Pharmaceuticals and Medical Devices Safety Information

No. 202 June 2004

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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. 202 June 2004

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

[Outline of Information]

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2	**Infliximab (Genetical recombination) (and 2 others)**	*P* *C*	Presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 201), together with reference materials.	7
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1

Safety measures relating to pharmaceuticals with high risks resulting from mix-ups

(1) Introduction

As indicated in the attachment "Pharmaceuticals that require caution when checking and formulating prescriptions, or when supplying to hospital wards" (Japanese Society of Hospital Pharmacists) (http://www.jshp.or.jp/031112.pdf, in Japanese) for the Joint Notification by the Secretary-Generals of the Health Policy Bureau and the Pharmaceutical and Food Safety Bureau of Ministry of Health, Labour and Welfare "Thoroughness of Measures for the Prevention of Medical Accidents in Medical Institutions" dated November 27, 2003, the drugs that may be linked to serious accidents if mixed up are narrowed down to a certain extent. With regard to such drugs that require caution, although requests have been made since the past to confirm the usage status and measures to prevent mix-ups, in addition to introducing improvements in labelings for the following combinations of drugs that have been planned from the perspective of accident prevention based on discussions in the "Working Group on Drug Similarity" within the Committee on Pharmaceuticals and Medical Devices of Medical Safety Measures Council. MHLW also requests again that thorough safety measures be implemented at medical institutions.

1) Taxol	—	Taxotere
2) Amaryl	—	Almarl
3) Utemerin	—	Metenarin
4) Xylocaine 10% formulation	—	Xylocaine 2% formulation
5) Potassium drug products		

(2) Combination of drugs that require cautions and safety measures

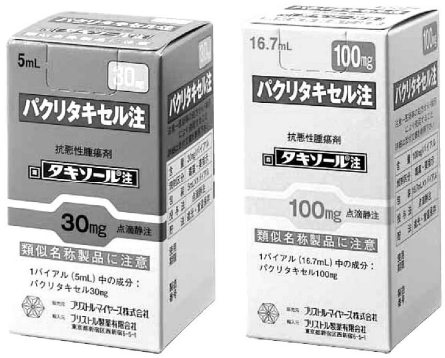
1) Taxol and Taxotere

For Taxol and Taxotere, as the names of the drugs are similar, there have been reports of accidents resulting from mistakes in prescription, leading to death in some cases. Both are antineoplastic plant extract preparations indicated for breast cancer, etc., but since there is an approximately 3 times difference per dose, accidental administration of Taxotere instead of Taxol can lead to fatal outcome. Two relevant companies recently improved the labeling for both Taxol and Taxotere through further emphasizing the nonproprietary name to promote the prevention of mix-ups (see **Figures 1 and 2**).

In the case of anticancer drugs, health hazards resulting from mistaken use are serious, and it is necessary to establish thorough preventive measures. When handling both Taxol and Taxotere at a medical institution, it is requested to thoroughly implement medication history management as well as thorough measures, such as double checks, when dispensing and prescribing the drugs, in addition to making the conditions for when formulating the drugs clear, such as by carrying out systematic formulation based on regimens and by also indicating the nonproprietary name on the formulation.

Figure 1 Taxol Injection

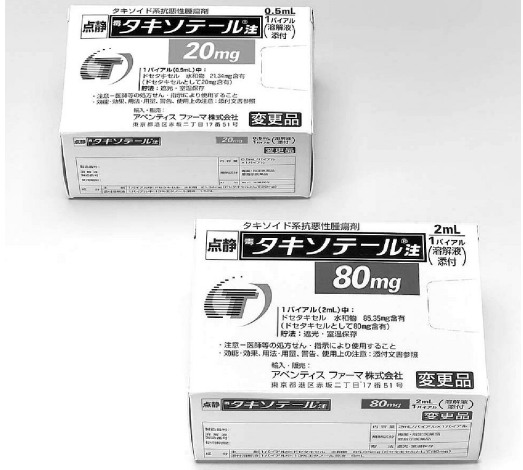
Old



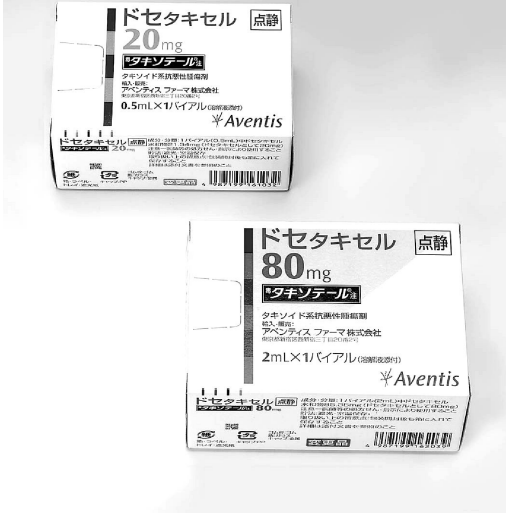
New

Figure 2 Taxotere Injection

Old



New



2) Amaryl and Almarl

Amaryl (antidiabetic drug) and Almarl (antiarrhythmic drug) have similar brand names. If Amaryl is mistakenly administered to a patient who is not diabetes mellitus, the outcome could be fatal. There have been several reports of accidents resulting from mix-ups, leading to death in some cases. The relevant company recently improved the PTP packaging of Amaryl so that the efficacy as an "antidiabetic agent" is clearer as the preventive measures for mix-ups, improvements have also been made for labels so that patients can recognize what kind of drug they are received so that they themselves do not take the wrong drug.

At medical institutions, in order to ensure that there are no mistakes resulting from the similarity of the names, it is effective to take measures such as by attaching reminder stickers on the dispensing shelves, etc. However, it is fundamental to develop a system so that antidiabetic agents are not mistakenly administrated to patients who are not diabetes mellitus. It is requested to make sure that all related persons conduct thorough safety confirmations, such as by developing a system for confirming the patient's medication history when dispensing antidiabetic agents, as well as always confirming that the patient has diabetes mellitus when dispensing such agents to the patient.

3) Utemerin and Metenarin

Utemerin (β_2-stimulant for the treatment of threatened abortion/premature delivery) and Metenarin (a drug for stimulating uterine contractions) have similar brand names, and there have been several reports of

accidents resulting from mix-ups in the past. Since these drugs have the opposite pharmacological action, mistaken administration of Metenarin, which acts to contract the uterus, to a patient with threatened abortion/premature delivery who should be administered Utemerin may result in abortion/premature delivery. Two relevant companies recently improved the labelings to promote warnings by displaying the efficacy and brand name in a size larger than before (see **Figures 3 and 4**).

It has been pointed out that a mix-up between these drugs results in confusion in medical environments where there is a complex mix of pregnant and parturient women, such as because pregnant women becoming parturient women after time elapses, not only because their names are similar, but also because they have actions related to uterine contractions, though the effects are the opposite. At medical institutions, it is requested to make sure that all related persons thoroughly confirm the drug efficacy on labeling, together with developing an environment where mix-ups do not occur easily, such as by not placing these drugs close to each other even when both drugs are managed in a hospital ward.

Figure 3 Utemerin

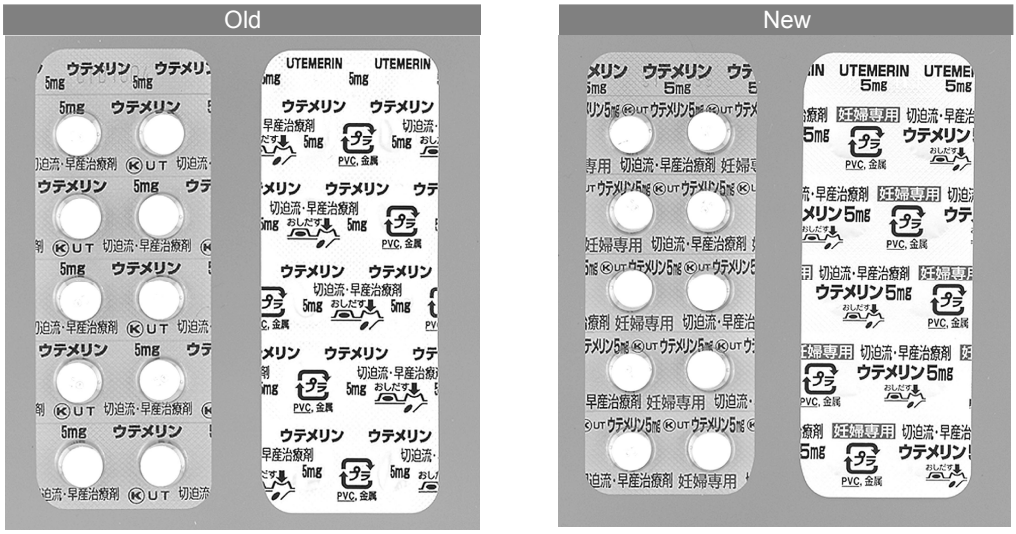
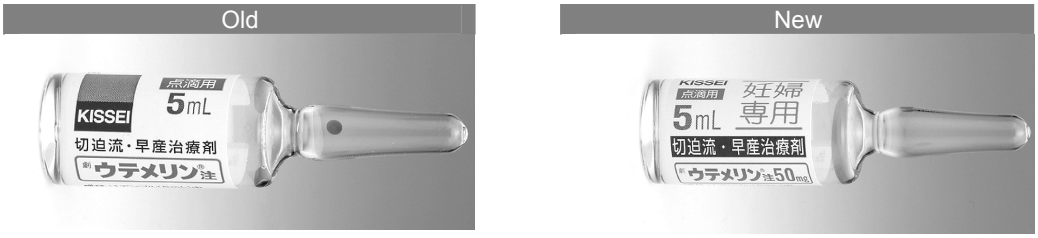


Figure 4 Utemerin Injection

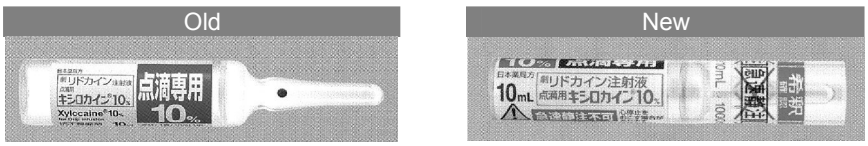


4) Xylocaine 10% formulation and Xylocaine 2% formulation

There have been reports of accidents resulting from mix-ups between Xylocaine 10% formulation for drip infusion and Xylocaine 2% formulation for intravenous injection, leading to death in some cases. The relevant company recently improved the labeling for the 10% formulation to clearly indicate that it is a drug to be used by diluting it before use, and that it is not a drug for intravenous injection (see **Figure 5**).

With regard to Xylocaine 10% formulation for drip infusion, warnings were issued from the Japanese Society of Hospital Pharmacists and the Japan Council for Quality Health Care stating that this formulation must not be stocked at hospital wards, but there have been reports of accidents resulting from mix-ups even after such warnings were released. Based on recent warnings from the Japanese Board of Cardiovascular Surgery regarding the handling of this drug such as removing it from all outpatient clinics and hospital wards including emergency departments, as well as emergency carts, it is requested for medical institutions with this drug still stocked in hospital wards or emergency carts to reconsider the management of this drug. It is also requested to establish thorough reminders for related persons, including new staff members, not to mix up the two drugs.

Figure 5 Xylocaine 10% for drip infusion



5) Potassium drug products

Potassium drug products for injections are administered after diluting them in principle. But there have been reports of accidents resulting from administration of the undiluted solution at medical sites. Based on recent warnings from the Japan Council for Quality Health Care and the Japanese Board of Cardiovascular Surgery regarding the handling of potassium drug products, such as removing it from all outpatient clinics and hospital wards including emergency departments, as well as emergency carts, it is requested for medical institutions with these drug products still stocked in hospital wards or emergency carts to reconsider the introduction of a safer drug, etc. It is also requested to establish thorough reminders for related persons, including new staff members, with regard to handling of such drug products.

(3) Conclusion

As described above, improvements in labeling are implemented for individual combinations of drug products with high risks, but it is necessary to listen to the opinions regarding the results of such improvements from the environments where they are actually used, and consider further improvements in the future. In addition, since mistaken use cannot be prevented only through improvements in labeling, etc., it is also important to develop a system for preventing accidents even at medical institutions, such as through cautions in prescription, dispensing, and administration. Particularly in recent instances, there are concerns regarding the necessary information not being conveyed sufficiently to all related persons within medical institutions. With regard to information related to these important safety measures, it is requested for the pharmaceutical departments to play a central role, receive cooperation from the medical safety control offices, etc. and make sure that information is thoroughly and broadly spread to all related persons in medical institutions.

(References)

Japanese Society of Hospital Pharmacists “Further Thorough Dispensing Methods that Contribute to Drug Management and Patient Safety” (In Japanese)
http://www.jshp.or.jp/cont/040511.pdf

Japan Council for Quality Health Care “Urgent Proposal” (In Japanese)
http://www.psp.jcqhc.or.jp/psp/teigenn.html

Japanese Board of Cardiovascular Surgery “Urgent Notice” (In Japanese)
http://cvs.umin.jp/topic/040602.html

2

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 previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 201).

1 Infliximab (Genetical recombination)

Brand Name (name of company)	Remicade for I.V. Infusion 100 (Tanabe Seiyaku Co., Ltd.)
Therapeutic Category	Digestive organ agents-Miscellaneous
Indications	Rheumatoid arthritis (only for cases which have had an inadequate response to conventional therapy) Treatment for Crohn's disease that demonstrate either of the following conditions (only for cases which have had an inadequate response to conventional therapy) Patients with moderately to severely active Crohn's disease Patients with external fistula

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

[Important Precautions]

Interstitial pneumonia may occur in combination with methotrexate. The patient should be advised to contact their primary physician immediately if symptoms such as pyrexia, cough and dyspnoea are observed after administration. Appropriate measures such as chest X-ray and chest CT tests, etc. and administration of adrenocortical hormone preparation should be taken in such cases.

[Adverse Reactions (clinically significant adverse reactions)]

Sepsis, pneumonia (including pnemocystis carinii pneumonia), and opportunistic infections such as fungal infectious disorders: These symptoms may occur. Patients should be carefully monitored and if abnormalities are observed, take appropriate measures such as discontinuation of administration. Many of the cases with death were caused by infectious diseases.
Interstitial pneumonia: Interstitial pneumonia may occur in cases with concomitant use of methotrexate drug products. Caution should be exercised for respiratory tract symptoms such as pyrexia, cough, and dyspnoea. If abnormalities are observed, chest X-ray, chest CT, blood gas tests, etc., should be performed , administration of this drug and methotrexate should be discontinued, and appropriate measures that take differential diagnosis (β-D glucan measurement, etc.) with pneumocystis carinii pneumonia into consideration, should be taken.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	Rheumatoid arthritis (hypertension, iron deficiency anaemia, depression, anxiety neurosis, weak constitution, constipation)	132 mg (3 mg/kg) 3 times	**Interstitial pneumonia** Medical history: old tuberculosis Duration affected with rheumatoid arthritis: 3 years and 3 months Approx. 1 year before administration: Administration of methotrexate (4 mg/week) was started. Subsequently, administration of 4 to 8 mg/week of methotrexate was continued for a period of 2.5 months. Afterwards, administration of the drug was suspended for approximately 8 months. 43 days before administration: Administration of methotrexate (6 mg/week) was restarted. On day 1 of administration: First administration of this drug was conducted. On day 14 of administration: Second administration of this drug was conducted. On day 42 of administration: Third administration of this drug was conducted. 26 days after 3rd administration: There was no pain from rheumatism and the course of rheumatoid arthritis was good. Approx. 40 days after 3rd administration: General malaise, dyspnoea, slight fever developed. 45 days after 3rd administration: Administration of methotrexate (6 mg/week) was discontinued. 46 days after 3rd administration: The patient visited this hospital. The patient was diagnosed with interstitial pneumonia and was hospitalized due to decrease in pulmonary permeability in right lower lung field confirmed by chest X-ray and faint ground-glass opacity over a wide range on the entire lung field confirmed through chest CT. Intravenous administration of 500 mg of methylprednisolone sodium succinate was started. Oral administration of 200 mg of minocycline hydrochloride was started. 48 days after 3rd administration: Value of cytomegalovirus (CMV) IgM antibody was 2.17 (positive). 49 days after 3rd administration: Administration of 500 mg of methylprednisolone sodium succinate was discontinued. Reduction in faint ground-glass opacity was confirmed through chest CT. 54 days after 3rd administration: Administration of 500 mg of methylprednisolone sodium succinate was restarted. 55 days after 3rd administration: Administration of 300 mg of tiopronin was started. 57 days after 3rd administration: Administration of 500 mg of methylprednisolone sodium succinate was discontinued. 58 days after 3rd administration: Although dyspnoea and slight fever were improved, general malaise and arthralgia thought to have been resulting from rheumatism developed.	Company report

				59 days after 3rd administration: Interstitial pneumonia shadow had mostly disappeared in chest CT. There were no symptoms of dyspnoea or slight fever. 60 days after 3rd administration: CMV IgM antibody value was 1.77 (positive). Interstitial pneumonia resulting from CMV was also considered, and drip infusion of 400 mg of ganciclovir was conducted for 3 days. 64 days after 3rd administration: Treatment for rheumatoid arthritis using 300 mg of actarit was started. 73 days after 3rd administration: Interstitial pneumonia shadow disappeared in chest CT. General malaise and arthralgia were also gone. 75 days after 3rd administration: Improvement in interstitial pneumonia was confirmed. 76 days after 3rd administration: Value of CMV IgM antibody was 0.7 (negative).	
	Concomitant medications: methotrexate, isoniazid, magnesium oxide, loxoprofen sodium, folic acid, Kamishoyosan extract, prednisolone, amlodipine besilate, sodium ferrous citrate, tandospirone citrate, milnacipran hydrochloride, polaprezinc, fludiazepam, candesartan cilexetil				

Clinical Laboratory Values

	15 days before 1st administration	27 days after 2nd administration	26 days after 3rd administration	46 days after 3rd administration	53 days after 3rd administration
RBC ($\times 10^4/mm^3$)	396	408	408	362	415
Haemoglobin (g/dL)	11.5	12.3	12.5	11.4	13.5
Haematocrit (%)	34.3	35.6	37.6	33.2	38.5
WBC ($/mm^3$)	6000	11800	8800	9700	7800
Neutrophils (%)	—	81	—	83	77
Eosinophils (%)	—	2	—	1	1
Basophils (%)	—	1	—	1	0
Lymphocytes (%)	—	13	—	10	14
Monocytes (%)	—	3	—	5	8
PLT ($\times 10^4/mm^3$)	25.0	24.6	25.7	24.7	24.1
Total protein (g/dL)	5.9	6.7	7.2	6.6	6.7
A/G ratio	1.68	1.92	1.74	1.46	1.30
AST (GOT) (IU/L)	15	14	21	39	38
ALT (GPT) (IU/L)	19	16	42	41	55
Al-P (IU/L)	327				484
LDH (IU/L)	—	—	271	470	317
Cholinesterase (IU/L)	—	5968	6308	—	5922
γ-GTP (IU/L)	—	30	46	43	45
CK (CPK) (IU/L)	—	—	—	19	—
Urate (mg/dL)	—	3.3	3.8	5.0	4.2
BUN (mg/dL)	—	25.6	19.9	17.4	15.8
Serum creatinine (mg/dL)	0.61	0.60	0.64	0.75	0.60
Total bilirubin (mg/dL)	—	—	—	—	0.3
Total cholesterol (mg/dL)		284	281	276	289
Neutral fat (mg/dL)	—	148	212	234	243
HDL cholesterol (mg/dL)	—	74	80	—	55
Serum iron (μg/dL)	—	89	46	48	56
Blood glucose (mg/dL)		107		120	106
RA test (qualitative)	38 (1+)	48 (1+)	113 (2+)	282 (2+)	272 (2+)
CRP (mg/dL)	2.1 (1+)	2.5 (2+)	4.8 (3+)	8.7 (6+)	8.3 (5+)

Erythrocyte sedimentation rate (mm/h)	30	27	32	60	56
HCV antibody 3	—	—	—	—	—
TSH (μU/mL)	—	—	—	6.43	—
KL-6 (mg/dL)	—	—	—	1140	—

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
A/G: Albumin/Globulin
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
CK (CPK): Creatine Kinase
BUN: Blood Urea Nitrogen
HDL: High-Density Lipoprotein
RA: Rheumatoid Arthritis
CRP: C-Reactive Protein
HCV: Hepatitis C Virus
TSH: Thyroid Stimulating Hormone

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 70s	Rheumatoid arthritis (none)	132 mg (3 mg/kg) 4 times	**Interstitial pneumonia** Approx. 3.5 years before administration: Administration of methotrexate (6.25 mg/week) was started. Afterwards, administration was continued at 5 to 8.75 mg/week. 14 days before administration: Dosage of methotrexate was switched to 6 mg/week from 8.75 mg/week. On day 1 of administration: 1st administration of this drug was conducted. On day 14 of administration: 2nd administration of this drug was conducted. On day 44 of administration: 3rd administration of this drug was conducted. On day 98 of administration: 4th administration of this drug was conducted. 5 days after 4th administration: Cough developed. 6 days after 4th administration: Pneumonia was suspected by the result of X-ray. 8 days after 4th administration: Pyrexia developed. 11 days after 4th administration: The patient visited a neighborhood doctor. Pneumonia image was confirmed. Administration of methotrexate was discontinued. 12 days after 4th administration: The patient received consultation as outpatient at this hospital, and was hospitalized. She was diagnosed with complicated pneumonia. Administration of 1 g of meropenem trihydrate and 0.4 g of clarithromycin was started. 15 days after 4th administration: Meropenem trihydrate and clarithromycin were ineffective. As increase in interstitial shadow was confirmed through X-ray, the patient was diagnosed with interstitial pneumonia. Steroid pulse therapy with 0.5 g of methylprednisolone sodium succinate was started (3 days). 18 days after 4th administration: Administration of 30 mg of prednisolone was conducted.	Company report

				19 days after 4th administration: Oxygen saturation was decreased [SaO_2 84% (oxygen 3 L/min. mask)]. In CT image, aggravation of interstitial pneumonia was confirmed. Methylprednisolone sodium succinate was increased to 1 g (3 days). 22 days after 4th administration: Administration of 30 mg of prednisolone was conducted. 23 days after 4th administration: Administration of 40 mg of prednisolone was conducted (3 days). 25 days after 4th administration: Steroid pulse therapy with 1 g of methylprednisolone sodium succinate was restarted (3 days). Administration of 500 mg of cyclophosphamide was conducted. 28 days after 4th administration: Administration of 60 mg of prednisolone was started. 30 days after 4th administration: Intratracheal intubation and respiratory management were conducted. Respiratory condition was gradually aggravated despite treatment with prednisolone and antibiotics. 44 days after 4th administration: The patient was died from respiratory failure. After her death, lung needle biopsy was conducted and pathological examination was performed. Pathologic report: The patient had DAD (diffuse alveolar damage) rather than UIP (usual interstitial pneumonia).	
	Concomitant medications: methotrexate, indometacin, prednisolone, lansoprazole, folic acid				

Clinical Laboratory Values

	37 days before 1st administration	27 days after 2nd administration	53 days after 3rd administration	12 days after 4th administration	15 days after 4th administration	19 days after 4th administration	26 days after 4th administration	32 days after 4th administration	33 days after 4th administration	40 days after 4th administration
RBC ($\times 10^4/mm^3$)	363	383	396	381	385	366	425	350	380	379
Haemoglobin (g/dL)	12.5	12.9	13.5	12.9	12.9	12.2	14.8	12.5	13.3	13.4
Haematocrit (%)	38.3	36.3	38.3	36.6	37.3	35.5	41.0	34.8	37.6	37.2
Erythroblasts (%)									0	0
WBC ($/mm^3$)	8800	6700	6400	7400	7900	12800	17000	19400	18900	14900
Neutrophils (%)	—	—	73	—	70	82	93	—	89	87
Stab cells (%)	—	—	—	—	—	3	4	—	7	5
Segmented cells (%)						79	89		82	82
Eosinophils (%)	—	—	4	—	1	0	1	—	0	0
Basophils (%)	—	—	0	—	1	0	0	—	0	0
Lymphocytes (%)	—	—	16	—	18	11	4	—	5	8
Monocytes (%)	—	—	7	—	10	7	2	—	6	5
Atypical lymphocytes (%)	—	—	0	—	0	0	0	—	0	0
PLT ($\times 10^4/mm^3$)	21.0	21.0	17.4	14.8	16.6	18.6	22.4	23.7	23.6	28.9
Total protein (g/dL)	7.0	7.3	7.5	6.7	—	5.5	6.4	5.2	5.7	5.5
Albumin (g/dL)	54.6	62.3	62.2	59.1	—	56.5	47.1	48.2	47.0	45.5
A/G ratio	1.20	1.66	1.65	1.44		1.30	0.89	0.93	0.89	0.83
AST (GOT) (IU/L)	16	19	22	24	24	37	31	26	31	28
ALT (GPT) (IU/L)	7	9	13	12	10	20	24	35	37	27
Al-P (IU/L)	257	—	—	264	201	—	—	—	—	—
LDH (IU/L)	224	—	—	445	397	—	628	559	—	554
γ-GTP (IU/L)	17	—	—	20	17	—	—	—	—	—

Urate (mg/dL)	4.0	4.5	4.9	4.7	3.6	—	1.7	3.4	—	1.0
BUN (mg/dL)	17.6	15.0	20.2	20.8	21.9	22.9	14.5	—	18.8	18.9
Serum creatinine (mg/dL)	0.52	0.65	0.58	0.51	0.53	0.52	0.58	0.42	0.37	0.28
Total bilirubin (mg/dL)				0.7						
Direct bilirubin (mg/dL)	—	—	—	0.2	—	—	—	—	—	—
Total cholesterol (mg/dL)	199	230	238	205	184	—	205	158	—	198
Neutral fat (mg/dL)	87	134	392	126	134	—	186	225	—	335
Serum iron (μg/dL)	50	54	69	53			63	55		80
Blood glucose (mg/dL)	—	99	144	—	—	—	—	—	—	—
RA test (qualitative)	78	71	81	91	(−)	96	164	198	226	168
CRP (mg/dL)	9.8	0.8	0.3	5.1	5.4	1.2	7.9	9.2	5.7	1.1
KL-6 (mg/dL)	—	—	—	556	—	—	—	—	—	—
Erythrocyte sedimentation rate (mm/h)	64	10	6	26	17	15	42	62	53	30
Na (mEq/L)	—	145	142	139	136	142	127	—	139	134
K (mEq/L)	—	5.0	5.3	5.0	4.1	3.9	5.7	—	5.4	5.9
Cl (mEq/L)		106	104	105	99	104	90		99	96
Ca (mg/dL)	—	—	—	9.2	—	—	—	—	—	—
P (mg/dL)	—	—	—	3.6	—	—	—	—	—	—

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
A/G: Albumin/Globulin
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase

BUN: Blood Urea Nitrogen
RA: Rheumatoid Arthritis
CRP: C-Reactive Protein
Na: Sodium
K: Potassium
Cl: Chloride
Ca: Calcium
P: Phosphorus

2 Imatinib Mesilate

Brand Name (name of company)	Glivec Capsules 100 mg (Nihon Ciba-Geigy K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	1. Chronic myelogenous leukemia 2. KIT (CD117)-positive gastrointestinal stromal tumor

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

[Important Precautions]

Tumor haemorrhage, gastrointestinal perforation, etc. with rapid necrosis/contraction of tumors may occur in patients with gastrointestinal stromal tumor due to administration of this drug. Periodic blood tests, etc. should be performed and patients should be carefully monitored for initial symptoms such as melena, haematemesis, anaemia, abdominal pain, abdomen enlarged feeling of. If abnormalities are observed, perform abdominal CT tests, etc. immediately and confirm the haemorrhage area and whether there are any findings of perforations. Administration should be discontinued as necessary and appropriate measures should be taken.

[Adverse Reactions (clinically significant adverse reactions)]

Tumor haemorrhage, gastrointestinal perforation: Tumor haemorrhage, gastrointestinal perforation, peritonitis, etc. with rapid necrosis/contraction of tumors may occur in patients with gastrointestinal stromal tumors. Periodic blood tests, etc., should be performed and patients should be carefully monitored for initial symptoms such as melena, haematemesis, anemia, abdominal pain, abdomen enlarged feeling of, queasy, vomiting, etc. If abnormalities are observed, perform abdominal CT tests, etc. immediately and confirm the haemorrhage area

and whether there are any findings of perforations. Administration should be discontinued as necessary and appropriate measures should be taken.
Interstitial pneumonia, pulmonary fibrosis: Interstitial pneumonia and pulmonary fibrosis may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
Pericarditis: Pancreatitis may occur. Patients should be carefully monitored and if symptoms such as chest pain are observed, administration should be discontinued and appropriate measures should be taken.
Brain oedema, intracranial pressure increased: Brain oedema and intracranial pressure increased may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
Ileus paralytic: Ileus paralytic may occur. Patients should be carefully monitored and if symptoms such as queasy, vomiting, abdominal pain, or constipation are observed, administration should be discontinued and appropriate measures should be taken.
Thrombosis, embolism: Deep vein thrombosis and pulmonary embolism may occur. Patients should be carefully monitored and if symptoms such as shortness of breath, chest pain, pain in extremity, or oedema are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	Intra-abdominal recurrence after operation for gastrointestinal stromal tumor of the stomach (none)	400 mg 22 days	**Tumour necrosis, peritonitis, platelets decreased** 107 days before administration: Total gastrectomy was performed for gastrointestinal stromal tumor (GIST) of the stomach. 79 days before administration: Afterwards, CT showed an intra-abdominal recurrence during follow-up. As the patient refused inpatient hospital care, 20 mg of doxorubicin hydrochloride (every 2 weeks, total of 13 times) was administered as outpatient treatment. However, tumor size increased afterwards and since liver metastases were also observed, 20 mg of docetaxel hydrate (every 2 weeks, total of 3 times) was administered. Afterwards, since the patient agreed to hospitalization, CYVADIC therapy (1.5 mg/m^2 of vincristine sulfate, 50 mg/m^2 of pirarubicin hydrochloride, 250 mg/m^2 of dacarbazine, and 500 mg/m^2 of cyclophosphamide) was conducted. 36 days before administration: Second course of CYVADIC therapy was conducted. On day 1 of administration: KIT was (+). Administration of 400 mg of this drug was started after gaining the consent of the patient and family members. On day 22 of administration (day of discontinuation): Abdominal pain developed, and administration of this drug was discontinued. (CT was performed → CT performed on day 14 of administration showed smaller tumor size than that of shown on 8 days before administration of this drug, but the CT performed on day 22 of administration showed much smaller tumor size.) 2 days after discontinuation: The patient fell into state of shock, with blood pressure in 60 mmHg range, vasopressor (dopamine hydrochloride) was used. CT showed ascites in upper abdominal area. Paracentesis for ascites was performed, but ascites were serous and incubation was also negative. 5 days after discontinuation: Platelet count was decreased to $1.8\times10^4/mm^3$. Platelet transfusion 20E × 2 was conducted. The patient was examined at the department of haematology. Aspiration bone marrow → marked hypoplasia of megakaryocytes. 12 days after discontinuation: Afterwards, platelet count was returned to normal range. 22 days after discontinuation: CT showed retained materials in abdominal cavity. Drainage was performed. 122 days after discontinuation: The patient died. (cause of death: recurrence of GIST)	Company report

				Finding of ascites: Cancer cells, bacteria were both negative. Reason for falling into state of shock: it was considered as resulting from rupture of tumor. Treatment for peritonitis: drainage, cefozopran hydrochloride	
	Concomitant medications: dacarbazine, vincristine sulfate, pirarubicin hydrochloride, cyclophosphamide, enalapril maleate, benidipine hydrochloride, camostat mesilate, mosapride citrate, bethanechol chloride, magnesium chloride, juzentaihoto, prednisolone, morphine hydrochloride				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 50s	Rectal stromal tumor (none)	400 mg 125 days ↓ (cessation of drug for 57 days) ↓ 400 mg continued	**Intestinal perforation, necrotising fasciitis** 26 days before administration: The patient was examined at Hospital A due to pains in anus and buttocks and pyrexia. Mass was palpated in rectal examination. 15 days before administration: The patient was refered to Hospital B and was hospitalized. On day 1 of administration: Administration of 400 mg of this drug was started. On day 125 of administration (day of discontinuation): Pain in buttocks developed. Administration of this drug was discontinued. 1 day after discontinuation: Pain and redness in buttocks were confirmed. There were swelling of scrotum and pyrexia of 38°C and higher. The patient was diagnosed with rectal stromal tumor perforation and Fournier's gangrene based on the result of CT. Incisional drainage of buttocks under caudal anesthesia was performed. 2 days after discontinuation: Pus accompanying foul odor was discharged through drain, cleaning drainage was continued. The patient had pyrexia of 38°C and higher, and was diagnosed with sepsis and serious infectious disease. 3 days after discontinuation: As blood pressure decreased and consciousness disturbed developed, the patient was diagnosed with septic shock. 6 days after discontinuation: Debridement of the scrotum was added. IVH catheter was inserted. 7 days after discontinuation: Infection on abdominal wall of lower abdominal region spread, incisional drainage was performed. 8 days after discontinuation: Scope of general abscess (gas gangrene) was confirmed through CT. 10 days after discontinuation: Debridement of buttocks to scrotum was added. 11 days after discontinuation: Incisional drainage of the right inguinal region was performed.	Company report

				15 days after discontinuation: Consciousness was lucid (analgesic drugs, etc. was discontinued). 23 days after discontinuation: Pyrexia dropped to 36°C to 37°C. The patient started eating after making sure that there is no communication with rectum in contrast of perforation site. 35 days after discontinuation: Closure of perforated area of rectal stromal tumor was confirmed through large intestine endoscopy and enema. 36 days after discontinuation: Drain in buttocks removed. 49 days after discontinuation: All of drains in abdominal wall and scrotum were removed. 51 days after discontinuation: Rectal stromal tumor and no abscess were confirmed through CT. 57 days after discontinuation (on day 1 of readministration): Administration of 400 mg of this drug was restarted. On day 3 of readministration: The treatment of wound for genital area improved, and it was for the patient to be treated as an outpatient , the patient was discharged from the hospital.	
	Concomitant medications: diclofenac sodium, famotidine, metoclopramide, furosemide				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 40s	Chronic myeloid leukaemia /chronic phase (none)	400 mg 302 days	**Pulmonary fibrosis** 43 days before administration: The patient was diagnosed with chronic myeloid leukaemia. On day 1 of administration: Administration of 400 mg of this drug was started. On day 81 of administration: Skin eruption (minor) developed. On day 262 of administration: Cough was developed around this time. On day 274 of administration: The patient visited the hospital and received consultation.Chest X-ray showed no abnormalities. On day 302 of administration (day of discontinuation): The patient visited the hospital and received consultation. Shortness of breath on exertion was observed. Reductions to SpO_2, %VC, and $FEV_{1.0\%}$ were decreased to 95%, 70.9%, and 45.0%, respectively. Although chest CT showed pleural thickening of apical portion of right lung, there were no other major abnormalities. Administration of this drug was discontinued. The patient was prescribed 45 mg of dextromethorphan hydrobromide. 7 days after discontinuation: The patient visited the hospital and received consultation. No improvements were confirmed with SpO_2 of 94% to 96%. 9 days after discontinuation: The patient was hospitalized. Administration of bronchodilator and steroid inhalation was started. 13 days after discontinuation: No improvement in respiratory function was confirmed in respiratory function test, and bronchodilator was considered as being ineffective. 22 days after discontinuation: Thoracoscopic lung biopsy was performed. Fibrosis under pleura was confirmed. Oral administration of steroid (60 mg of prednisolone) was started. 37 days after discontinuation: The symptoms improved. 121 days after discontinuation: Although subjective symptoms improved, SpO_2 was around 95%. Prednisolone was reduced to 15 mg.	Company report
	Concomitant medications: rebamipide				

Clinical Laboratory Values

	On day 15 of administration	On day 246 of administration	Day of discontinuation	7 days after discontinuation	13 days after discontinuation	43 days after discontinuation
RBC ($\times 10^4/mm^3$)	—	393	394	414	—	—
Haemoglobin (g/dL)	—	10.4	10.7	11.2	—	—
Haematocrit (%)	—	32.5	33.1	34.5	—	—
WBC ($/mm^3$)	—	7080	2950	3070	—	—
Neutrophils (%)	—	77.9	53.9	47.4	—	—
Lymphocytes (%)	—	11.6	32.7	35.6	—	—
PLT ($\times 10^4/mm^3$)	—	20.3	18.9	20.5	—	—
Arterial blood O_2 partial pressure (Torr)			66.6		68.2	76.2
Arterial blood CO_2 partial pressure (Torr)	—	—	46.8	—	46.2	46.7
SpO_2 (%)	97	—	95	—	94	95.5
%VC (%)	—	—	70.9	—	65.3	—
$FEV_{1.0\%}$ (%)			45.08		42.07	

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
SpO_2: Percutaneous Oxygen Saturation
VC: Vital Capacity
FEV: Forced Expiratory Volume

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Female 60s	Chronic myeloid leukaemia /chronic phase (diabetes mellitus)	400 mg 19 days ↓ 300 mg 7 days	**Ileus paralytic, platelets decreased, and white blood cell decreased** Approx. 4.5 years before administration: The patient was diagnosed with chronic myeloid leukaemia (chronic phase). Treatment with daunorubicin hydrochloride, hydroxycarbamide, and interferon alfa-2b (Genetical recombination) was conducted for approximately 1 year. On day 1 of administration: Administration of 400 mg of this drug was started. On day 20 of administration: Platelets decreased and white blood cell decreased developed. Dosage of this drug was reduced to 300 mg. On day 26 of administration (day of discontinuation): Administration of this drug was discontinued. 5 days after discontinuation: Queasy, vomiting, and abdominal pain were developed, and the patient was diagnosed with ileus. 6 days after discontinuation: The patient was managed under fasting and fluid replacement. Bowel sound had decreased at the hospitalization. Niveau was confirmed in X-ray. Intestinal tract (both small intestine and large intestine) was dilated. No clear obstruction site was confirmed in CT, and ileus paralytic was considered. Gastric tube was inserted. Platelet count was $2.4 \times 10^4/mm^3$ at the time of hospitalization.	Company report

				7 days after discontinuation: There was tendency towards alleviation of queasy and abdominal pain. Platelet count was decreased to $1.4 \times 10^4/mm^3$. Platelet transfusion was started (total of 13 times, 130 units; platelet transfusion performed) 9 days after discontinuation: Gastric tube was removed. There was discharge of gas. 10 days after discontinuation: The patient started eating meals (soft cooked rice). No particular changes were observed in symptoms. 18 days after discontinuation: The patient was recovered from ileus. Platelet count was $2.7 \times 10^4/mm^3$.	
	Concomitant medications: cimetidine, teprenone, insulin human (Genetical recombination), magnesium oxide, furosemide, ranitidine hydrochloride				

Clinical Laboratory Values

	On day 20 of administration	6 days after discontinuation	7 days after discontinuation	9 days after discontinuation	11 days after discontinuation	14 days after discontinuation	16 days after discontinuation
RBC ($\times 10^4/mm^3$)	—	—	307	299	341	317	340
Haemoglobin (g/dL)	11.3	12.9	9.9	9.7	10.9	10.1	10.8
WBC ($/mm^3$)	3300	10800	5000	3300	3400	3600	4300
PLT ($\times 10^4/mm^3$)	8.1	2.4	1.4	2.4	1.7	2.0	1.1
LDH (IU/L)	—	649	241	226	—	300	—
Blood glucose level (mg/dL)	—	268	214	222	—	—	—

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
LDH: Lactate Dehydrogenase

3 Oseltamivir Phosphate

Brand Name (name of company)	Tamiflu Capsules 75, Tamiflu Dry Syrup 3% (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Antivirals
Indications	Viral infection of influenza A or B

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

[Adverse Reactions (clinically significant adverse reactions)]

Pneumonia: Pneumonia has been reported to occur. If abnormalities are observed, causes (e.g. drug-induced, infectious) should be determined by examinations such as radiography, and appropriate measures should be taken.

Psychoneurological symptoms: Psychoneurological symptoms (e.g. disturbances in consciousness, abnormal behaviour, delirium, hallucination, delusion, convulsions) may occur. If abnormalities are observed, administration should be discontinued. Patients should be carefully monitored and appropriate measures should be taken according to individual symptoms.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 10s	Suspicion of influenza viral infections (none)	150 mg 3 days	**Acute eosinophilic pneumonia** 1 day before administration: Pyrexia developed. The patient took an OTC cold medicine. On day 1 of administration: Pyrexia of 38°C developed. The patient visited an emergency room and was prescribed this drug and loxoprofen sodium. On day 3 of administration (day of discontinuation): The patient was examined at the department of respiratory medicine. He was hospitalized due to pneumonia and respiration failure. Influenza test was performed. The result was negative. Pyrexia developed during the night (39°C). 25 mg of diclofenac sodium was anally inserted. 2 days after discontinuation: Chest CT demonstrate ground-glass opacity in both lung fields. Bronchoalveolar lavage and transbronchial lung biopsy were performed. Bronchoalveolar lavage fluid: White blood cell count was 2230/mm^3, eosinophils was 75% Transbronchial lung biopsy: Infiltration of lymphocytes, macrophage, eosinophil from terminal bronchiole to alveolar duct was noted. Based on the test findings, the patient was diagnosed with acute eosinophilic pneumonia. DLST: Both this drug and loxoprofen sodium were negative. The patient was treated through drip infusion of methylprednisolone sodium succinate at 125 mg during nighttime. 3 days after discontinuation: The patient was treated through drip infusion of methylprednisolone sodium succinate at 125 mg in the morning. 4 days after discontinuation: The patient was treated through drip infusion of methylprednisolone sodium succinate at 125 mg in the morning. 7 days after discontinuation: As improvement in pneumonia was confirmed through findings on blood test and chest X-ray, the patient was discharged from the hospital.	Company report
	Concomitant medications: loxoprofen sodium, diclofenac sodium				

Clinical Laboratory Values

	On day 3 of administration	2 days after discontinuation	7 days after discontinuation
Body temperature (°C)	39.0	37.9	
WBC (/mm^3)	12000	10400	7500
Lymphocytes (%)	5.3	14.1	30.2
Monocytes (%)	6.1	10.9	6.8
Neutrophils (%)	84.7	71.7	62.1

Eosinophils (%)	3.8	3.0	0.1
Basophils (%)	0.1	0.3	0.8
CRP (mg/dL)	3.38	1.97	<0.20

WBC: White Blood Cell CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 70s	Suspicion of influenza viral infections (intervertebral disc herniation)	150 mg 4 days	**Interstitial pneumonia** Medical history: pneumonia (treatment was given from 141 days before administration to 100 days before administration) On day 1 of administration: Pyrexia, chills, and arthralgia developed suddenly. The patient was diagnosed with influenza viral infections (no definite diagnosis). 150 mg of this drug (twice daily), 15 mg of serrapeptase (three times daily), clarithromycin, sodium azulene sulfonate/L-glutamine were prescribed. After examined at this hospital, the patient was orally administered only this drug at the hospital. Pyrexia of 40°C developed 2 hours after administration of this drug (before administration of other drugs). Afterwards, pyrexia of approximately 40°C developed 2 hours after administration of this drug every time. In all instances, pyrexia was alleviated by the administration of 25 mg of a diclofenac sodium suppository. On day 4 of administration (day of discontinuation): Cough and sputum also developed in addition to pyrexia. Respiratory discomfort also developed. Administration of this drug and serrapeptase was discontinued. Administration of clarithromycin and diclofenac sodium suppositories was also discontinued. 1 day after discontinuation: [chest X-ray test] Interstitial shadows, such as diffuse permeability loss of entire lung field, granular to fine granular shadows and pleural effusion on both sides, were confirmed. Significant hypoxemia with SpO_2 83%, blood gases pH 7.466, $PaCO_2$ 31.5 mmHg, and PaO_2 47.3 mmHg was confirmed. The patient was hospitalized. After hospitalization, the patient was diagnosed with drug-induced pneumonia. Administration of minocycline hydrochloride was started. Pyrexia was rapidly alleviated after initiating drip infusion of steroid (200 mg of hydrocortisone sodium succinate for 5 days). SpO_2 recovered gradually as well. DLST: negative for this drug Pyrexia was improved. 3 days after discontinuation: The patient was recovered from pyrexia. Influenza-like symptoms were also improved.	Company report

				5 days after discontinuation: Administration of hydrocortisone sodium succinate, minocycline hydrochloride was completed. 6 days after discontinuation: Oral administration of 20 mg of prednisolone was started. 9 days after discontinuation: [chest X-ray test] Pleural effusion mostly disappeared. Shadows were improved as well. Dosage of prednisolone was reduced to 15 mg. Respiration failure was improved with SpO_2 96% in room air. Interstitial pneumonia was also improved. 10 days after discontinuation: The patient was discharged. 11 days after discontinuation: Dosage of prednisolone was reduced to 10 mg. 15 days after discontinuation: [chest X-ray test] Pleural effusion disappeared. Interstitial shadows nearly fully improved. 16 days after discontinuation: Dosage of prednisolone was reduced to 5 mg. 22 days after discontinuation: Administration of prednisolone was completed. 23 days after discontinuation: [chest X-ray test] Interstitial shadows disappeared. The patient recovered.	
	Concomitant medications: serrapeptase, clarithromycin, sodium azulene sulfonate/L-glutamine				

Clinical Laboratory Values

	On day 1 of administration	1 day after discontinuation	5 days after discontinuation	9 days after discontinuation
Body temperature (°C)	37.8	37.1	36.7	38.6
WBC (/mm^3)	13700	6700	7000	6600
CRP (mg/dL)	22.98	23.48	2.63	0.76
SpO_2 (%) [measurement conditions]	—	83 [room air]	93 [O_2 2Liter/nasal]	96 [room air]

WBC: White Blood Cell
SpO_2: Percutaneous Oxygen Saturation
CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 10s	Influenza viral infections (none)	37.5 mg 1 day ↓ 75 mg 1 day	**Depressed level of consciousness** On day 1 of administration: Pyrexia of 39°C developed in the afternoon. The patient had no cough and little bit of snivel. 75 mg of this drug (twice daily) was prescribed for influenza viral infections. This drug was administrated in the evening. On day 2 of administration (day of discontinuation): The patient was administered this drug in the morning and evening. Pyrexia was alleviated, but the patient felt tired and laid down. The patient started feeling sick, woke up and vomited in sink. Then, state of consciousness worsened immediately. His response was weak when addressed to, consciousness decreased persisted for approximately 3 minutes. Upon confirming with the patient at a later time, the patient stated that he was aware of being addressed to. Consciousness returned suddenly. When the patient went to the toilet he had faecal incontinence. The patient gradually recovered afterwards. Complexion ill was observed when the patient visited the hospital, but consciousness was lucid. There were no neurological abnormalities. The patient was hospitalized for follow-up, as a precautionary measure. Blood test and biochemical test showed no abnormalities. 1 day after discontinuation: There were trends in alleviation of pyrexia through drip infusion. There was no vomiting afterwards, and the patient was discharged from the hospital. 2 days after discontinuation: Symptoms recovered.	Company report
	Concomitant medications: acetaminophen, clemastine fumarate, tulobuterol hydrochloride, carbocisteine				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Female 10s	Influenza A virus infection (none)	150 mg 5 days	**Hallucination NOS** On day 1 of administration: Cough developed in the morning. The patient visited this hospital. Body temperature was 39°C. The patient was diagnosed with influenza A virus infection from nasal cavity sample. Administration of 150 mg of capsule formulation of this drug was started in the evening. On day 2 of administration: Together with a decrease in body temperature (39°C), the patient starting running around and tried to jump from the window. The patient's mother took notice and held the patient down. While in the same kind of state afterwards, the patient uttered strange sounds. On day 3 of administration: The patient was in the same state as the previous day, uttered strange sounds. The patient's mother understood that this was driven by pyrexia. On day 4 of administration: Pyrexia was alleviated (37°C) in the morning, and instances of the previous day did not occur. On day 5 of administration (day of discontinuation): No particular problem was observed at her visit to the hospital. Administration of this drug was discontinued after final administration in the morning. 29 days after discontinuation: The patient visited the hospital due to other disease. No problems were observed at this time as well.	Company report
	Concomitant medications: tiaramide hydrochloride, dihydrocodeine phosphate, dl-methylephedrine hydrochloride, chlorpheniramine maleate				

3

Revision of PRECAUTIONS

(No. 156)

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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 201) (excluding those presented in "1. Important Safety Information" of this Bulletin.), together with reference materials.

<Hypnotics and sedatives, anxiolytics>

1 Tandospirone Citrate

[Brand Name]	Sediel Tablets 5 and 10 (Sumitomo Pharmaceuticals Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Serotonin syndrome:** Serotonin syndrome of which main symptoms are excitement, myoclonus, sweating, tremor, fever etc. may occur. If abnormalities are observed, this drug should be discontinued and appropriate measures with whole body control such as hydration etc. should be taken.
<Reference Information>	Company report

<Psychotropics>

2 Clomipramine Hydrochloride (oral dosage form)
Imipramine Hydrochloride

[Brand Name]	Anafranil Tablets 10 mg and 25 mg (Nihon Ciba-Geigy K.K.) Tofranil Tablets 10 mg and 25 mg (Nihon Ciba-Geigy K.K.), and others
[Contraindications]	Patients with QT prolongation syndrome
[Important Precautions]	Caution should be exercised as there is a risk of suicide attempt in patients with depression. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
[Adverse Reactions (clinically significant adverse reactions)]	**Serotonin syndrome:** Serotonin syndrome of which main symptoms are anxiety, feeling irritated, delirium, excitement, pyrexia, sweaty, tachycardia, tremor, myoclonus, hyperreflexia, diarrhoea, etc. may occur. If abnormalities are observed, this drug should be discontinued and appropriate measures with whole body control such as hydration etc. should be taken.
<Reference Information>	Company report

3 <Psychotropics> Clomipramine Hydrochloride (injectable dosage form)

[Brand Name]	Anafranil Injection (Nihon Ciba-Geigy K.K.)
[Contraindications]	Patients with QT prolongation syndrome
[Adverse Reactions (clinically significant adverse reactions)]	**Serotonin syndrome:** Serotonin syndrome of which main symptoms are anxiety, feeling irritated, delirium, excitement, pyrexia, sweaty, tachycardia, tremor, myoclonus, hyperreflexia, diarrhoea, etc. may occur. If abnormalities are observed, this drug should be discontinued and appropriate measures with whole body control such as hydration etc. should be taken.
<Reference Information>	Company report

4 <Psychotropics> Milnacipran Hydrochloride

[Brand Name]	Toledomin Tablets 15 and 25 (Asahi Kasei Pharma Corporation)
[PRECAUTIONS of Indications]	Prescribers must balance the risk and benefit in using this drug in patients under age of 18 (Refer to "Use in children").
[Use in Children]	Tests to verify the efficacy and safety of this drug in children have not been conducted. It has been reported that in placebo-controlled clinical trials of paroxetine hydrochloridein in patients aged 7 to 18 with Major Depressive Disorder (MDD) (classified by DSM-IV) conducted overseas,could not confirm the efficacy of the drug, and revealed a greater risk of suicidal ideation or attempts compared with the placebo group. When this drug is administrated in patients with a MMD under age of 18, patients should be carefully monitored since the beginning of the treatment. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation is observed, treatment should be carefully discontinued by tapering-off, etc.
<Reference Information>	Company report

5 <Psychotropics> Fluvoxamine Maleate

[Brand Name]	Depromel Tablets 25 and 50 (Meiji Seika Kaisha, Ltd.) Luvox Tablets 25 and 50 (Solvay Seiyaku K.K.)
[PRECAUTIONS of Indications]	Prescribers must balance the risk and benefit in using this drug in patients under age of 18 (Refer to "Use in children").

[Use in Children]	Safety of this drug in low birth weight babies, neonates, sucklings, infants, or children has not been established. (No clinical experiences in low birth weight babies, neonates, sucklings, or infants, and insufficient clinical experiences in children.) Tests to verify the efficacy and safety of this drug in children have not been conducted. It has been reported that in placebo-controlled clinical trials of paroxetine hydrochloridein in patients aged 7 to 18 with MDD (classified by DSM-IV) conducted overseas,could not confirm the efficacy of the drug, and revealed a greater risk of suicidal ideation or attempts compared with the placebo group. When this drug is administrated in patients with a MMD under age of 18, patients should be carefully monitored since the beginning of the treatment. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation is observed, treatment should be carefully discontinued by tapering-off, etc. (Refer to "Important Precautions") As there have been reports that hyporexia and weight decreased/increased were observed when SSRI were administered in children with obsessive-compulsive disorder, children should be monitored height and weight when administering this drug over a long term.
<Reference Information>	Company report

<Central nervous system agents-Miscellaneous>

6 Donepezil Hydrochloride

[Brand Name]	Aricept Tablets 3 mg and 5 mg, Aricept Fine Granules 0.5% (Eisai Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Syncope, bradycardia, heart block, myocardial infarction, and cardiac failure:** Syncope, bradycardia, heart block (sinoatrial block or atrioventricular block), myocardial infarction, or cardiac failure may occur. In such symptoms are observed, appropriate measures, such as discontinuation of the m, should be taken. **Acute renal failure:** Acute renal failure may occur. In the event of abnormal findings, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report
