued. Blood amantadine concentration was 2300 ng/mL. The hallucination and the associated abnormal behaviours were persisted. Jitteriness was noted. | Company report |
1 day after discontinuation:
The symptoms began to improve, but jitteriness, soliloquy, and dyslalia were prominent.

3 days after discontinuation:
The patient was able to hold arms extended and also to make conversations.

5 days after discontinuation:
Haemodialysis filtration (HDF) was performed. The patient became able to eat by himself.

6 days after discontinuation:
The patient had infrequent jitteriness and could make conversations.

7 days after discontinuation:
HDF was performed again.

9 days after discontinuation:
The symptoms were almost resolved. Dexamethasone sodium phosphate was discontinued.

Concomitant medications: precipitated calcium carbonate, ticlopidine hydrochloride, estazolam, sennoside, amezinium metilsulfate
<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Daily dose/ Treatment duration</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex/Age</td>
<td>Reason for use (complications)</td>
<td>Clinical course and therapeutic measures</td>
</tr>
<tr>
<td>3</td>
<td>Female 60s</td>
<td>Hypobulia [cerebral haemorrhage] (hypertension, diabetes mellitus, hyperuricaemia, chronic renal failure, diabetic retinopathy)</td>
<td>Myoclonus, delirium, and exacerbation of chronic renal failure</td>
</tr>
</tbody>
</table>

**Company report**

- **Concomitant medications:** nifedipine, temocapril hydrochloride, candesartan cilexetil, carvedilol, doxazosin mesilate, methyldopa, lafutidine, allopurinol, nicergoline

- **Remarks**
  - Approximately 18 years before administration: Hypertension was diagnosed.
  - Approximately 11 years before administration: Diabetes mellitus was diagnosed.
  - Approximately 2 years and 8 months before administration:
    - The patient received outpatient treatment for hypertension and diabetes mellitus.
  - Approximately 1 year before administration:
    - The patient was hospitalized for control of hypertension and diabetes mellitus (for 22 days).
  - Approximately 5 months before administration:
    - The patient had malignant hypertension and was hospitalized for blood pressure control (for 25 days).
  - 11 days before administration:
    - Disturbances of consciousness, conjugate deviation of left eye, and right hemiplegia developed. Left thalamus haemorrhage was diagnosed by CT.
  - 10 days before administration:
    - The patient also developed haemorrhage into ventricle-associated acute hydrocephalus and received external ventricular drainage.
  - On day 1 of administration:
    - Amantadine hydrochloride at 150 mg was started. The hypobulia was gradually improved and the patient’s rehabilitation went well.
  - On day 56 of administration:
    - The patient was transferred to a rehabilitation hospital. She had eating disorder and poor water intake resulting from environmental change.
  - On day 69 of administration:
    - Delirium and systemic myoclonus developed.
  - On day 70 of administration (day of discontinuation):
    - Amantadine hydrochloride was discontinued.
  - 2 days after discontinuation:
    - The patient was rehospitalized in our hospital with no improvement in delirium and myoclonus. Fluid replacement and medication adjustment were performed. Blood amantadine concentration was 2800 ng/mL.
  - 3 days after discontinuation:
    - Spinal amantadine concentration was 2200 ng/mL.
  - 5 days after discontinuation:
    - The symptoms (delirium and myoclonus) were gradually improved.
  - 8 days after discontinuation:
    - The symptoms were resolved. The systemic conditions were stable.
Ceftriaxone Sodium

<table>
<thead>
<tr>
<th>Brand Name (name of company)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sefirom Intravenous 0.5 g and 1 g (Maruko Pharmaceutical Co., Ltd.)</td>
<td>Ceftriaxone Sodium Intravenous 1 g “TX” (TRY-X Co., Ltd.)</td>
</tr>
<tr>
<td>Cefxone Intravenous 1 g (Shiono Chemical Co., Ltd.)</td>
<td>Ceftriaxone Sodium for Intravenous 1 g bag “NP” (Nipro Pharma Corporation)</td>
</tr>
<tr>
<td>Ceftraxone Sodium Intravenous 1 g “TX” (TRY-X Co., Ltd.)</td>
<td>Liasophin for Intravenous Injection 0.5 g and 1 g (Chemix Inc.)</td>
</tr>
<tr>
<td></td>
<td>Rozeclart Intravenous 1 g, Rozeclart Kit for Intravenous Infusion 1 g (Taiyo Yakuhin Co., Ltd.)</td>
</tr>
<tr>
<td></td>
<td>Rocephin Intravenous 0.5 g and 1 g, Rocephin Infusion Bag 1 g (Chugai Pharmaceutical Co., Ltd.)</td>
</tr>
<tr>
<td></td>
<td>Rocemerck Intravenous 1 g (Merck Pharma Ltd.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Antibiotics acting mainly on gram-positive and gram-negative bacteria</th>
</tr>
</thead>
</table>

Indications

- **Susceptible strains**

- **Indications**
  - Sepsis, laryngopharyngitis, tonsillitis, acute bronchitis, pneumonia, lung abscess, empyema thoracis, secondary infection in chronic respiratory lesions, cystitis, pyelonephritis, epididymitis, urethritis, cervicitis, pelvic inflammatory disease, proctitis, peritonitis, intra-abdominal abscess, cholecystitis, cholangitis, Bartholinitis, intrauterine infection, uterine adnexitis, parametritis, purulent meningitis, keratitis (including corneal ulcer), otitis media, sinusitis, jaw cellulitis, jaw inflammation

**<<PRECAUTIONS (underlined parts are additions)>>**

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

- **Hepatitis fulminant, hepatic function disorder, jaundice**: Serious hepatitis such as hepatitis fulminant, hepatic function disorder with an increase in AST (GOT), ALT (GPT), G-GTP etc., jaundice may occur. Patients should be carefully monitored through periodic testing etc. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

**<Reference Information>**

Company report

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to June 30, 2006) (events for which a causality to the drug could not be denied)

- Hepatitis fulminant etc.: 3 cases (of which 3 had fatal cases)

The number of patients treated with Ceftriaxone for a year estimated by MAH: approximately 1.04 million (July 2005 to June 2006)

Marketed in Japan in: 1986
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/Age</th>
<th>Reason for use (complications)</th>
<th>Daily dose/Treatment duration</th>
<th>Adverse reactions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female 80s</td>
<td>Infectious disease prophylaxis, suspected pneumonia (cardiac failure, atrioventricular block complete)</td>
<td>1 g 7 days</td>
<td><strong>Hepatitis fulminant</strong>&lt;br&gt;12 days before administration:&lt;br&gt;Metildigoxin treatment was completed.&lt;br&gt;9 days before administration&lt;br&gt;The patient was hospitalized with senile dementia. She became wheelchair-dependent.&lt;br&gt;HBs antigen (−), HCV-3rd (−)&lt;br&gt;8 days before administration:&lt;br&gt;Ultrasound examination results: no abnormal findings in the biliary system.&lt;br&gt;6 days before administration:&lt;br&gt;Atrioventricular block complete developed.&lt;br&gt;On day 1 of administration:&lt;br&gt;Dyspnœa (cardiac failure) developed. A central venous catheter was placed. Oxygen inhalation therapy was initiated. Morphine hydrochloride and nitroglycerin were started for the treatment of cardiac failure.&lt;br&gt;Concomitant pneumonia was suspected by chest X-ray. In addition, the CRP was (2+). Ceftriaxone sodium was started.&lt;br&gt;Severity of cardiac failure at onset (NYHA classification) was Grade IV. Concomitant chest pain, seizure, and cardiac failure congestive were noted.&lt;br&gt;The result of methylidygxin concentration measurement (specimen: blood) was 1.0 ng/mL (normal range).&lt;br&gt;On day 4 of administration:&lt;br&gt;EF value was 25%. The cardiac failure was temporarily improved.&lt;br&gt;On day 6 of administration:&lt;br&gt;The patient developed general malaise, skin coloring yellow, disturbances of consciousness, and somnolence.&lt;br&gt;On day 7 of administration (day of discontinuation):&lt;br&gt;Marked increase in transaminase values and Grade 3 coma hepatic were noted. Ceftriaxone sodium was discontinued.&lt;br&gt;1 day after discontinuation:&lt;br&gt;Fresh frozen human plasma (FFP), gabexate mesilate, liver extract/flavin adenine dinucleotide, and glycyrhrizin/glycine/cysteine were administered.&lt;br&gt;2 days after discontinuation:&lt;br&gt;FFP, gabexate mesilate, liver extract/flavin adenine dinucleotide, and glycyrhrizin/glycine/cysteine were administered.&lt;br&gt;3 days after discontinuation:&lt;br&gt;FFP, gabexate mesilate, liver extract/flavin adenine dinucleotide, and glycyrhrizin/glycine/cysteine were administered.</td>
<td>Company report</td>
</tr>
</tbody>
</table>
4 days after discontinuation:
The patient died of multi-organ failure
(heart/kidneys/liver).
Autopsy: not performed.

Concomitant medications: ranitidine hydrochloride, morphine hydrochloride, nitroglycerin, furosemide, citicoline, multivitamin product for hyperalimentation

**Clinical Laboratory Values**

<table>
<thead>
<tr>
<th></th>
<th>9 days before administration</th>
<th>On day 1 of administration</th>
<th>On day 4 of administration</th>
<th>On day 7 of administration (day of discontinuation)</th>
<th>2 days after discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (GOT) (IU/L)</td>
<td>36</td>
<td>155</td>
<td>89</td>
<td>2257</td>
<td>1310</td>
</tr>
<tr>
<td>ALT (GPT) (IU/L)</td>
<td>25</td>
<td>128</td>
<td>102</td>
<td>1468</td>
<td>1424</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.9</td>
<td>2.4</td>
<td>1.1</td>
<td>2.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Platelet count (×10⁴/mm³)</td>
<td>13.1</td>
<td>11.2</td>
<td>10.8</td>
<td>10.1</td>
<td>6</td>
</tr>
<tr>
<td>WBC (/mm³)</td>
<td>5100</td>
<td>7700</td>
<td>9700</td>
<td>12400</td>
<td>9800</td>
</tr>
<tr>
<td>CRP</td>
<td>(2+)</td>
<td>(3+)</td>
<td>(3+)</td>
<td>(4+)</td>
<td>(3+)</td>
</tr>
</tbody>
</table>

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
WBC: White Blood Cell
CRP: C-Reactive Protein

**Patient Adverse reactions**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/ Age</th>
<th>Reason for use (complications)</th>
<th>Daily dose/ Treatment duration</th>
<th>Adverse reactions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Male 80s</td>
<td>Bronchitis (asthma, diabetes mellitus)</td>
<td>2 g 2 days</td>
<td><strong>Hepatitis fulminant</strong></td>
<td>Company report</td>
</tr>
</tbody>
</table>

Approx. 13 days before administration:
The patient developed bronchitis-induced asthma bronchial.
Severity: severe (difficulty moving due to dyspnoea), SpO₂ 91%, O₂ at 3 L by mask

8 days before administration:
Asthma developed. The patient was treated with theophylline, procaterol hydrochloride, carbocisteine, and norfloxacin (until on day 1 of administration).

On day 1 of administration:
The patient visited the hospital with grand mal of asthma bronchial. He was hospitalized.
A nebulizer treatment didn't work.
Methylprednisolone sodium succinate and aminophylline were administered.
Bronchitis symptoms were noted. CRP was 2 mg/dL. Ceftriaxone sodium was started.
Pathogenic bacteria test (ear) results: pseudomonas aeruginosa

On day 2 of administration (day of discontinuation):
Ceftriaxone sodium, methylprednisolone sodium succinate, and aminophylline were administered (in the morning).
AST (GOT) 583 IU/L, ALT (GPT) 325 IU/L.
Drug-induced liver disorder was suspected.
Ceftriaxone sodium, methylprednisolone sodium succinate, and aminophylline were discontinued in the afternoon.

2 days after discontinuation:
Japan Coma Scale (JCS) increased to 3 digits.
AST (GOT) 4660 IU/L, ALT (GPT) 2930 IU/L, PT 11%. Hepatitis fulminant was suspected because of Grade III coma hepatic.
Plasmapheresis (FFP 30 units).
Method: simple plasmapheresis
3 days after discontinuation:
Plasmapheresis: PT 28%

4 days after discontinuation:
Plasmapheresis: PT 34%

5 days after discontinuation:
PT 33%, JCS decreased to 2 digits.

7 days after discontinuation:
PT 19%, Plasmapheresis was conducted.

8 days after discontinuation:
SpO$_2$ was ≥95%, but suddenly dropped to between 70% and 80%.
SpO$_2$ did not improve with 10 L of O$_2$ by mask.
The patient was intubated.
Bradycardia occurred, followed by cardiac arrest. Resuscitation was attempted, but the patient died.

Cause of death: hepatitis fulminant

[Evaluation items related to hepatic function disorder]
- Initial symptoms: pyrexia and coma
- Hepatitis panel:
  IgM-HA antibody, HBs antigen, HBs antibody,
  HBc antibody: (−)
- Autoantibody: (−)
- Drug susceptibility test: DLST (performed 2 days after discontinuation)
  Methylprednisolone sodium succinate: (−)
- Alcohol intake: none
- Liver biopsy: not performed
- Ultrasound examination (performed 2 days after discontinuation): no abnormal findings

Concomitant medications: methylprednisolone sodium succinate, aminophylline, theophylline, procaterol hydrochloride, carbocisteine, norfloxacin, insulin human (Genetical recombination), prednisolone, fluticasone propionate

---

**Clinical Laboratory Values**

<table>
<thead>
<tr>
<th></th>
<th>On day 1 of administration</th>
<th>On day 2 of administration (day of discontinuation)</th>
<th>2 days after discontinuation</th>
<th>3 days after discontinuation</th>
<th>4 days after discontinuation</th>
<th>5 days after discontinuation</th>
<th>6 days after discontinuation</th>
<th>7 days after discontinuation</th>
<th>8 days after discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (GOT) (IU/L)</td>
<td>33</td>
<td>583</td>
<td>4660</td>
<td>1165</td>
<td>276</td>
<td>135</td>
<td>63</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>ALT (GPT) (IU/L)</td>
<td>16</td>
<td>325</td>
<td>2930</td>
<td>1011</td>
<td>385</td>
<td>197</td>
<td>142</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.8</td>
<td>1.5</td>
<td>2.1</td>
<td>2.3</td>
<td>3.7</td>
<td>4.7</td>
<td>7.7</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>--</td>
<td>0.8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.2</td>
<td>--</td>
<td>3.4</td>
<td>3.5</td>
<td>3.6</td>
<td>3.2</td>
<td>2.8</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Platelet count (×10$^4$/mm$^3$)</td>
<td>20.9</td>
<td>16.1</td>
<td>5.9</td>
<td>4.0</td>
<td>3.8</td>
<td>5.1</td>
<td>4.1</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>WBC (/mm$^3$)</td>
<td>7500</td>
<td>9600</td>
<td>11600</td>
<td>9900</td>
<td>11900</td>
<td>14200</td>
<td>15500</td>
<td>30700</td>
<td></td>
</tr>
<tr>
<td>PT (sec)</td>
<td>--</td>
<td>--</td>
<td>32.1</td>
<td>18.5</td>
<td>16.5</td>
<td>16.9</td>
<td>23.2</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>PT (%)</td>
<td>--</td>
<td>--</td>
<td>11</td>
<td>28</td>
<td>34</td>
<td>33</td>
<td>19</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.25</td>
<td>2.31</td>
<td>2.53</td>
<td>--</td>
<td>--</td>
<td>0.43</td>
<td>1.33</td>
<td>3.22</td>
<td></td>
</tr>
</tbody>
</table>

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
WBC: White Blood Cell
PT (sec): Prothrombin Time (sec)
PT (%): Prothrombin Activity (%)
CRP: C-Reactive Protein
Revision of PRECAUTIONS

(No. 181)

This section presents details of revisions of PRECAUTIONS in package inserts and brand names of drugs that have been revised according to the Notification after the issue before previous one (Pharmaceuticals and Medical Devices Safety Information No. 228) (excluding those presented in “2. Important Safety Information” of this Bulletin), together with reference materials.

1 <Antipyretics and analgesics, anti-inflammatory agents>

Sulindac

[Brand Name] Clinoril Tablets 50 and 100 (Banyu Pharmaceutical Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] Acute renal failure, acute nephritis interstitial, nephrotic syndrome: Oliguria, haematuria, proteinuria, BUN/blood creatinine increased, hyperkalaemia, hypoalbuminaemia, etc. may occur.

<Reference Information> Company report

2 <Antiarrhythmic agents>

Pilsicainide Hydrochloride (oral dosage form)

[Brand Name] Sunrythm Capsules 25 mg and 50 mg (DAIICHI ASUBIO PHARMA CO., LTD.) and others

[Adverse Reactions (clinically significant adverse reactions)] Ventricular fibrillation, ventricular tachycardia, sinus arrest, atrioventricular block complete, syncope: These adverse reactions may occur. Electrocardiography should be frequently performed. If abnormal findings are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

3 Pilsicainide Hydrochloride (injectable dosage form)

[Brand Name] Sunrythm Injection 50 (DAIICHI ASUBIO PHARMA CO., LTD.)

[Adverse Reactions (clinically significant adverse reactions)] Ventricular fibrillation, ventricular tachycardia, sinus arrest, atrioventricular block complete, syncope: These adverse reactions may occur. Continuous monitoring of electrocardiography should be performed. If abnormal findings are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report
<Antiarrhythmic agents>

4 Bepridil Hydrochloride

[Brand Name] Bepricor Tablets 50 and 100 (Nippon Organon K.K.)

[Adverse Reactions (clinically significant adverse reactions)] Interstitial pneumonia: Interstitial pneumonia may occur. If pyrexia, cough, dyspnoea, abnormal chest sound (crepitations) etc. is observed, administration should be immediately discontinued and appropriate measures such as administration of adrenocortical hormones should be taken in addition to prompt examinations such as chest X-ray.

<Reference Information> Company report

<Antihypertensives>

5 Carvedilol

[Brand Name] Artist Tablets 1.25 mg, 2.5 mg, 10 mg, and 20 mg (Daiichi Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] Acute renal failure: Acute renal failure may occur. Patients should be carefully monitored. If abnormalities are observed, appropriate measures such as discontinuation of treatment should be taken.

<Reference Information> Company report

<Digestive organ agents-Miscellaneous>

6 Trimebutine Maleate

[Brand Name] Cerekinon Fine Granules, Cerekinon Tablets (Tanabe Seiyaku Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] Hepatic function disorder, jaundice: Hepatic function disorder with an increase in AST (GOT), ALT (GPT), Al-P, LDH, γ-GTP etc, jaundice may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

<Hemorrhoidal preparations>

7 Aluminum Potassium Sulfate/Tannic Acid

[Brand Name] Zione Injection, Zione Injection/Lidocaine (Mitsubishi Pharma Corporation)

[Important Precautions] Serious rectal ulcer and rectal stenosis etc. may occur following administration of this drug. Patients should be followed-up periodically after treatment. Prior to administration, patients should be adequately advised on treatment, including adverse reactions associated with this product. Patients should also be instructed to consult a primary doctor immediately, if abnormalities such as haemorrhage and anal pain are noted.

[Adverse Reactions (clinically significant adverse reactions)] Rectal ulcer: Rectal ulcer associated with haemorrhage and anal pain etc. may occur following administration of this drug. Patients should be periodically monitored after treatment. If such symptoms are observed, appropriate measures such as administration of antibiotics/suppositories should be taken. Rectal stenosis: Rectal stenosis may occur following administration of this drug. Patients should be periodically monitored after treatment. If such symptoms are observed, appropriate measures such as incision of stenosis and bougienage should be taken.

<Reference Information> Company report
8 Synthetic antibacterials

Moxifloxacin Hydrochloride

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

[Important Precautions] Syncope, loss of consciousness, and dizziness may occur. Patients should be advised to refrain from engaging in potentially hazardous operations of machinery including driving a car. Prior to treatment, patients should be fully informed of these potential adverse reactions.

[Adverse Reactions (clinically significant adverse reactions)] Syncope and loss of consciousness: Syncope, loss of consciousness, depressed level of consciousness may occur. Appropriate measures such as discontinuation of treatment should be taken in such cases.

<Reference Information> Company report

9 Vaccines

Freeze-dried Live Attenuated Varicella Vaccine

[Brand Name] Freeze-dried Live Attenuated Varicella Vaccine “BIKEN” (Research Institute for Microbial Diseases, Osaka University)

[Precautions of Dosage and Administration] Target population
This vaccine is used for persons aged 12 months and older without history of varicella and to whom the following (1) to (6) apply. However, persons to whom the following (1) to (6) apply should not receive the vaccination when they are expected to have peripheral lymphocyte count decreased or immunological competence decreased by treatment or any reasons within 2 weeks after vaccination. [Those persons may become susceptible to infection with the vaccine virus, such as developing disseminated symptoms.]

<Reference Information> Company report

10 Over the counter drugs Containing Ibuprofen

[Brand Name] Eve (SSP Co., Ltd.), Feria (Takeda Pharmaceutical Company Limited), Ringl IB Gel Capsules (Sato Pharmaceutical Co., Ltd.) and others

[When not to use the product] These products should not be used in the following persons.
Children aged under 15

<Reference Information> Company report

11 Over the counter drugs Containing Scopolamine Butylbromide

[Brand Name] Buscopan-A Tablets, Buscopan-M Capsules (SSP Co., Ltd.) and others

[When not to use the product] These products should not be used in the following persons.
Persons with a history of allergic reactions to this product

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.
If the following symptoms are observed after taking this drug
In rare instances, the following serious symptoms may occur. Visit a physician immediately in such cases.

Shock (anaphylaxis): Immediately after administration, urticaria, oedema, chest distress, etc. may occur concurrently with pallor facial, cold hands and feet, cold sweat, and respiratory discomfort.
12 Over the counter drugs

Products Containing Trimebutine Maleate

[Brand Name] Inoseaact (Sato Pharmaceutical Co., Ltd.), Tanabe Gastrointestinal drug <Tuning>, Tanabe Gastrointestinal Granules (Tanabe Seiyaku Co., Ltd.), Pansiron Trim <Granules>, Pansiron Trim <Tablets> (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.

In rare instances, the following serious symptoms may occur. Visit a physician immediately in such cases,

**Hepatic function disorder:** General malaise, jaundice (skin and white of the eyes become yellow) may occur.
List of products subject to Early Post-marketing Phase Vigilance

<table>
<thead>
<tr>
<th>Nonproprietary name</th>
<th>Brand name</th>
<th>Name of the marketing authorisation holder</th>
<th>Date of EPPV initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel Sulfate</td>
<td>Plavix Tablets 25 mg and 75 mg</td>
<td>Sanofi-Aventis K.K.</td>
<td>May 8, 2006</td>
</tr>
<tr>
<td>Silodosin</td>
<td>Urief Cap. 2 mg and 4 mg</td>
<td>Kissei Pharmaceutical Co., Ltd.</td>
<td>May 11, 2006</td>
</tr>
<tr>
<td>Tosufloxacin Tosilate</td>
<td>Ozex Ophthalmic Solution 0.3%</td>
<td>Toyama Chemical Co., Ltd.</td>
<td>May 11, 2006</td>
</tr>
<tr>
<td>Follitropin Alfa</td>
<td>Gonalef for S.C. Injection 75 and 150</td>
<td>Serono Japan Co., Ltd.</td>
<td>May 11, 2006</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Femara Tablets 2.5 mg</td>
<td>Novartis Pharma K.K.</td>
<td>May 11, 2006</td>
</tr>
<tr>
<td>Loxoprofen Sodium</td>
<td>Loxonin PAP 100 mg</td>
<td>LEAD CHEMICAL Co., Ltd.</td>
<td>May 23, 2006</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify Tablets 3 mg and 6 mg, Abilify Powder 1%</td>
<td>Otsuka Pharmaceutical Co., Ltd.</td>
<td>June 8, 2006</td>
</tr>
<tr>
<td>Solifenacin Succinate</td>
<td>Vesicare Tablets 2.5 mg and 5 mg</td>
<td>Astellas Pharma Inc.</td>
<td>June 8, 2006</td>
</tr>
<tr>
<td>Tolterodine Tartrate</td>
<td>Detrusitol Capsules 2 mg and 4 mg</td>
<td>Pfizer Japan Inc.</td>
<td>June 8, 2006</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>AmBisome for Intravenous Infusion 50 mg</td>
<td>Dainippon Sumitomo Pharma Co., Ltd.</td>
<td>June 20, 2006</td>
</tr>
<tr>
<td>Magnesium Sulfate/Glucose</td>
<td>Magsent Injection 100 mL</td>
<td>TOA Pharmaceuticals Co., Ltd.</td>
<td>June 20, 2006</td>
</tr>
<tr>
<td>Sertraline Hydrochloride</td>
<td>Jzoloft Tablets 25 mg and 30 mg</td>
<td>Pfizer Japan Inc.</td>
<td>July 7, 2006</td>
</tr>
<tr>
<td>Somatropin (Genetical recombination)</td>
<td>Genotropin 5.3 mg, Genotropin Inj. 12 mg, Genotropin MiniQuick s.c. Inj. 0.6 mg, 1.0 mg, and 1.4 mg”</td>
<td>Pfizer Japan Inc.</td>
<td>July 26, 2006</td>
</tr>
<tr>
<td>Inulin</td>
<td>Inulead Inj.</td>
<td>FUJIYAKUHIN Co., Ltd.</td>
<td>August 22, 2006</td>
</tr>
<tr>
<td>Alendronate Sodium Hydrate</td>
<td>Fosamac Tablets 35 mg</td>
<td>Banyu Pharmaceutical Co., Ltd.</td>
<td>September 15, 2006</td>
</tr>
<tr>
<td>Alendronate Sodium Hydrate</td>
<td>Bonalon Tablet 35 mg</td>
<td>Teijin Pharma Limited</td>
<td>September 15, 2006</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Itrizole Oral Solution 1%</td>
<td>Janssen Pharmaceutical K.K.</td>
<td>September 15, 2006</td>
</tr>
<tr>
<td>Product Name</td>
<td>Manufacturer</td>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------------------------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Schering-Plough K.K.</td>
<td>September 15, 2006</td>
<td></td>
</tr>
<tr>
<td>Temodal Capsules 20 mg and 100 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>AstraZeneca K.K.</td>
<td>September 15, 2006</td>
<td></td>
</tr>
<tr>
<td>Pulmicort Respules 0.25 mg and 0.5 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entecavir Hydrate</td>
<td>Bristol Pharmaceuticals Y.K.</td>
<td>September 21, 2006</td>
<td></td>
</tr>
<tr>
<td>Baraclude Tablets 0.5 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetorelix Acetate</td>
<td>Nippon Kayaku Co., Ltd.</td>
<td>September 21, 2006</td>
<td></td>
</tr>
<tr>
<td>Cetrotide for Injection 0.25 mg and 3 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manganese Chloride Tetrahydrate</td>
<td>Meiji Dairies Corporation</td>
<td>September 25, 2006</td>
<td></td>
</tr>
<tr>
<td>Bothdel Oral Solution 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Pfizer Japan Inc.</td>
<td>September 25, 2006</td>
<td></td>
</tr>
<tr>
<td>Gabapen Tablets 200 mg, 300 mg, and 400 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>Kirin Brewery Company, Limited</td>
<td>October 10, 2006**</td>
<td></td>
</tr>
<tr>
<td>Busulfex Injection 60 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fexofenadine Hydrochloride</td>
<td>Sanofi-Aventis K.K.</td>
<td>October 20, 2006**</td>
<td></td>
</tr>
<tr>
<td>Allegra Tablets 60 mg**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1: An additional indication for “adult growth hormone hyposecretion (for severe cases only)”
*2: For the adult dose initially approved
*3: An additional administration for “pediatrics”
*4: An additional administration for “pediatrics (aged 7 and older)”