Pharmaceuticals and Medical Devices Safety Information

No. 210 February 2005

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

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

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Pharmaceuticals and Medical Devices Safety Information

No. 210 February 2005

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

[Outline of Information]

D: Distribution of Dear Dr. Letters *P*: Revision of PRECAUTIONS *C*: Case Reports

1

Interstitial pneumonia due to leflunomide

Active ingredient Brand name (name of company)	Active ingredient	Brand name
	Leflunomide	Arava Tablets 10 mg, 20 mg, and 100 mg (Aventis Pharma Limited)
Therapeutic Category	Miscellaneous metabolism agents	
Indications	Rheumatoid arthritis	

(1) Introduction

Leflunomide is an antirheumatic drug approved in April 2003. The following terms have been set as conditions for the drug's approval based on information from Japanese clinical trials and overseas usage conditions.

① For a certain period after marketing of the drug, all cases administered this drug should be registered for review, and in addition to investigating the drug's safety and efficacy, the accumulated results should be periodically reported.

② A large-scale post-marketing surveillance should be conducted to sufficiently review the drug's safety, as well as a more focused inspection of the drug's long term safety and the onset of liver disorder, infectious disease, and bone marrow depression, etc.

In September of the same year following the marketing of this drug, adverse reactions of interstitial pneumonia including death cases were reported. Therefore, revisions to PRECAUTIONS were made on January 30, 2004 and awareness regarding interstitial pneumonia etc. was promoted. Main revisions made included the following:

1) [Warning]

- In starting treatment with this drug, the suitability of administering this drug should be carefully determined by confirming through chest X-ray, etc. for the presence/absence of lung disorders such as interstitial pneumonia or pulmonary fibrosis, complicated pneumonia due to opportunistic infection, or any medical history.
- In administering this drug, patients should be sufficiently advised of the possibility of adverse reactions. Patients should be instructed to discontinue administration and inform their physicians promptly if they develop such symptoms.

2) [Careful Administration]

- Patients with lung disorders such as interstitial pneumonia or pulmonary fibrosis, pneumonia resulting from opportunistic infection, or a medical history of these diseases.

3) [Important Precautions]

- Administration of this drug should only be commenced after confirming the presence/absence of lung disorders such as interstitial pneumonia or pulmonary fibrosis, complication by pneumonia resulting from opportunistic infection, and a medical history of these diseases. During administration, extra caution should be exercised to the onset of clinical symptoms of pyrexia, cough, and dyspnoea, as well as to test results of KL-6 and CRP, etc. If abnormalities are observed, chest X-rays or other examinations should promptly be conducted. Administration should be discontinued and appropriate measures, such as administration of an adrenocortical hormone preparation, should be taken. Moreover, it is desirable that drug elimination is implemented.

Even after revisions were made to PRECAUTIONS, while the number of reported interstitial pneumonia cases declined, reports of such cases continued. As 58 cases of adverse reactions report relating to interstitial pneumonia were accumulated by the end of November 2004, an assessment and investigation of these cases were recently conducted by respiratory and rheumatoid arthritis experts from Pharmaceuticals and Medical Devices Agency. The results of this assessment are presented hereafter.

(2) Status of post-marketing surveillance

A post-marketing surveillance was conducted on the basis of approval conditions for this drug aimed to registering 3000 cases scheduled for investigation (all-patient survey). As interstitial pneumonia including cases resulting in death were reported, directions to make revisions to the PRECAUTIONS were given on January 30, 2004 and promotion of awareness regarding interstitial pneumonia was carried out. In response to it, a part of the protocol for the all-patient survey was amended, interstitial pneumonia etc. was added as an important investigative item, and 2400 cases were added to the scheduled number of cases to be investigated, amounting to a total 5400 cases. The all-patient survey has been continuing as of January 2005.

(3) Leflunomide-related interstitial pneumonia

1) Characteristics

Radiographic images of leflunomide-related interstitial pneumonia present shadows spreading preponderantly over the upper to all lung fields and middle lung field. This is different from the dispersion commonly observed in interstitial pneumonia accompanying rheumatoid arthritis which is focused at the lower lung field, back of the lung, and margin of the lung field. Distribution according to lobular units can also be observed.

In early and mild cases, there is ground-glass opacity which becomes infiltrative shadows (consolidation) after the disease progresses. They may also be accompanied by pleural effusion.

If the disease becomes less severe, the condition will return to normal and fibrosis will not left behind.

2) Number of reported adverse reactions cases (added up on day 1 of administration)

Period	Number of reported adverse reaction cases	Number of patients starting administration **
August 2003*–January 2004	49 cases	Approx. 3650 patients
February 2004–November 2004	9 cases	Approx. 1400 patients

Note) *: Month the provision of investigational drug was started **: Number of registered cases in the all-patient survey

(4) Case evaluation by experts

Among cases for which radiographic images (X-ray and CT, etc.) could be obtained, diagnosis of interstitial pneumonia and causality with leflunomide was assessed based on those images and adverse reaction reports. For all other cases, assessment was conducted based on the entry content of adverse reaction reports.

Of the 58 cases reported as cases of interstitial pneumonia, 42 cases (27/40 with images; 15/18 without images) were diagnosed as interstitial pneumonia, and causality with leflunomide could not be denied (hereafter, interstitial pneumonia cases) for 41 cases of interstitial pneumonia (26 cases with images; 15 cases without images).

Of the 41 interstitial pneumonia cases, there were 23 cases (56%) with a medical history of interstitial pneumonia, etc.

In addition, of the 41 interstitial pneumonia cases, 30 cases were treated with Questran for drug elimination. Of these, there were 10 cases of death (mortality rate: 33.3%). On the other hand, of the 11 cases which did not undergo drug elimination, there were 6 cases of death (mortality rate: 55%).

In addition, there were 10 cases with a smoking history (of whom 5 cases died).

(5) Responses after onset of interstitial pneumonia based on expert assessment

If the first symptoms of interstitial pneumonia such as cough, dyspnoea, and pyrexia occur, the patient should promptly receive an X-ray examination (CT if possible), oxygen saturation test, and blood gas test,

etc.

Among the adverse reactions reported as interstitial pneumonia, there are also those which are strongly suggestive of carinii pneumonia when diagnosed based on X-ray images. As the treatment method for this type of pneumonia differs from interstitial pneumonia resulting from leflunomide, it is necessary to conduct differential diagnosis (measurement of ß-D-glucan, etc.).

Moreover, as this drug demonstrates a long elimination half-life in the blood, onsets of interstitial pneumonia have also been reported a few days after discontinuation of administration. If symptoms appear, not only should drug administration be suspended, but drug elimination should be conducted using Questran, etc. to the extent possible.

(6) Closing comments

Currently, Aventis Pharma Limited is conducting an all-patient survey to investigate the onset conditions of interstitial pneumonia in patients without a medical history of lung disorders such as interstitial pneumonia and complications. As this survey is attempting to review the factors influencing the onset of interstitial pneumonia from the administration of this drug, MHLW would like to request your cooperation in the collection of information on the proper use of pharmaceuticals conducted by pharmaceuticals companies in accordance with article 77-3-2 of the Pharmaceutical Affairs Law.

If you obtain information on adverse reactions relating to interstitial pneumonia associated with the use of this drug, MHLW requests that you make out an adverse reactions report etc. in accordance with article 77-4-2-2 of the Pharmaceutical Affairs Law.

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. 209).

1 Epirubicin Hydrochloride

Brand Name (name of company)	Farmorubicin RTU Inj., Farmorubicin for Injection (Pfizer Japan Inc.)
Therapeutic Category	Antibiotics
Indications	Relief from the following subjective and objective symptoms Acute leukaemia, malignant lymphoma, breast cancer, ovarian cancer, gastric cancer, liver carcinoma, urothelial carcinoma (bladder carcinoma, renal pelvic tumor, ureteral tumor)

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

[Adverse Reactions (clinically significant adverse reactions)]

Bone marrow depression: Pancytopenia, white blood cell decreased, neutropenia, platelets decreased, anemia, bleeding tendency may occur. In addition, life-threatening infectious disease (sepsis) or haemorrhage of digestive tract may occur resulted from severe bone marrow depression. If abnormalities are observed, discontinue administration and take appropriate measures.

Liver and biliary tract disorders: Liver and biliary tract disorders such as intrahepatic biloma, cholangitis, bile duct necrosis, and hepatic necrosis may occur through hepatic artery infusion. Drug distribution area should be carefully confirmed with the contrast medium, etc. If abnormalities are observed, discontinue administration and take appropriate measures.

Gastric ulcer, duodenal ulcer: Gastric ulcer and duodenal ulcer may occur through hepatic artery infusion. Patients should be carefully monitored and if abnormalities are observed, take appropriate measures.

<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 70s	Intrahepatic bile duct carcinoma (none)	72 mg 3 days	**Sepsis** Approx. 5 months before administration: The patient was examined at his previous hospital for abdominal pain. Upon close examination, the patient was diagnosed with intrahepatic bile duct carcinoma and metastases to the lymph nodes. Approx. 4 months before administration: The patient was examined at the department of general internal medicine (liver, gall bladder, pancreas). Approx. 3 months before administration: The patient was hospitalized. The first course of chemotherapy (this drug, cisplatin, fluorouracil: hereafter, CEF therapy) was started. Grade 3 neutropenia occurred. Approx. 2 months before administration: The second course of CEF therapy was started. Grade 3 neutropenia occurred. On day 1 of administration: The third course of CEF therapy was started. 8 days after discontinuation: Pyrexia of 39°C developed. 9 days after discontinuation: Pyrexia of 40°C accompanied by chills and shivering developed. Although definite source of infection was unknown, considering sepsis, administration of antibiotics was started (cefminox sodium). 10 days after discontinuation: Pyrexia of 39°C persisted. The patient was diagnosed with disseminated intravascular coagulation and administration of gabexate mesilate was started. The antibiotic was replaced by imipenem/cilastatin sodium and freeze-dried sulfonated human normal immunoglobulin was used for 3 days. Filgrastim (Genetical recombination) was started. Concentrated human platelets were transfused. 14 days after discontinuation: Consciousness disturbed developed. Later, renal failure was aggravated. 18 days after discontinuation: Renal failure was aggravated and the patient died.	Company report
	Concomitant medications: cisplatin, fluorouracil, morphine sulfate, famotidine, metoclopramide, digestant				

Clinical Laboratory Values

	On day 1 of administration	8 days after discontinuation	9 days after discontinuation	10 days after discontinuation	11 days after discontinuation	14 days after discontinuation	16 days after discontinuation
WBC (/mm^3)	15100	5500	1800	2000	1200	18200	29100
Neutrophils (%)	87.0	80.0	83.3	85.0	75.0	77.0	62.0
RBC ($\times 10^4$/mm^3)	237	176	—	248	—	258	227
Haemoglobin (g/dL)	8.2	5.8	—	8.1	—	8.4	7.3
PLT ($\times 10^4$/mm^3)	21.1	6.5	4.0	2.1	4.5	3.1	2.1
BUN (mg/dL)	28	39		50		69	111
Creatinine (mg/dL)	0.9	1.0	—	1.2	—	2.7	3.6
CRP (mg/dL)	2.4	2.3	—	8.5	—	25.2	13.4

WBC: White Blood Cell BUN: Blood Urea Nitrogen PLT: Platelet
RBC: Red 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	Bladder cancer (none)	50 mg 1 day	**Hemorrhage of digestive tract** 1 day before administration: Administration of methotrexate was conducted. On day 1 of administration: Administration of this drug, vincristine sulfate, and cisplatin was conducted. 2 days after discontinuation: Generalized pain developed. 6 days after discontinuation: Urine volume decreased and ileus-like symptoms developed. 7 days after discontinuation: As general condition improved, infusion and tetracosactrin zinc phosphate (5 days) was administered. Although there were signs of recovery, pyrexia and watery diarrhoea developed. 10 days after discontinuation: Parotid swelling of the left ear developed. 11 days after discontinuation: Fresh frozen human plasma was transfused for 2 days. 13 days after discontinuation: Cefazolin sodium hydrate was administered for 7 days to treat acute parotitis. The swelling subsided and pyrexia tended to alleviate. 14 days after discontinuation: There was melaena and reoccurrence of pyrexia. Ileus improved. 16 days after discontinuation: Renal function disorder improved. 17 days after discontinuation: Concentrated human red blood cells were transfused for 2 days to treat anaemia. 19 days after discontinuation: The patient experienced a relatively large amount of melaena during the night, as well as mild consciousness disturbed before and after melaena. 20 days after discontinuation: The patient fell into shock symptom due to a large amount of haemorrhage of digestive tract. Although transfusion of fresh frozen human plasma, concentrated human red blood cells, whole human blood, and concentrated human platelets was performed, haemostasis was not achieved. 23 days after discontinuation: The patient died.	Company report
	Concomitant medications: methotrexate, vincristine sulfate, cisplatin				

Clinical Laboratory Values

	1 day before administration	6 days after discontinuation	7 days after discontinuation	16 days after discontinuation	18 days after discontinuation	20 days after discontinuation
WBC (/mm^3)	6700	2600	700	9500	12200	20100
Neutrophils (%)	59.0	46.9	9.2	72.1		
Eosinophils (%)	3.7	1.6	4.6	0.4	—	—
Basophils (%)	0.6	0.4	6.2	0.4	—	—
Lymphocytes (%)	30.4	44.1	72.3	21.5	—	—
Monocytes (%)	6.3	7.0	7.7	5.6		

RBC ($\times 10^4/mm^3$)	347	355	318	274	305	161
Haemoglobin (g/dL)	11.0	11.3	10.3	8.6	9.8	4.9
PLT ($\times 10^4/mm^3$)	22.6	5.8	4.0	5.1	9.9	8.0

WBC: White Blood Cell PLT: Platelet
RBC: Red Blood Cell

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex /Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female 70s	Hepatocellular carcinoma (none)	20 mg 1 day	**Intrahepatic biloma** Approx. 6 years before administration: The patient was receiving out-patient treatment for hepatitis C virus-associated cirrhosis. Approx. 1 year before administration: As 2 cm tumor lesion was found on the lateral segment of the left hepatic lobe, the patient was diagnosed with hepatocellular carcinoma (HCC). Approx. 10 months before administration: Iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil were infused by TAE from the left hepatic artery. As the effect of TAE was insufficient, percutaneous ethanol injection therapy (PEIT) was conducted 4 times after TAE. Approx. 1 month before administration: The patient was hospitalized due to local recurrence of HCC found on the lateral segment of the hepatic lobe. On day 1 of administration: Although angiography for tumor stain of the lateral segment was unclear, 20 mg of this drug and 4 ml of iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil were infused from the left hepatic artery, followed by TAE using gelatin. 9 days after discontinuation: Pyrexia persisted and did not improve with antibiotics. 27 days after discontinuation: Development of a 10 cm diameter cystic lesion extending from the lateral segment of the left hepatic lobe to the left subdiaphragm was confirmed by CT. As post-TAE biloma was suspected, the cyst was punctured with echocardiographic guidance on the same day, initial yellowish bile, followed by turbid grayish-white pus was collected. As biloma abscess was suspected, percutaneous drainage was performed. Angiography was conducted again at the indwelling drainage, communication between the cystic cavity and left lateral branch of the bile duct was confirmed. Thus, the patient was diagnosed with biloma. Systemic administration of cefozopran hydrochloride at 2 g was continued, and 40 mg of gentamycin sulfate was injected 2 times from the drainage tube. Although disappearance of inflammatory reaction and reduction of biloma were confirmed, emission of bile persisted.	Company report

				Approx. 3 months after discontinuation: After injection of 6 ml of fibrin adhesive, disappearance of bile emission was confirmed. Drainage tube was removed. Approx. 4 months after discontinuation: The patient was discharged from the hospital.	
	Concomitant medications: gelatin, iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Male 70s	Primary hepatocellular carcinoma (hepatic cirrhosis, varices oesophageal)	50 mg unknown	**Duodenal ulcer** Approx. 4 years before administration: TAE therapy was conducted 6 times toward HCV positive carcinoma hepatocellular (child category: A). 5 days before administration: No particular pathological lesion was confirmed by endoscopy of the descending portion of the duodenum. Unknown: Before performing TAE, H_2 receptor antagonist was administered for prevention of ulcer formation. The seventh TAE was performed through the arterial plexus of bile duct (50 mg this drug, 3 ml of iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil). Black stools were evacuated after TAE. 7 days after administration: Hemorrhagic massive ulceration over approximately half the circumference of the descending duodenum was confirmed by endoscopy. 1 month after administration: Endoscopic image revealed H_2 stage ulcer. 2 months after administration: Cicatrization of ulcer was confirmed by endoscopic image of the same region.	Company report
	Concomitant medications: iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil				

2 Freeze-dried Sulfonated Human Normal Immunoglobulin, pH4 Treated Acidic Human Normal Immunoglobulin, Polyethylene Glycol Treated Human Normal Immunoglobulin, Freeze-dried Polyethylene Glycol Treated Human Normal Immunoglobulin

Brand Name (name of company)	Kenketsu Venilon-I, Venilon (The Chemo-Sero-Therapeutic Research Institute) Polyglobin-N (Bayer Yakuhin, Ltd.) Kenketsu Venoglobulin-IH YOSHITOMI, Venoglobulin-IH (Benesis Corporation) Kenketu Glovenin-I-NICHIYAKU (Nihon Pharmaceutical Co., Ltd.)
Therapeutic Category	Human blood preparations
Indications	● Hypogammaglobulinaemia or agammaglobulinaemia ● Concomitant use with antibiotics to treat serious infectious diseases ● Idiopathic thrombocytopenic purpura (when other drugs are ineffective and there is marked haemorrhagic tendency, and surgical measures or temporary haemostatic management such as during delivery is required)

	● Acute phase of Kawasaki's disease (when condition is serious and there is risk of coronary artery disorders) ● Guillain Barre syndrome (serious cases with walking difficulty in the acute exacerbation phase) (Kenketsu Venilon-I only) ● For the improvement of muscular weakness (Kenketu Glovenin-I-NICHIYAKU only) from chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)

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

[Adverse Reactions (clinically significant adverse reactions)]

Thromboembolism: Symptoms of thromboembolism such as cerebral infarction, myocardial infarction, pulmonary embolism, and deep vein thrombosis may occur due to increase in blood viscosity etc. in cases given high dosages. Patients should be carefully monitored and if central nervous system symptoms (dizziness, consciousness disturbed, quadriplegia, etc.), chest pain, sudden dyspnoea, shortness of breath, lower limb pain or edema, etc. are observed, discontinue administration and take appropriate measures. For patients at high risk for thromboembolism, the dosage should be suitably reduced. It is desirable that the drug be administered as slowly as possible.

Cardiac failure: Onset or aggravation of cardiac failure may be induced from excessive circulation of plasma volume mainly in patients with Kawasaki's disease given high dosages. Patients should be carefully monitored. If symptoms of dyspnoea, cardiac murmur, cardiac function failed, oedema, urine output decreased, etc. are confirmed, discontinue administration and take appropriate measures. For patients with reduced cardiac function, the dosage should be suitably reduced. It is desirable that drug be administered as slowly as possible.

<Reference Information> Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse drug reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 20s	Guillain Barre syndrome (none)	24 g 5 days	**Deep vein thrombosis leg** On day 1 of administration: Administration of this drug was started to treat Guillain Barre syndrome for 5 days. 3 days after discontinuation: As pain developed in lower limbs and thrombus near the popliteal regions of limbs was confirmed by echogram, the patient was treated with elastic stockings, heparin calcium, heparin sodium, and warfarin potassium. 8 days after discontinuation: The second administration of this drug was started. Although transaminases increased was confirmed, it was improved during follow up. 12 days after discontinuation: The second administration of this drug was completed. 28 days after discontinuation: Pyrexia, cloudy urine, and lower abdominal discomfort developed and the urinary balloon was removed. The symptoms were promptly resolved with cefotiam hydrochloride and levofloxacin. 55 days after discontinuation: The patient was recovered from deep vein thrombosis leg.	Company report
	Concomitant medications: methylprednisolone sodium succinate, cefotiam hydrochloride				

No.	Patient		Daily dose/ Treatment duration	Adverse drug reactions	Remarks
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female under age of 10	Kawasaki's disease (none)	13.5 g 2 days	**Cardiac failure** On day 1 of administration: This drug was administered. On day 2 of administration (day of discontinuation): This drug was administered. After discontinuation of this drug, oedema, oliguria (less than 100 ml/day), and hepatomegaly (three-finger-breadth below the right hypochondrium on palpation) developed. Cardiomegaly was confirmed by X-ray. Systolic murmurs were heard. Moderate MR and moderate TR were confirmed by echocardiogram. Poor ventricular systolic function (FS 20%) was observed. Diuretic and cardiotonic were administered. ACE inhibitor was also administered. 6 days after discontinuation: Cardiac failure improved.	Company report
	Concomitant medications: flurbiprofen				

3 Telithromycin

Brand Name (name of company)	Ketek Tablets 300 mg (Aventis Pharma Limited)
Therapeutic Category	Acting mainly on gram-positive bacteria and mycoplasma
Indications	<Susceptible strains> Bacterial strains susceptible to this drug include *staphylococcus*, *streptococcus*, *pneumococcus*, *moraxella* (*branhamella*) *catarrhalis*, *haemophilus influenza*, *legionella*, *peptostreptococcus*, *prevotella*, *chlamydia pneumoniae*, and *mycoplasma pneumoniae* <Indications> Laryngopharyngitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory lesion, sinusitis, periodontitis, pericoronitis, jaw inflammation

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

[Important Precautions] Loss of consciousness, accommodation disorder, vision blurred, etc. may occur. Patients <u>should be prevented from operating</u> machines with hazardous activities such as driving a car. <u>Prior to treatment, patients etc. should be fully informed of these adverse reactions. Patients should be instructed to immediately discontinue administration and inform their physicians if they develop such symptoms.</u>

<Reference Information> Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse drug reactions	Remarks
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 50s	Laryngopharyngitis (none)	600 mg 2 days	**Loss of consciousness** 4 days before administration: The patient was first examined for cough, sputum, pharyngeal pain. As she was diagnosed with pharyngitis, cefteram pivoxil, antitussive, antihistamine/antipyretic was administered. On day 1 of administration: Although the medicine was taken for 4 days, the patient complained that cough and sputum did not improve. Administration of cefteram pivoxil, antitussive, antihistamine/antipyretic was discontinued, and medication was replaced by this drug. On that day, 600 mg of this drug was taken. At that time, there was nothing wrong with the patient. On day 2 of administration (day of discontinuation): After taking this drug (probably taken after breakfast), at around noon (approx. 4 to 5 hours after administration), the patient lost consciousness while driving near a river embankment. The car fell into the river at a curve in the road and the patient regained consciousness. As the river was small and water level was low, this did not lead to a major accident or drowning. The patient did not suffer any sequelae such as cervical vertebra injury or bruising. Afterward, administration of this drug was discontinued. The patient told that loss of consciousness was sudden with no precursory symptoms. Electrocardiogram and head CT had not been performed. Although the patient underwent head CT 7 years before, there were no particular abnormalities. A physical examination conducted in September last year revealed no particular abnormalities other than protein urine caused by urinary tract infection.	Company report
	Concomitant medications: cefteram pivoxil, antitussive/antihistamine/antipyretic				

4 Prednisolone (oral dosage form)

Brand Name (name of company)	"Junsei" Prednisolone Tablets (Junsei Chemical Co., Ltd.)etc.
Therapeutic Category	Adrenal hormone preparations
Indications	○ Chronic adrenocortical insufficiency (primary, secondary, pituitary, iatrogenic), acute adrenocortical insufficiency (adrenal crisis), adrenogenital syndrome, subacute thyroiditis, thyrotoxicosis [thyrotoxic (toxic) crisis], malignant exophthalmos accompanying thyroid disease, isolated ACTH deficiency ○ Chronic rheumatoid arthritis, juvenile rheumatoid arthritis (including Still disease), rheumatic fever (including rheumatic carditis), polymyalgia rheumatica ○ Erythematosus (systemic and chronic discoid), systemic vasculitis (including aortitis syndrome, periarteritis nodosa, polyarteritis, Wegener's

	granulomatosis), polymyositis (dermatomyositis), scleroderma ○ Nephrosis and nephrotic syndrome ○ Congestive heart failure ○ Bronchial asthma, asthmatic bronchitis (including infantile asthmatic bronchitis), allergies and poisoning (including drug rash and toxicoderma) caused by drugs and other chemical substances, serum sickness ○ Serious infectious disease (used concomitantly with chemotherapy) ○ Haemolytic anaemia (those suspected of involving the immune system or immune mechanism), leukaemia (including acute leukaemia, chronic myeloid leukaemia transformation, chronic lymphatic leukaemia) (including leukaemia cutis), granulocytopenia (essential and secondary), peliosis (thrombocytopenic and nonthrombocytopenic), aplastic anaemia, haemorrhagic diathesis due to hindrance by coagulation factors ○ Regional enteritis, ulcerative colitis ○ General improvement of serious wasting disease (including terminal cancer and sprue) ○ Hepatitis fulminant (including those deemed clinically serious), cholestatic acute hepatitis, chronic hepatitis (active, acute reactivated, cholestatic) (limited to intractable conditions which do not respond to general treatment and with persisting conspicuous significant liver function abnormality), hepatic cirrhosis (active, with accompanying intractable ascites, or accompanying cholestasia) ○ Sarcoidosis (except for cases limited to bilateral hilar lymphadenopathy), diffuse interstitial pneumonia (pulmonary fibrosis) (including radiation pneumonitis) ○ Pulmonary tuberculosis (limited to miliary tuberculosis and severe tuberculosis) (used concomitantly with antituberculosis drug), tuberculous meningitis (used concomitantly with antituberculosis drug), tuberculous pleuritis (used concomitantly with antituberculosis drug), tuberculous peritonitis (used concomitantly with antituberculosis drug), tuberculous pericarditis (used concomitantly with antituberculosis drug) ○ Encephalomyelitis (including encephalitis and myelitis) (however, this drug should be used for a short period in the case of primary encephalitis when symptoms of increased intracranial pressure are observed and effect from other drugs is insufficient), peripheral neuritis (including Guillain-Barré syndrome), myotonia, myasthenia gravis, multiple sclerosis (including neuromyelitis optica), chorea minor, facial palsy, spinal arachnoiditis ○ Malignant lymphoma (lymphosarcomatosis, reticulosarcomatosis, Hodgkin disease, cutaneous reticulosis, mycosis fungoides) and similar diseases (closely related diseases), eosinophilic granuloma, recurrent and recurrent metastatic breast cancer ○ Idiopathic hypoglycemia ○ Pyrexia of unknown cause ○ Adrenalectomy, organ and tissue transplantation, post invasive pulmonary oedema, surgical invasion for patients with adrenocortical insufficiency ○ Snake and insect venom (including serious insect bites) ○ Ankylosing spondylitis (rheumatoid spondylitis) ○ Prevention of post operative adhesions for salpingoplasty, ovulation disorder due to adrenocortical dysfunction ○ Prostate cancer (if other therapies are ineffective), penile induration ○ * Eczema and dermatitis (acute eczema, subacute eczema, chronic eczema, contact dermatitis, nummular eczema, autosensitization dermatitis, atopic dermatitis, infantile eczema, lichen simplex chronicus Vidal, other neurodermatitis, seborrheic dermatitis, keratodermia tylodes palmaris progressiva, other dermatitis of finger, genital or anal eczema, eczema or dermatitis of the auricle and ear canal, eczema or dermatitis of the nasal vestibule and nose wings, etc.) (however, administration in cases that are not severe should be avoided as much as possible), * prurigo (including strophulus infantum, urticarial lichen, urticaria perstans) (however, administration should be limited to severe cases. Local injection is desirable for urticaria perstans), urticaria (except chronic cases) (limited to severe cases), * psoriasis and similar diseases [psoriasis vulgaris (severe cases), psoriatic arthropathy, psoriatic erythrodermia, pustular psoriasis, acrodermatitis continua, impetigo herpetiformis, Reiter syndrome], * palmoplantar pustulosis (limited to severe

	cases), * pityriasis rubra pilaris (limited to severe cases), * lichen planus (limited to severe cases), scleredema adultorum, erythema (* erythema exsudativum multiforme, erythema nodosum) (however, limited to severe cases in erythema exsudativum multiforme), anaphylactoid purpura (simple, Schönlein, Henoch) (limited to severe cases), Weber-Christian disease, muco-cutaneo-ocular syndrome [ectodermosis erosiva orificialis, Stevens-Johnson syndrome, dermatostomatitis, Fuchs syndrome, Behcet disease (provided there are no ocular symptoms), Lipschutz' acute vulva ulcer], Raynaud disease, * alopecia areata (limited to pernicious forms), pemphigus (pemphigus vulgaris, pemphigus foliaceous, Senear-Usher syndrome, pemphigus vegetans), Duhring herpetiform dermatitis (including pemphigoid, herpes gestationis), epidermolysis bullosa hereditaria, herpes zoster (limited to severe cases), * erythroderma (including pityriasis rubra Hebra), lupus miliaris disseminatus faciei (limited to severe cases), allergic vasculitis and similar diseases (including pityriasis lichenoides et varioliformis acuta), ulcerative chronic pyoderma, sclerema neonatorum ○ Symptomatic therapy for inflammatory diseases of the inner eye, optic nerves, arcula, and eye muscle (uveitis, retinochorioiditis, retinal vasculitis, optic neuritis, inflammatory pseudotumor of orbit, orbital apex syndrome, ophthalmoplegia), when eye drops are unsuitable or insufficient in symptomatic therapy for inflammatory diseases of the outer and anterior region of the eye (blepharitis, conjunctivitis, keratitis, scleritis, iridocyclitis), post-operative inflammation of the opthalmic area ○ Acute and chronic otitis media, exudative otitis media, stenosis of the auditory tube, Ménière disease and Ménière syndrome, acute neuro sensory deafness, vasomotor (nervous) rhinitis, allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, progressive gangrenous rhinitis, laryngitis/laryngeal oedema, oesophagitis (corrosive oesophagitis, after using an directoscope) and post-oesophageal dilation, postoperative aftercare of the ear, nose, and throat region, intractable stomatitis and glossitis (those that do not heal with local treatment) ○ Smell disorder, acute and chronic (recurrent) sialadenitis * The drug should only be administered when it is surmised that the effect of external dosage form is insufficient or when sufficient effect cannot be expected.

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

[Adverse Reactions (clinically significant adverse reactions)]	**Tendon rupture:** Tendon rupture such as the Achilles tendon may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as reduction of dosage 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 50s	Dermatomyositis (pulmonary fibrosis, chronic sinusitis)	10-40 mg approx. 11 years	**Tendon rupture** Medical history: unknown On day 1 of administration: Treatment with 10 to 40 mg of this drug was initiated for dermatomyositis. In the 9th year of administration: After exerting left thumb, extension disorder of the left thumb (tendon rupture of the extensor hallucis longus muscle) developed. But the patient left it alone. Approx. in the 11th year of administration (day of onset): Without any particular cause for onset, extension disorder of the left fifth finger developed and the patient was diagnosed with tendon rupture of the extensor digiti minimi muscle. On day 20 of onset: The patient was hospitalized and tendon transfer of the left thumb and fifth finger were conducted. Weakening of the tendinous tissue was confirmed by pathological examination (even at healthy areas). On day 50 of onset: The patient was discharged from the hospital. On day 70 of onset: The patient's condition was judged as improved at out-patient examination. Administration of this drug was continued. Opinion of the physician in charge: This was a case of long term steroid use with symptoms occurring from slight external force. No other factors such as joint deformity were confirmed. Decrease in fibroblastic cells at the healthy region of the tendon, as well as meandering fibers, suggesting weakening of the tendon were confirmed by the pathological diagnosis. From the above findings, tendon rupture of the finger extensor muscle due to the long term use of steroids was strongly suspected.	Company report
	Concomitant medications: unknown				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	Systemic lupus erythema tosus	Unknown approx. 13 years	**Tendon rupture** Medical history: gastric ulcer On day 1 of administration: Administration of this drug was started for treatment of systemic lupus erythematosus. Approx. in the 13th year of administration (15 days before onset): Treatment with 3 g of salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate and 400 mg of clarithromycin was initiated for upper respiratory inflammation (for 3 days). 12 days before onset: Administration of 300 mg of levofloxacin was started (for 7 days). 8 days before onset: Listlessness of the back of the lower limbs developed. Day of onset: When the patient lost his footing on his hind limb, pain at the back of both lower limbs was aggravated. Bilateral Achilles tendon rupture occurred. On day 3 of onset: The patient received first examination at this department and was hospitalized on the same day. On day 7 of onset: Tenorrhaphy was performed through the Lindholm method. Stricture of the vascular cavity due to intima proliferation within the smallest arteries within the tendon and tendon surroundings was observed in histopathological findings. On day 114 of onset: The patient was discharged from the hospital. Administration of this drug was continued. Opinion of physician in charge: The onset mechanism of this case involved vasculitis within the tendon and tendon surroundings due to systemic lupus erythematosus, hindrance of tendon repair due to steroids, and tendinitis due to levofloxacin. It is surmised that these 3 events coincided to weaken the Achilles tendon resulting in rupture due to slight external force.	Company report
	Concomitant medications: levofloxacin, clarithromycin, salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate				

5 Mizoribine

Brand Name (name of company)	Bredinin Tablets 25 mg and 50 mg (Asahi Kasei Pharma Corporation)
Therapeutic Category	Miscellaneous metabolism agents

Indications	1. Suppression of rejection in renal transplantation 2. Nephrotic syndrome caused by primary glomerular disease (Limited to cases difficult to treat using adrenocortical hormone preparation alone. Also excluding frequently recurring nephrotic syndrome) 3. Lupus nephritis (Limited to cases with persistent proteinuria, nephrotic syndrome, or decreased renal function, which are difficult to treat using adrenocortical hormone preparation alone) 4. Chronic rheumatoid arthritis (Limited to cases of past treatment which did not show sufficient effects through the use of a nonsteroidal anti-inflammatory plus at least one other anti-rheumatism drug)

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

[Adverse Reactions (clinically significant adverse reactions)]

Gastrointestinal ulceration, digestive tract haemorrhage, gastrointestinal perforation: Gastrointestinal ulceration, digestive tract haemorrhage, or gastrointestinal perforation may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures, such as discontinuation of administration, should be taken.

Severe skin disorder: Severe skin disorders such as oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored and if symptoms such as pyrexia, erythema, pruritis, ocular hyperaemia, or oral sores are observed, administration should be discontinued and appropriate measures should be taken.

Pancreatitis: Pancreatitis may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Hyperglycaemia and diabetes mellitus: Hyperglycaemia, diabetes mellitus, and aggravation of diabetes mellitus may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as discontinuation of administration 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 30s	Post kidney transplant, chronic renal failure (none)	125-300 mg 40 days	**Small intestine perforation** On day 1 of administration: Immunosuppressant drug therapy using this drug, ciclosporin, and prednisolone was started. On day 3 of administration: Living kidney transplantation was performed. Postoperative course was good. On day 39 of administration: Urine output decreased, pyrexia, and abdominal pain developed. Emergency laparotomy was performed and the patient was diagnosed with bowel perforation. Fistula of small intestine and artificial anus was established. The patient recovered. On day 40 of administration (day of discontinuation): Administration of this drug was discontinued. Other immunosuppressive drugs were reduced in dosage and continued. General condition gradually improved.	Company report
	Concomitant medications: ciclosporin, prednisolone, prednisolone acetate, methylprednisolone sodium succinate, carbenicillin sodium				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 40s	Nephrotic syndrome, chronic renal failure, IgA nephropathy (hypertension, diabetes mellitus, angina pectoris)	150 mg 48 days	**Oculomucocutaneous syndrome** On day 1 of administration: Administration of this drug at 150 mg was started. On day 40 of administration: Exanthema generalised developed. Pyrexia, pain pharynx, cough and sputum were noted. Drug therapy was conducted due to suspicion of rubella. On day 41 of administration: Rash was also confirmed in the mouth and on the scalp. On day 48 of administration (day of discontinuation): The patient was hospitalized due to aggravation of rash and findings on the marked inflammation of the mouth. Administration of this drug was discontinued. 3 days after discontinuation: The patient was diagnosed with oculomucocutaneous syndrome by a dermatologist. Steroid pulse therapy was started. 9 days after discontinuation: Respiratory status was bad. As blood-oxygen concentration did not improve with high doses of oxygen, the patient was intubated and put on an artificial respirator. 11 days after discontinuation: Marked inflammation and swelling reached to the bronchial mucosa was observed by bronchoscopy and insufficient ventilation was ascertained. 12 days after discontinuation: The patient died. (cause of death: respiratory failure; autopsy: no performed)	Company report
	Concomitant medications: loxoprofen sodium, serrapeptase, spherical charcoal, amlodipine besilate, prednisolone, ranitidine hydrochloride, saireito, dilazep dihydrochloride, dipyridamole.				

Clinical Laboratory Values

	128 days before administration	On day 44 of administration	On day 48 of administration (day of discontinuation)	2 days after discontinuation	3 days after discontinuation	8 days after discontinuation
WBC (/mm^3)	13060	—	23140	—	17780	5590
RBC (×10^4/mm^3)	422	—	389	—	401	314
PLT (×10^4/mm^3)	352	—	360	—	218	44
BUN (mg/dL)	—	46.5	72.7	—	84.3	101.0
Serum creatinine (mg/dL)	—	3.2	5.9	—	6.8	5.3
AST (GOT) (IU/L)	8	—	—	66	61	33
ALT (GPT) (IU/L)	11			180	164	27
Na (mEq/L)	—	140	136	—	139	144
K (mEq/L)	—	4.4	5.6	—	5.4	5.2

WBC: White Blood Cell
RBC: Red Blood Cell
PLT: Platelet
BUN: Blood Urea Nitrogen
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Na: Sodium
K: Potassium

No.	Patient		Daily dose/ Treatment duration	Adverse drug reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female 30s	SLE, lupus nephritis (antiphospholipid syndrome)	200 mg 95 days ↓ 100 mg 108 days	**Stevens-Johnson syndrome** On day 1 of administration: Administration of this drug at 200 mg was started. On day 96 of administration: Dosage of this drug was reduced to 100 mg. Administration of allopurinol and sulfamethoxazole/trimethoprim was started. On day 148 of administration: Administration of itraconazole was started. On day 165 of administration: Administration of isoniazid was started. On day 201 of administration: Pyrexia of 38ºC range developed. Sultamicillin tosilate was prescribed for cold symptoms. On day 202 of administration: Facial rash developed. The rash gradually spread to the trunk of the body. On day 203 of administration (day of discontinuation): The patient was emergently hospitalized on suspicion of Stevens-Johnson syndrome and measles. The patient had generalised erythema, mouth ulcer, and conjunctivitis. General oedema was aggravated. Oral administration was discontinued completely. Medication was switched to intravenous drip infusions. 2 days after discontinuation: Oxygen was administered for low oxygen. 4 days after discontinuation: Pathological diagnosis of toxic epidermal necrolysis was confirmed by the results of skin biopsy conducted at department of dermatology. 5 days after discontinuation: As the possibility of drug-induced or viral disease was strong, administration of methylprednisolone and γ globulin preparation was started. 7 days after discontinuation: Central venous nutrition was started. 12 days after discontinuation: White blood cell was less than 1100/mm^3, haemoglobin was 13.1 g/dL, and platelet was less than $3.74 \times 10^4/mm^3$. Heparin preparation was administrated in pre-DIC state. 13 days after discontinuation: White blood cell, haemoglobin, and platelet were recovered to 3000/mm^3, 8.0g/dL, and $6.24 \times 10^4/mm^3$, respectively. The rash was tended to improve.	Company report

				25 days after discontinuation: DLST was positive for this drug, DLST was negative for all other drugs. 38 days after discontinuation: Skin symptoms improved virtually.	
	Concomitant medications: allopurinol, sulfamethoxazole/trimethoprim, itraconazole, sultamicillin tosilate, isoniazid, lansoprazole, valsartan, aspirin, furosemide, prednisolone, folic acid, teprenone, potassium chloride				

Clinical Laboratory Values

	On day179 of administration	On day 201 of administration	On day 203 of administration (day of discontinuation)	8 days after discontinuation	10 days after discontinuation	12 days after discontinuation	13 days after discontinuation	45 days after discontinuation
Body temperature (˚C)	—	38 ºC range	37.6	36.4	37.4			36.8
Haemoglobin (g/dL)	10.5	—	10.6	6.6	10.1	13.1	8.0	11.0
WBC (/mm^3)	3000	—	2500	2500	1300	1100>	3000	3500
PLT (×10^4/mm^3)	12.0	—	11.7	8.4	5.1	3.74>	6.24	12.8

WBC: White Blood Cell PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Female 60s	Rheumatoid arthritis (acute pancreatitis)	100 mg unknown	**Acute pancreatitis (increase in serum pancreatic enzymes)** On day 1 of administration: Administration of this drug at 100 mg was started at another hospital. 18 days before discontinuation: Diarrhoea developed. Later improved. 4 days before discontinuation: Abdominal pain and queasy developed. 2 days before discontinuation: The patient took initial examination at this hospital. As high levels of serum amylase 317 IU/L, lipase 194 IU/L, and CRP 9.67 mg/dL were confirmed, the patient was diagnosed with acute pancreatitis, and therapy was started. The patient was hospitalized. 1 day before discontinuation: No signs of pancreatitis were confirmed in CT. No gallstones and bile duct stones were found. No findings suggested original chronic pancreatitis. Day of discontinuation: Administration of this drug was discontinued. As the symptoms improved over approximately 1 week, oral ingestion of meals was started. Camostat mesilate and multiple digestive enzyme preparation were administrated. 7 days after discontinuation: No abnormal findings were confirmed in echogram. 11 days after discontinuation: The symptoms improved. The patient was discharged from the hospital.	Company report
	Concomitant medications: prednisolone, diclofenac sodium, famotidine				

Clinical Laboratory Values

	2 days before discontinuation	1 day before discontinuation	1 day after discontinuation	3 days after discontinuation	6 days after discontinuation	9 days after discontinuation
Serum amylase (IU/L)	317	88	212	101	163	182
Lipase (IU/L)	194	94	257	—	144	170
CRP (mg/dL)	9.67	10.93	3.59	4.31	1.36	1.31
WBC (/mm^3)	8100	5900	7000	7900	10300	8300

CRP: C-Reactive Protein WBC: White Blood Cell

No.	Patient		Daily dose/ Treatment duration	Adverse drug reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
5	Male 60s	Nephrotic syndrome (avascular necrosis of the right femoral head)	150 mg 26 days	**Hyperglycaemia** On day 1 of administration: Administration of this drug at 150 mg was started. On day 26 of administration (day of discontinuation): Hyperglycaemia developed. The patient was hospitalized. Administration of this drug for the treatment of hyperglycaemia was discontinued. Blood glucose was controlled through insulin treatment 4 times/day. 9 days after discontinuation: The symptoms improved.	Company report
	Concomitant medications: prednisolone, sodium risedronate hydrate, dilazep hydrochloride, aspirin, rebamipide, simvastatin, tamuslosin hydrochloride				

Clinical laboratory values

	On day 1 of administration	On day 15 of administration	On day 26 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	10 days after discontinuation	17 days after discontinuation
Blood glucose (mg/dL)	114	250	625	274	124	95	138

3

Revision of PRECAUTIONS

(No. 163)

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. 209) (excluding those presented in "2. Important Safety Information" of this Bulletin), together with reference materials.

1 <Antipyretics and analgesics, anti-inflammatory agents>
Mefenamic Acid

[Brand Name]

Pontal Powder, Pontal Fine Granules, Pontal Capsules 125 mg and 250 mg, Pontal Capsules 250 mg, ajd pontal Syrup (Sankyo Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)]

Haemolytic anaemia, agranulocytosis: Autoimmune haemolytic anaemias, agranulocytosis, and granulocytopenia may occur. Patients should be carefully observed through blood tests etc. and if abnormalities are observed, administration should be immediately discontinued and appropriate measures should be taken. As autoimmune haemolytic anaemias may occur when the drug is administered over the long term in the elderly, patients should be carefully monitored through blood tests etc. and if abnormalities are observed, administration should be immediately discontinued and appropriate measures should be taken.

Acute renal failure, nephrotic syndrome, interstitial pneumonia: Acute renal failure, nephrotic syndrome, and interstitial pneumonia may occur. Patients should be carefully monitored and if laboratory findings such as oliguria, haematuria, proteinuria, BUN increased, blood creatinine increased, hyperkalaemia, and hypoalbuminaemia are observed, administration should be immediately discontinued and appropriate measures should be taken.

Hepatitis fulminant, hepatic function disorder, jaundice: Hepatic function disorder with significant elevations of AST (GOT), ALT (GPT), Al-P, and γ-GTP levels, etc. and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

[Reference Information]

Company report

2 <Hyperlipidaemia agents>
Colestyramine

[Brand Name]

Questran (Aventis Pharma Limited)

[Adverse Reactions (clinically significant adverse reactions)]

Intestinal obstruction: Intestinal obstruction may occur. Patients should be carefully monitored and if abnormalities such as serious constipation, persistent abdominal pain, and vomiting are confirmed, discontinue administration and take appropriate measures.

[Reference Information]

Company report

<Bronchodilators>

3 Theophylline (sustained-release oral dosage form), (containing pediatric dosage and administration)

[Brand Name] Slo-bid Granule, Slo-bid 100 (Nippon Hekisaru Co., Ltd.), Theodur Granules 20%, Theodur Tablets 50 mg and 100 mg, Theodur Syrup 2%, Theodur Dry Syrup 20% (Mitsubishi Pharma Corporation), Theolong Granules 50%, Theolong Tablets 50 mg and 100 mg (Eisai Co., Ltd.), and others

[Precautions of Dosage and Administration] This drug should be administered with caution observing clinical symptoms and monitoring while its blood level. Especially when administering this drug in infants, children with pyrexia, and children with medical history of epilepsy and convulsions, consideration should be given to start administration at a lower dosage than normal (refer to the guidelines).

[Reference Information] Japan Society of Pediatric Allergy and Clinical Immunology: Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002

<Adrenal hormone preparations>

4 Betamethasone, Betamethasone Sodium Phosphate (injection and enema dosage form not having indication of asthma), Betamethasone Acetate/Betamethasone Sodium Phosphate

[Brand Name] Rinderon Powder, Rinderon Tablets (Bushu Pharmaceuticals Ltd.), Rinderon Syrup, Rinderon Suppositories 0.5 mg and 1.0 mg, Rinderon Injection 20 mg and 100 mg, Rinderon Injectable Suspension (Shionogi & Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Gastrointestinal ulceration, gastrointestinal perforation:** Gastrointestinal ulceration and gastrointestinal perforation may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
Pancreatitis

[Reference Information] Company report

<Adrenal hormone preparations>

5 Betamethasone Sodium Phosphate (injectable dosage form having indication of asthma)

[Brand Name] Rinderon Injection (Shionogi & Co., Ltd.), and others

[Important Precautions] Administration of this drug may aggravate asthmatic attack in patients with asthma bronchial. Extra caution should be exercised when treating patients with asthma sensitive to drugs, foods, or additives etc.

[Adverse Reactions (clinically significant adverse reactions)] **Aggravation of asthmatic attack:** Caution should be exercised as this drug may aggravate asthmatic attack in patients with asthma bronchial.
Gastrointestinal ulceration, gastrointestinal perforation: Gastrointestinal ulceration and gastrointestinal perforation may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
Pancreatitis

[Reference Information] Company report

6 <Acting mainly on gram-positive and gram-negative bacteria>

Cefcapene Pivoxil Hydrochloride

[Brand Name]	Flomox Fine Granules 100 mg for Children, Flomox Tablets 75 mg and 100 mg (Shionogi & Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythroderma (exfoliative dermatitis):** Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal **necrolysis** (Lyell syndrome) or erythroderma (exfoliative dermatitis) may occur. Patients should be carefully monitored, and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Interstitial pneumonia, eosinophilic pneumonia:** Interstitial pneumonia or eosinophilic pneumonia may occur. If any of such symptoms as pyrexia, cough, or dyspnoea etc. occurs, the therapy should be discontinued and conduct chest X-ray tests, blood tests, etc immediately, and appropriate measures such as corticosteroid therapy should be taken.
[Reference Information]	Company report

7 <Chemotherapeutics-Miscellaneous>

Terbinafine Hydrochloride (oral dosage form)

[Brand Name]	Lamisil Tablets 125 mg (Nihon Ciba-Geigy K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if symptoms such as dyspnoea, generalised flushing, angioedema, and urticaria are observed, discontinue administration and take appropriate measures.
[Reference Information]	Company report

8 <Human blood preparations>

Freeze-dried pH4 Treated Human Normal Immunoglobulin

[Brand Name]	Sanglopor (ZLB Behring K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Thromboembolism**: Symptoms of thromboembolism such as cerebral infarction, myocardial infarction, pulmonary embolism, and deep vein thrombosis may occur due to increase in blood viscosity etc. in cases given high dosages. Patients should be carefully monitored. If central nervous system symptoms (dizziness, consciousness disturbed, quadriplegia, etc.), chest pain, sudden dyspnoea, shortness of breath, pain of lower extremities or oedema, etc. are observed, administration should be discontinued and appropriate measures should be taken. For patients at high risk for thromboembolism, the dosage should be suitably reduced. It is desirable that the drug be administered as slowly as possible.
[Reference Information]	Company report

9 <Biological preparations-Miscellaneous>

Anti-human Thymocyte Immunoglobulin, Equine

[Brand Name]	Lymphoglobuline Injection 100 mg (Aventis Pharma Limited)
[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia, pulmonary oedema:** Interstitial pneumonia and pulmonary oedema may occur. Patients should be carefully monitored and if symptoms such as pyrexia, cough, dyspnoea, or chest X-ray abnormal are observed, discontinue administration and take appropriate measures.
[Reference Information]	Company report

10 **<Various function testing reagents>**

Glucagon (Genetical recombination), Glucagon

[Brand Name] Glucagon G Novo for Injection (Novo Nordisk Pharma Ltd.), and others

[Important Precautions] If this drug is administered as pretreatment for digestive tract X-ray and endoscopy, blood pressure decreased may occur immediately after administration, as well as after the tests. For this reason, patients should be carefully monitored even after the tests are completed and if the symptoms are observed, take appropriate measures.

[Reference Information] Company report

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11 **Over the counter drugs**

Anchusan/Shakuyakukanzoto [containing daily maximum amount of glycyrrhiza no less than 1 g (extract containing raw herbs no less than 1 g)].

[Brand Name] Taisho Ichoyaku K (Taisho Pharmaceutical Co., Ltd.), and others

[Consultation] In the 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 a case.
Hepatic function disorder: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

[Reference Information] Company report

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12 **Over the counter drugs**

Anchusan/Shakuyakukanzoto [containing daily maximum amount of glycyrrhiza no more than 1 g (extract containing raw herbs no more than 1 g)].

[Brand Name] Taisho Kampo Ichoyaku (Taisho Pharmaceutical Co., Ltd.) and others

[Consultation] In the 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 a case.
Hepatic function disorder: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

[Reference Information] Company report