Pharmaceuticals and Medical Devices Safety Information

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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).

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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 issue (Pharmaceuticals and Medical Devices Safety Information No. 214).

1 Ethionamide

Brand Name (name of company)	Tubermin Tablets (Meiji Seika Kaisha, Ltd.)
Therapeutic Category	Antituberculosis agents
Indications	<Susceptible strains> Tubercle bacillus sensitive to this drug <Indications> Pulmonary tuberculosis and other tuberculosis

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

[Adverse Reactions (clinically significant adverse reactions)]

Serious liver disorder <u>such as fulminant hepatitis and acute hepatitis etc.</u> may occur. Patients should be carefully monitored through periodic testing etc. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

Company report
Number of reported relevant adverse reaction cases since the initial marketing (approximately 40 years)
(excluding cases for which "causality could be denied" and including cases for which "causality is unknown")
• Fulminant hepatitis etc.: 8 cases (4 fatal cases)
The number of patients treated with Ethionamide for a year estimated by MAH (Marketing Authorisation Holder): approximately 750 (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 60s	Pulmonary tuberculosis (none)	200 mg 24 days	**Hepatitis fulminant** Medical history: appendicitis 23 years before administration: The patient was diagnosed with pulmonary tuberculosis and was treated with an oral dosage form (details unknown). 3 months before administration: Emaciation was suggested. 2 months before administration: Exertional shortness of breath, yellowish viscous sputum, sputum bloody developed. 33 days before administration: The patient was examined at hospital A. Acid-fast bacilli in the sputum showed Gaffky scale 1.	Company report

				29 days before administration: The patient was referred to hospital B. He was diagnosed with pulmonary tuberculosis and was hospitalized. Treatment with isoniazid, rifampicin, ethambutol hydrochloride was started. On day 1 of administration: Drug resistance was ascertained, and medication was switched to this drug, rifampicin, streptomycin sulfate, and levofloxacin. On day 14 of administration: No abnormal clinical laboratory value was confirmed. On day 24 of administration (day of discontinuation): The patient complained of general malaise, anorexia, and pyrexia. Clinical laboratory tests showed AST (GOT) 1460 IU/L, ALT (GPT) 1640 IU/L, LDH 3740 IU/L, prothrombin time 42%, eosinophils 12%, and hepatic encephalopathy was suspected. Moreover, due to dramatic worsening of symptoms, hepatitis fulminant was diagnosed. Administration of this drug, streptomycin sulfate, and levofloxacin was discontinued. Thereafter, plasma exchange and haemofiltration was performed 5 times. 36 days after discontinuation: As clinical laboratory findings became total bilirubin 0.5 mg/dL, AST (GOT) 32 IU/L, ALT (GPT) 27 IU/L, LDH 335 IU/L, prothrombin time 110%, eosinophils 3%, the patient recovered. Tuberculosis treatment was recommenced with sparfloxacin 0.2 g/day and streptomycin sulfate 0.5 g × 3/week. 44 days after discontinuation: Administration was started with sparfloxacin, streptomycin sulfate, with the addition of rifampicin.	
	Concomitant medications: rifampicin, streptomycin sulfate, levofloxacin, isoniazid, ethambutol hydrochloride				

Clinical Laboratory Values

	29 days before administration	On day 1 of administration	On day 14 of administration	On day 24 of administration (day of discontinuation)	36 days after discontinuation	44 days after discontinuation
Total bilirubin (mg/dL)	0.3	0.4	--	--	0.5	0.5
AST (GOT) (IU/L)	26	64	17	1460	32	33
ALT (GPT) (IU/L)	17	97	17	1640	27	27
Al-P (IU/L)	215	292	--	--	278	278
γ-GTP (IU/L)	31	--	--	--	--	--
LDH (IU/L)	310	285	--	3740	335	257
PT (%)	107	--	--	42	110	--

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
γ-GTP: γ-Glutamyltranspeptidase
LDH (IU/L): Lactate Dehydrogenase
PT: Prothrombin Time

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 80s	Pulmonary tuberculosis (none)	300 mg 43 days	**Hepatitis fulminant, liver disorder** 7 months before administration: Pulmonary tuberculosis developed. Thereafter, the patient was treated in a pulmonology ward. 6 months before administration: Oral administration of rifampicin, ethambutol hydrochloride, isoniazid, and pyridoxal phosphate was started. Later, as adverse reactions such as skin eruption and eosinophilia etc. occurred on several occasions, administration method of antituberculosis drugs was changed to frequent dosing. Although streptomycin sulfate was also administrated, it was discontinued due to adverse reactions. Continued drug therapy with the exception of rifampicin was difficult. 28 days before administration: Single administration of rifampicin was started. On day 1 of administration: In addition to rifampicin, administration of this drug was started. On day 15 of administration: Clinical laboratory findings from out-patient examination did not confirm hepatic function abnormal. On day 43 of administration (day of discontinuation): As elevated hepatic enzymes from values of AST (GOT) 965 IU/L, ALT (GPT) 891 IU/L were confirmed during out-patient examination, the patient was diagnosed with drug-induced liver disorder. She was hospitalized in a pulmonology ward. The patient complained of general malaise and appetite impaired from around the time of diagnosis (before and after diagnosis). Administration of this drug and rifampicin was discontinued. 11 day after discontinuation: As somnolence, abdomen enlarged feeling, and jaundice manifested, abdominal CT and blood samples were taken. Hepatitis B and C virus were negative (EBV and CMV were not tested). Considering clinical symptoms, the patient was diagnosed with hepatitis fulminant. 19 days after discontinuation: General care and circulatory (infusion, diuresis), respiratory (oxygen administration), glucose control (insulin administration), and administration of an amino acid preparation were performed as symptomatic treatment. Moreover, as the patient complicated by DIC, fresh frozen human plasma, concentrated human antithrombin III, and ulinastatin were administrated. Although osmotic diuretic was being administrated to treat brain oedema, coma developed and the patient died.	Company report
	Concomitant medications: rifampicin				

Clinical Laboratory Values

	28 days before administration	On day 15 of administration	On day 43 of administration (day of discontinuation)	11 days after discontinuation	12 days after discontinuation	15 days after discontinuation	17 days after discontinuation
Total bilirubin (mg/dL)	--	--	--	--	12.2	13.1	17.5
AST (GOT) (IU/L)	16	16	965	210	142	114	144
ALT (GPT) (IU/L)	9	6	891	206	144	92	100
Al-P (IU/L)	--	--	--	--	332	276	301
γ-GTP (IU/L)	--	--	--	--	--	--	46
LDH (IU/L)	308	187	522	307	263	--	321
PT (%)	--	--	--	32.9	46.9	56.7	39.2
NH_3 (μg/dL)	--	--	--	--	147	198	152

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
γ-GTP: γ-Glutamyltranspeptidase
LDH (IU/L): Lactate Dehydrogenase
PT (%): Prothrombin Activity (%)
NH_3: Ammonia

2 Etodolac

Brand Name (name of company)	Akomicol Tab. 200 mg (Daito Pharmaceutical Co., Ltd.) Etodoraku Tablets 200 mg "TATSUMI" (Tatsumi Kagaku Co., Ltd.) Etodolac Tablets 200 "KN" (Kobayashi Kako Co., Ltd.) Etopen Tablets 200 (Towa Pharmaceutical Co., Ltd.) Osteluc Tabs 100 and 200 (Wyeth K.K.) Ospain Tablets 200 (Nichi-iko Pharmaceutical Co., Ltd.) Niconas Tablets 200 mg (OHARA Pharmaceutical Co., Ltd.) Hisrack Tablets 200 mg (Taiyo Yakuhin Co., Ltd.) Hypen Tablets 100 mg and 200 mg (Nippon Shinyaku Co., Ltd.) Paipelac Tablets 200 mg (Taisho Pharmaceutical Industries, Ltd.) Raipeck Tablets 200 (Sawai Pharmaceutical Co., Ltd.)
Therapeutic Category	Antipyretics and analgesics, anti-inflammatory agents
Indications	Antiinflammation and analgesia in the following diseases and symptoms: Chronic rheumatoid arthritis, osteoarthrosis, lumbago, scapulohumeral periarthritis, cervicobrachial syndrome, and tendovaginitis. Antiinflammation treatment and analgesia after operation or trauma

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

[Adverse Reactions (clinically significant adverse reactions)]

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

<Reference Information>

Company report
Number of reported relevant adverse reaction cases since the initial marketing (approximately 11 years)
(excluding cases for which "causality could be denied" and including cases for which "causality is unknown")
• Toxic epidermal necrolysis: 3 cases (1 fatal case)
The number of patients treated with Etodolac for a year estimated by MAH: approximately 7.5 million (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 80s	Relief of low back pain and Pain in right thigh(none)	400 mg 139 days	**Toxic epidermal necrolysis** 336 days before administration: The patient was in serious postoperative condition of right femur fracture and lumbago developed. On day 1 of administration: Administration of this drug and mecobalamin was started. On day 133 of administration: From around this time, erythema (soybean-sized to chicken egg-sized) developed on the face and torso. Later, the erythema increased in number and size. The patient had mild pruritus. On day 139 of administration (day of discontinuation): His eldest son noticed that erosion occurred over the whole surface of patient's back. Administration of all drugs was discontinued. 1 day after discontinuation: After examination at internal medicine of hospital A in her area, the patient was referred to hospital B (reporting physician) and was hospitalized. During examination, dark-red generalised erythema (quail egg-sized to palm-sized) was observed, as well as erosion over a wide area of the back, both thighs, and both arms. Erosion was found also within the mouth (buccal mucosa and tongue). There were blutborke on the lips. Nikolsky's sign of the erythemic areas was positive. Ophthalmological findings were limited to blepharitis. After hospitalization and the following treatment, the erythema was healed through epithelialization except for a portion of pigmentation without being complicated by sepsis etc. 19 days after discontinuation: The patient recovered. She was discharged from the hospital. 44 days after discontinuation: At time of out-patient reexamination, there was no recurrence of skin eruption. 102 days after discontinuation: After the patient orally readministrated (1 time) 1 packet of acetaminophen/ethenzamide/caffeine at her own discretion, the same skin eruption manifested (recurred). 107 days after discontinuation: After appearance of lip erosion, erythema of the torso and limbs, and skin eruption, when betamethasone valerate/gentamicin sulfate was externally applied, the skin eruptions disappeared after about 7 days. 119 days after discontinuation: She returned visit to Hospital B. Blood tests (hematological value, liver/renal function) and Urine test indicated normal. 1/100 of the weight of 1 tablet of this drug (200mg) per day was readministered one time.	Company report

				After readministration, there were recurrence of erythema on the cicatrices of healed skin eruption on the torso and development of new erythema on the torso and limbs. After onset of skin eruption, when betamethasone valerate/gentamicin sulfate was externally applied, the skin eruptions disappeared in 1 day. Blood sample tests etc. were not performed. 131 days after discontinuation: 1/100 of the weight of 1 tablet of this drug (200 mg) per day was readministrated one time. After readministration, there were recurrence of erythema on the cicatrices of healed skin eruption on the torso and development of new erythema on the torso and limbs. After onset of skin eruptions, when betamethasone valerate/gentamicin sulfate was externally applied, the skin eruption disappeared in 1 day. Blood sample tests etc. were not performed. [Treatment drugs] Methylprednisolone sodium succinate (div) 500 mg: 1-2 days after discontinuation Levofloxacin (po) 300 mg: 2-15 days after discontinuation Azelastine hydrochloride (po) 2 mg: from 3 days after discontinuation and still being administrated Famotidine (po) 40 mg: from 2 days after discontinuation and still being administrated From the time of hospitalization until discharge, treatment consisted of once daily application of ointment of gentamicin sulfate and fradiomycin sulfate patch to the erosive areas, and application of betamethasone valerate/gentamicin sulfate to the erythemic areas. **Causality confirmation test** DLST (44 days after discontinuation)	
	Concomitant medications: acetaminophen/ethenzamide/caffeine, mecobalamin				

	cpm	S. I. (%)
Control drug	184	--
This drug	241	130
Mecobalamin	264	143
Acetaminophen/ethenzamide/caffeine	260	141

Clinical Laboratory Values

	1 day after discontinuation	9 days after discontinuation	15 days after discontinuation	30 days after discontinuation
WBC (/mm^3)	5200	6000	4500	4900
RBC ($\times 10^4$/mm^3)	395	331	312	321
Haemoglobin (g/dL)	11.7	9.7	9.3	9.4
PLT ($\times 10^4$/mm^3)	21.7	23.2	21.4	19.5
CRP (mg/dL)	12.42	4.93	2.43	0.82
Total protein (g/dL)	6.9	5.4	--	7.0
LDH (IU/L)	188	140	--	152
AST (GOT) (IU/L)	26	13	--	16
ALT (GPT) (IU/L)	25	10	--	7
γ-GTP (IU/L)	23	18	--	18
Al-P (IU/L)	215	188	--	277
BUN (mg/dL)	43	16	--	14
Creatinine (mg/dL)	1.0	0.7	--	0.7

WBC: White Blood Cell
RBC: Red Blood Cell
PLT: Platelet
CRP: C-Reactive Protein
LDH: Lactate Dehydrogenase
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
γ-GTP: γ-Glutamyltranspeptidase
LDH (IU/L): Lactate Dehydrogenase
Al-P (IU/L): Alkaline Phosphatase
BUN: Blood Urea Nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 70s	Pain relief (none)	400 mg 25 days	**Toxic epidermal necrolysis** On day 1 of administration: The patient was examined at hospital A for neck pain and muscular weakness of the limbs. As she was diagnosed with osteoporosis and lumbar spondylosis deformans, this drug, irsogladine maleate, alendronate sodium hydrate, menatetrenone, and ketoprofen were prescribed. On day 6 of administration: The patient took first examination at the orthopedic of hospital B (reporting physician). She was diagnosed with cervical spondylotic myelopathy, and conservative treatment, with rest as main treatment, and rehabilitation was also implemented. The symptoms gradually improved and the patient could walk independently. On day 22 of administration: Skin eruptions on torso developed mainly on the back. As symptoms did not improve, the patient was examined at dermatology. On day 25 of administration (day of discontinuation): Oral administration of this drug and irsogladine maleate etc. was discontinued. 5 days after discontinuation: Pyrexia and erosion of the face developed. TEN type drug eruption was surmised and prednisolone was started. Inflammatory reaction was intensified. Sepsis due to infection from the erosive areas of the skin was surmised and meropenem trihydrate IV drip infusion was given. Skin condition gradually improved. 9 days after discontinuation: Erosion expanded over the entire body. Erosion inside the mouth was significant and ingestion was decreased. Hypoproteinaemia, electrolyte abnormality, and symptoms of dehydration due to exudates were developed. 12 days after discontinuation: IVH catheter inserted to compensate for hypoproteinaemia, electrolyte abnormality, and symptoms of dehydration. 20 days after discontinuation: Arrhythmia developed. Hyperkalaemia was recovered through the administration of calcium polystyrene sulfonate etc. 27 days after discontinuation: Sudden bradycardia occurred, and heart rate decreased to thirties. P-wave disappeared, ST-T wave depression appeared. Although heart rate recovered due to drip infusion of atropine sulfate, P-wave and ST-T wave didn't change.	

				29 days after discontinuation: Before noon, monitor showed sudden short run of VT. The patient was intubated, respirator was attached, and resuscitation was attempted, but unresponsive. 47 minutes later, death was confirmed. Cause of death: toxic epidermal necrolysis DLST Test on day 25 of administration (day of discontinuation) S. I. This drug: 119% (negative) Ticlopidine hydrochloride: 112% (negative) Test on day 20 after discontinuation (steroid being administrated orally) S. I. Irsogladine maleate: 188% (positive) Furosemide: 135% (negative) Amlodipine besilate: 132% (negative) Imidapril hydrochloride: 166% (negative) Alendronate sodium hydrate: 98% (negative) Menatetrenone: 124% (negative) Metoprolol tartrate: 165% (negative) Diclofenac sodium: 110% (negative) S.I. 180% or less: negative; 181% and more: positive	Company report
	Concomitant medications: irsogladine maleate, ticlopidine hydrochloride, furosemide, amlodipine besilate, imidapril hydrochloride, alendronate sodium hydrate, menatetrenone, ketoprofen, metoprolol tartrate, diclofenac sodium, meropenem trihydrate				

Clinical Laboratory Values

	On day 6 of admin.	On day 25 of admin. (day of discontin-uation)	2 days after discontin-uation	6 days after discontin-uation	9 days after discontin-uation	14 days after discontin-uation	20 days after discontin-uation	21 days after discontin-uation	23 days after discontin-uation
WBC (/mm^3)	11800	5200	2200	1200	3900	9600	20900	16200	11300
CRP (mg/dL)	11.60	3.08	6.52	9.37	2.39	3.87	4.22	4.43	11.47
Neutrophils (%)	82	80	65	30	60	87	89	74	90
Basophils (%)	0	0	0	0	0	0	0	0	0
Eosinophils (%)	0	0	14	2	0	0	0	0	0
Lymphocytes (%)	15	17	19	59	36	9	9	24	7
Monocytes (%)	3	3	2	9	4	4	2	2	4

WBC: White Blood Cell CRP: C-Reactive Protein

3 Gemcitabine Hydrochloride

Brand Name (name of company)	Gemzar Injection 200 mg and 1 g (Eli Lilly Japan K.K.)
Therapeutic Category	Antimetabolites
Indications	Non-small cell lung cancer, pancreatic carcinoma

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

[Adverse Reactions (clinically significant adverse reactions)]

Myocardial infarction: Myocardial infarction may occur.
Skin disorder: Serious skin disorders (erythema, blister, desquamation etc.) may occur.

<Reference Information>

Company report
Number of reported relevant adverse reaction cases since initial marketing (approximately 5 and a half years)
(excluding cases for which "causality could be denied" and including cases for which "causality is unknown")
• Myocardial infarction: 4 cases (no fatal case)
• Skin disorder: 10 cases (1 fatal case)
The number of patients treated with Gemcitabine for a year estimated by MAH: approximately 46000 (2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 50s	Non-small cell lung cancer (none)	1600 mg once	**Acute myocardial infarction** The patient with non-small cell lung cancer. He had no medical history of myocardial infarction, hypertension, and diabetes mellitus. The patient smoked 10 cigarettes/day. Total cholesterol was normal. Approx. 2 years before administration: Non-small cell lung cancer developed. 1 year and 11 months before administration: Carboplatin and paclitaxel were administrated. 1 year and 9 months before administration: Radiation therapy was implemented (for 9 days). 1 year and 3 months before administration: Carboplatin and docetaxel hydrate were administrated. 8 months before administration: Carboplatin and docetaxel hydrate were administrated. On day 1 of administration: This drug at 1600 mg and carboplatin were administrated. On day 8 of administration: Although the patient experienced pain precordial on exertion, he left it. On day 10 of administration: While sleeping at home, the patient had pain precordial from late at night. He visited hospital during the morning. Pain precordial persisted. Electrocardiography performed at around noon showed QS pattern of leads III, V_{1-5}, and ST elevation of leads III, aVF, V_{1-5}. Based on CK (CPK) 2172 IU/L, AST (GOT) 175 IU/L, ALT (GPT) 45 IU/L, LDH 551 IU/L, the patient was diagnosed with anterior myocardial infarction. Emergency cardiac catheter test (CAG) was performed from the evening. Complete occlusion of the anterior descending branch was confirmed, and percutaneous coronary intervention (PCI) was implemented as the treatment. On day 32 of administration: CAG was conducted again, and stent was placed in the area of stenosis. On day 34 of administration: The patient was discharged from hospital.	Company report
	Concomitant medications: carboplatin (suspected drug), paclitaxel (suspected drug), docetaxel hydrate (suspected drug), dexamethasone sodium phosphate, metoclopramide, granisetron hydrochloride				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 50s	Pancreatic carcinoma (obstructive jaundice, gastritis)	1400 mg once	**Erythema** 6 weeks before administration: The patient was diagnosed with pancreatic carcinoma. On day 1 of administration: 1400 mg of this drug was administrated. On day 5 of administration: Pruritus from the right side of the back to the right axillary developed. Rash appeared from both sides of the back to both arms. Hydrocortisone/crotamiton was applied. On day 6 of administration: Upon examination by dermatologist, oedematous disseminated erythema was confirmed symmetrically on the right and left sides of the torso, and the patient was diagnosed with a high possibility of drug eruption induced from this drug. Olopatadine hydrochloride and mometasone furoate ointment were administrated (for 7 days). On day 7 of administration: As skin eruption slightly worsened, betamethasone was orally administrated (for 3 days). On day 11 of administration: Skin eruption left behind pigmentation and showed signs of subsiding. On day 13 of administration: Heparinoid was prescribed and symptoms improved.	Company report
	Concomitant medications: loxoprofen sodium (suspected drug), sulbactam sodium/cefoperazone sodium, teprenone, famotidine, sennoside, ramosetron hydrochloride				

4 Omeprazole, Omeprazole Sodium

Brand Name (name of company)	**Omeprazole** Ovulanze Tablets 10 and 20 (Taiyo Yakuhin Co., Ltd.) Omeptorol Tablets 20 mg (Taisho Pharmaceutical Industries, Ltd.) Omeprazole Tablets 20 mg "AMEL" (Kyowa Pharmaceutical Industry Co., Ltd.) Omeprazole Tab. 20 mg "Merck" (Merck Hoei Ltd.) Omeprazole Tablets 20 "SW" (Medisa Shinyaku Inc.) Omeprazole Tablets "Towa" 10 mg and 20 mg (Towa Pharmaceutical Co., Ltd.) Omeprazon Tablets 10 mg and 20 mg (Mitsubishi Pharma Corporation) Omerap Tablets 10 and 20 (Nichi-iko Pharmaceutical Co., Ltd.) Omepral Tablets 10 and 20 (AstraZeneca K.K.) **Omeprazole sodium** Omepral Injection 20 (AstraZeneca K.K.)
Therapeutic Category	Peptic ulcer agents
Indications	**Omeprazole** Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, and aids helicobacter pylori bacterial eradication in gastric ulcer or duodenal ulcer **Omeprazole sodium** 1. The following diseases for which oral administration is not possible: Gastric ulcer accompanied by haemorrhage, duodenal ulcer, acute stress ulcer

	and acute gastric mucosal lesion 2. Zollinger-Ellison syndrome which cannot be treated by oral administration

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

[Adverse Reactions (clinically significant adverse reactions)]

Agranulocytosis, pancytopenia, haemolytic anaemia, platelets decreased: Agranulocytosis, pancytopenia, haemolytic anaemia, and platelets decreased may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

Nephritis interstitial, acute renal failure: Nephritis interstitial and acute renal failure may occur. Caution should be exercised to renal function tests (BUN, creatinine, etc.) and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

Company report
Number of reported relevant adverse reaction since October 1998
(excluding cases for which "causality could be denied" and including cases for which "causality is unknown")
• Platelets decreased: 24 cases (of which 2 were fatal cases)
Number of reported relevant adverse reaction since initial marketing (approximately 14 years)
(excluding cases for which "causality could be denied" and including cases for which "causality is unknown")
• Acute renal failure: 11 cases (1 fatal case)
The number of patients treated with Omeprazole for a year estimated by MAH: approximately 1.3 million (2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 80s	Chronic gastritis (visceroptosis, osteoporosis, upper respiratory inflammation)	10 mg 77 days	**Platelets decreased** On day 1 of administration: Administration of this drug at 10 mg for chronic gastritis was started in the morning. Administration of alfacalcidol, calcium L-aspartate, and octotiamine/B_2/B_6/B_{12} was started. On day 15 of administration: Antibiotics (levofloxacin, ceftriaxone sodium) were administrated to treat symptoms of upper respiratory inflammation. On day 17 of administration: Symptoms of upper respiratory inflammation were improved with antibiotics. On day 29 of administration: As the patient ate little and had hyporexia, upper gastric imaging was performed and confirmed chronic gastritis. Administration of this drug was continued. On day 43 of administration: Antibiotics (levofloxacin) were administrated to treat symptoms of upper respiratory inflammation. On day 68 of administration: Blood was found in stool. On day 71 of administration: As internal haemorrhoids (+) was confirmed through proctoscopy, bromelain/tocopherol acetate was used. There were multiple oral submucosal haematomas .	Company report

				On day 77 of administration (day of discontinuation): Aggravation of oral submucosal haematomas and haemorrhage of the lips developed. Blood tests showed platelets decreased and the patient was hospitalized. Administration of this drug was discontinued. 17 days after discontinuation: Platelet count was returned to 100000 level and the condition was good. 22 days after discontinuation: The patient recovered.	
	Concomitant medications: alfacalcidol, calcium L-aspartate, octotiamine/B_2/B_6/B_{12}, levofloxacin, ceftriaxone sodium, Rikkunshito, Shoseiryuto, Kakkonto, rebamipide, ascorbic acid/calcium pantothenate				

Clinical Laboratory Values

	92 days before administration	On day 3 of administration	On day 77 of administration (day of discontinuation)
WBC (/mm^3)	4000	4600	4600
RBC ($\times10^4$/mm^3)	370	385	370
Haemoglobin (g/dL)	12.2	12.4	11.8
Haematocrit (%)	37.5	37.9	35.5
PLT ($\times10^4$/mm^3)	18.6	19.5	0.7

WBC: White Blood Cell PLT: Platelet
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	Female 70s	Reflux oesophagitis (gastritis erosive)	20 mg 19 days	**Acute renal failure** On day 1 of administration: Upon diagnosis of reflux oesophagitis, 20 mg of this drug was prescribed by a nearby physician. Later, nausea and general malaise etc. also manifested and the patient was reexamined by the nearby physician. On day 15 of administration: Teprenone and domperidone were added to regimen. Thereafter, general malaise continued and the patient also experienced urine output decreased. Face oedema etc. also developed. On day 19 of administration (day of discontinuation): The patient was referred to another hospital by the nearby physician. Blood samples collected at another hospital showed severe renal disorder and acidosis, platelets decreased and white blood cell decreased. The patient was referred to this hospital and took examination. At this time, there were symptoms of uraemia including nausea and general malaise. Administration of all oral drugs was discontinued. 2 days after discontinuation: Haemodialysis was started. 5 days after discontinuation: The patient was recovered from leukopenia. 6 days after discontinuation: The patient was recovered from thrombocytopaenia.	Company report

				12 days after discontinuation: BUN 47.7 mg/dL, serum creatinine 4.2 mg/dL (before haemodialysis). 13 days after discontinuation: As haemodialysis repeated, symptoms of uraemia including general malaise and nausea resolved. 17 days after discontinuation: Serum creatinine reached 3 mg/dL level and haemodialysis was reduced from 3 times/week to 2 times/week. Normal urination gradually became possible (about 500 mL/day). 24 days after discontinuation: Serum creatinine was return to 1.7 mg/dL and haemodialysis was withdrawn. From around this time, urination was about 1000 mL/day (started 1000 mL/day of IV drip infusion). 31 days after discontinuation: Serum creatinine was 1.3 mg/dL. Drip infusion was terminated, symptoms of uraemia did not occur, and the patient was stabilizing with urination at about 1000 mL/day. The patient was recovered from acute function kidney decreased 35 days after discontinuation: The patient was discharged from hospital.	
	Concomitant medications: teprenone, domperidone				

Clinical Laboratory Values

	On day 19 of administration (day of discontinuation)	1 day after discontinuation	5 days after discontinuation	9 days after discontinuation	12 days after discontinuation	14 days after discontinuation	24 days after discontinuation	31 days after discontinuation
BUN (mg/dL)	117.8	128.0	57.6	45.2	47.7	40.4	24.0	14.3
Serum creatinine (mg/dL)	9.9	10.0	7.9	5.3	4.2	3.4	1.7	1.3

BUN: Blood Urea Nitrogen

2

Revision of PRECAUTIONS

(No. 167)

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. 214) (excluding those presented in "1. Important Safety Information" of this Bulletin), together with reference materials.

<Antipyretics and analgesics, anti-inflammatory agents>

1 Tiaprofenic Acid

[Brand Name] Surgam Tablets, Surgam Tablets 200 mg (Aventis Pharma Limited), and others

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if symptoms of chest distressed feeling of, cold sweat, blood pressure decreased, tachycardia, dyspnoea, wheezing, angioedema, urticaria, and itching etc. are observed, discontinue administration and take appropriate measures.

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

<Reference Information> Company report

<Antipyretics and analgesics, anti-inflammatory agents>

2 Loxoprofen Sodium

[Brand Name] Loxonin Fine Granules, Loxonin Tablets (Sankyo Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)]

Cardiac failure congestive: Cardiac failure congestive may occur. Patients should be carefully monitored and if any abnormalities are observed, immediately discontinue administration and take appropriate measures.

<Reference Information> Company report

<Psychotropics>

3 Paroxetine Hydrochloride Hydrate

[Brand Name] Paxil Tablets 10 mg and 20 mg (GlaxoSmithKline K.K.)

[Important Precautions]

Dizziness, perceptual disturbance (paraesthesia, electric shock sensation, etc.), sleep disorder (including nightmare), anxiety, feeling irritated, excitement, nausea, tremor, confusion, sweaty, headache, diarrhoea etc. may occur due to the discontinuation (especially sudden discontinuation) or dosage reduction. Most symptoms appear within a few days of discontinuation of administration and are mild to moderate in degree. Symptoms resolve within about 2 weeks, although depending on the patient, symptoms may become serious or may require longer than 2 to 3 months for recovery. Based on information available to date, it is surmised that these symptoms are not the result of drug dependency.

When reducing the dosage or discontinuing administration of this drug, take heed of the following points:

1) Avoid sudden discontinuation of administration. When discontinuing

administration, gradually reduce the dosage over a period of several weeks or several months while monitoring the patient's condition.

2) If intolerable symptoms occur after dose reduction or discontinuation, consider readministering the drug at the dosage before implementing dose reduction or discontinuation and then reducing the dose more gradually should be considered.
3) The patient should be instructed not to discontinue administration at his/her own discretion. As the above symptoms of dizziness and perceptual disturbance etc. may occur by forgetting to take this drug, the patient should be instructed to take the drug as directed.

[Adverse Reactions (clinically significant adverse reactions)] **Confusion, hallucination, delirium, convulsion:** Confusion, hallucination, delirium, and convulsion may occur. If abnormalities are observed, take appropriate measures such as reducing dosage or discontinuing administration.

<Reference Information> Company report

<Otological agents>

4 Fluticasone Propionate (nasal solution)

[Brand Name] Flunase Nasal Solution, Flunase Nasal Solution 25 for Pediatric (GlaxoSmithKline K.K.)

[Relative contraindications] "Patients with tuberculosis, respiratory infection", "Patients with hypertension", and "Patients with diabetes mellitus" were omitted.

[Careful Administration] Patients with nasopharyngeal infection

<Reference Information> Company report

<Antihypertensives>

5 Alacepril, Imidapril Hydrochloride, Enalapril Maleate, Captopril, Quinapril Hydrochloride, Temocapril Hydrochloride, Delapril Hydrochloride, Trandolapril, Benazepril Hydrochloride, Perindopril Erbumine, Lisinopril

[Brand Name] Cetapril Tablets 12.5 mg, 25 mg, and 50 mg (Dainippon Pharmaceutical Co., Ltd.), Tanatril Tablets 2.5, 5, and 10 (Tanabe Seiyaku Co., Ltd.), Renivace Tablets-2.5 and 5 (Banyu Pharmaceutical Co., Ltd.), Captoril Fine Granules, Captoril Tablets 12.5 mg and 25 mg, Captoril-R (Sankyo Co., Ltd.), Conan Tablets 5 mg, 10 mg, and 20 mg (Mitsubishi Pharma Corporation), Acecol Tablets 1 mg, 2 mg, and 4 mg (Sankyo Co., Ltd.), Adecut 7.5 mg, 15 mg, and 30 mg Tablets (Takeda Pharmaceutical Company Limited), Odric Tablet 0.5 mg and 1 mg (Aventis Pharma Limited), Preran 0.5 mg and 1 mg Tablets (Chugai Pharmaceutical Co., Ltd.), Cibacen Tablets 2.5 mg and 5 mg (Novartis Pharma K.K.), Coversyl Tablets 2 mg and 4 mg (Daiichi Pharmaceutical Co., Ltd.), Zestril Tablets 5, 10, and 20 (AstraZeneca K.K.), Longes Tablets 5 mg, 10 mg, and 20 mg (Shionogi & Co., Ltd.), and others

[Contraindications] Patients under apheresis using dextran sulfate cross linked cellulose, tryptophan cross linked polyvinyl alcohol, or polyethylene terephthalate as absorbent.

[Interactions (contraindications for concomitant use)] Implementation of apheresis using dextran sulfate cross linked cellulose, tryptophan cross linked polyvinyl alcohol, or polyethylene terephthalate as absorbent.

[Adverse Reactions (other adverse reactions)] Hypoglycaemia

<Reference Information> Company report

6 <Antihypertensives> Cilazapril

[Brand Name] Inhibace Tablets 0.25, 0.5, and 1 (Chugai Pharmaceutical Co., Ltd.), and others

[Contraindications] Patients under apheresis using dextran sulfate cross linked cellulose, tryptophan cross linked polyvinyl alcohol, or polyethylene terephthalate as absorbent.

[Interactions (contraindications for concomitant use)] Implementation of apheresis using dextran sulfate cross linked cellulose, tryptophan cross linked polyvinyl alcohol, or polyethylene terephthalate as absorbent.

[Adverse Reactions (clinically significant adverse reactions)] **Pancreatitis:** Since pancreatitis may occur, patients must be carefully observed. If abnormal symptoms develop, appropriate measures must be taken.

[Adverse Reactions (Other adverse reactions)] Others: Hypoglycaemia, total cholesterol/uric acid/serum calcium increased, malaise, fatigue, chest pain, foreign body sensation in mouth, dysgeusia, hot flush, shoulder muscle stiffness, oedema, and redness

<Reference Information> Company report

7 <Bronchodilators> Salmeterol Xinafoate

[Brand Name] Serevent 25 and 50 Rotadisk, Serevent 50 Diskus (GlaxoSmithKline K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms (dyspnoea, bronchospasm, oedema, angioedema, etc.) may occur, patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

8 <Respiratory organ agents-Miscellaneous> Fluticasone Propionate (inhalant)

[Brand Name] Flutide 50 and 100 Air, Flutide 50, 100, and 200 Diskus, Flutide 50, 100, and 200 Rotadisk (GlaxoSmithKline K.K.)

[Relative contraindications] Patients with tuberculous disease

"Patients with hypertension" was omitted.

[Careful Administration] Patients with infectious diseases (except acute respiratory infection)

<Reference Information> Company report

9 <Antidiarrheals, intestinal regulators> LAC-B, LAC-B Granular Powder

[Brand Name] LAC-B, LAC-B Granular Powder (Nikken Chemicals Co., Ltd.)

[Contraindications] "Patients with a history of hypersensitivity to this drug" and "Patients allergic to milk" were omitted.

[Adverse Reactions (clinically significant adverse reactions)] "Anaphylactoid symptoms may occur. Patients should be carefully monitored. If symptoms are observed, administration should be discontinued and appropriate measures should be taken" was omitted.

<Reference Information> Company report

10 <Thyroid and parathyroid hormone preparations>
Thiamazole

[Brand Name] Mercazole Tablets (Chugai Pharmaceutical Co., Ltd.), Mercazole Injection (Kobayashi Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Rhabdomyolysis:** Rhabdomyolysis characterized by myalgia, feelings of weakness, CK (CPK) increased, and myoglobin blood increased and myoglobin urine increased may occur. Administration should be discontinued and appropriate measures should be taken in such cases. In addition, caution should be exercised for the onset of acute renal failure resulting from rhabdomyolysis.

<Reference Information> Company report

11 <Estrogen and progesterone preparations, Mixed hormone preparations>
Estradiol Preparation (indications include climacteric disturbance), Estriol Preparation (indications include climacteric disturbance), Androgen/Estrogen combinations preparation

[Brand Name] Estraderm M (Kissei Pharmaceutical Co., Ltd.), Estrana (Hisamitsu Pharmaceutical Co., Inc.), Estolmon Depot (Fuji Pharma Co., Ltd.), Ovahormon Aqueous Suspension 0.2 and 1, Ovahormon Depot 5 mg (Teikoku Hormone Medical Co., Ltd.), Femiest 2.17 mg and 4.33 mg (Yakult Honsha Co., Ltd.), Progynon-Depot 10 mg (Fuji Pharma Co., Ltd.), Pelanin Depot (5 mg) and 10 mg (Mochida Pharmaceutical Co., Ltd.), Estriol Tablets 1 mg (Fuji Pharma Co., Ltd.), Estriol Tablets 1 mg "Kayaku" (Kayaku Co., Ltd.), Estriel Tab. 100 γ, 0.5 mg, and 1 mg, Estriel Depot 10 mg (Mochida Pharmaceutical Co., Ltd.), Holin Tablets 1 mg, Holin Depot (Teikoku Hormone Medical Co., Ltd.), Meristrak Tablets 1 mg (Towa Pharmaceutical Co., Ltd.), Esjin Depot, Primodian-Depot (Fuji Pharma Co., Ltd.), Bothermon Injection 5.0 mg, Bothermon Depot 50 mg (Teikoku Hormone Medical Co., Ltd.), and others

[Contraindications]

Patients having or suspected of having estrogen-dependent tumors (e.g. breast cancer, endometrial cancer)
Patients with serious liver disorder
Patients with abnormal genital haemorrhage for which diagnosis has not been confirmed
Patients with a history of breast cancer

[Other Precautions]

Hormone replacement therapy (HRT) and the risk of breast cancer

①A randomized clinical trial in postmenopausal women conducted in the United States reported that the risk of breast cancer increased significantly higher in women receiving conjugated estrogen/progesterone compared to women receiving placebo (Hazard Ratio: 1.24). The sub study for women treated post-hysterectomy reported that the risk of breast cancer didn't increase significantly higher in women receiving conjugated estrogen alone compared to women receiving placebo (Hazard Ratio: 0.77).

②A result of epidemiologic investigation conducted in the United Kingdom reported that the risk of breast cancer increased significantly higher in women receiving conjugated estrogen/progesterone compared to women receiving placebo (2.00 times). It was reported that this risk increased the longer the period of concomitant administration became (less than 1 year: 1.45 times; 1–4 years: 1.74 times; 5–9 years: 2.17 times; more than 10 years: 2.31 times).

HRT and the risks of coronary heart disease

A randomized clinical trial in postmenopausal women conducted in the United States reported that the risk of coronary artery disease relatively increased higher in women receiving conjugated estrogen/progesterone compared to women receiving placebo, especially, increased significantly after receiving 1 year (Hazard Ratio: 1.81). The sub study for women treated post-hysterectomy reported that the risk of coronary artery disease didn't increase significantly in women receiving conjugated estrogen alone compared to women receiving placebo (Hazard Ratio: 0.91).

HRT and the risks of stroke

A randomized clinical trial in postmenopausal women conducted in the United States reported that the risk of stroke (mainly cerebral infarction) relatively increased higher in women receiving conjugated estrogen/progesterone compared to women receiving placebo (Hazard Ratio: 1.31). The sub study for women treated post-hysterectomy reported that the risk of stroke (mainly cerebral infarction) increased significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.39).

HRT and the risks of dementia

A randomized clinical trial in postmenopausal women conducted in the United States for postmenopausal women 65 years of age and older reported that the risk of dementia including Alzheimer's disease increased significantly higher in women receiving conjugated estrogen/progesterone compared to women receiving placebo (Hazard Ratio: 2.05). The sub study for women treated post-hysterectomy reported that the risk of dementia including Alzheimer's disease increased relatively high but not significant in women receiving conjugated estrogen alone compared to women receiving placebo (Hazard Ratio: 1.49).

Epidemiological studies reported that the risk of ovarian cancer increased in postmenopausal women who used estrogens for a long period compared to control group.

A randomized clinical trial in postmenopausal women conducted in the United States reported that the risk of ovarian cancer didn't increase significantly in women receiving conjugated estrogen/progesterone compared to women receiving placebo, but increased relatively high (Hazard Ratio: 1.58).

<Reference Information> Company report

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12 <Estrogen and progesterone preparations> Conjugated Estrogens

[Brand Name] Premarin Tablets 0.625 mg (Wyeth K.K.)

[Contraindications]

Patients having or suspected of having estrogen-dependent tumors (e.g. breast cancer, endometrial cancer)
Patients with serious liver disorder
Patients with abnormal genital haemorrhage for which diagnosis has not been determined
Patients with a history of breast cancer

[Other Precautions]

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<Reference Information> Company report

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13 <Miscellaneous metabolism agents> Camostat Mesilate

[Brand Name] Foipan Tablets (Ono Pharmaceutical Co., Ltd.), and others

[Contraindications] Patients with a history of hypersensitivity to any of the ingredient of this product.

[Adverse Reactions (clinically significant adverse reactions)]

Shock or anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored. If any symptoms such as blood pressure decreased, dyspnoea, and pruritus are observed, administration should be discontinued and appropriate measures be taken.

Hepatic function disorder or jaundice: Hepatic function disorder accompanied by remarkable increase of AST (GOT), ALT (GPT), γ-GTP, Al-P, or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate therapeutic measures such as discontinuing the administration should be taken.

<Reference Information> Company report

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14 <Miscellaneous metabolism agents> Methotrexate (having indication of chronic rheumatoid arthritis)

[Brand Name] Rheumatrex Capsules 2 mg (Wyeth K.K.), and others

[Important Precautions]

Malignant lymphoma, lymphoproliferative disorder, acute leukaemia, and myelodysplastic syndrome (MDS) etc. may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

The patient should not be inoculated with live vaccines during the administration of this drug as there is risk that inoculating a patient with suppressed immune function with a live vaccine may increase or sustain infection originating from the vaccine.

<Reference Information> Company report

15 <Antimetabolites> Capecitabine

[Brand Name] Xeloda Tablets 300 (Chugai Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Interstitial pneumonia:** Interstitial pneumonia (initial symptoms: cough, shortness of breath, dyspnoea, pyrexia etc.) may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued, chest X-ray etc. should be conducted, and appropriate measures such as administration of an adrenocortical hormone preparation should be taken.

<Reference Information> Company report

16 <Antineoplastics Plant extract preparations> Docetaxel Hydrate

[Brand Name] Taxotere Injection (Aventis Pharma Limited)

[Adverse Reactions (clinically significant adverse reactions)] **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythema polymorphe:** Bullous eruption and exudative skin eruption such as oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), and erythema polymorphe etc. may occur. Patients should be carefully monitored and if abnormalities are observed, take appropriate measures such as discontinuation of administration.

<Reference Information> Company report

17 <Antineoplastics-Miscellaneous> Cisplatin (for hepatic arterial injection)

[Brand Name] IA-Call 100 mg for Intra-arterial Injection (Nippon Kayaku Co., Ltd.), etc.

[Adverse Reactions (clinically significant adverse reactions)] **Platelets decreased:** Sudden platelets decreased may occur 1 to 4 days after administration. Patients should be carefully monitored after administration through frequent blood tests, etc. and if abnormalities are observed, take appropriate measures.

<Reference Information> Company report

18 <Sulfonamides> Salazosulfapyridine

[Brand Name] Azulfidine EN Tablets 250 mg, Azulfidine EN Tablets, Salazopyrin Tablets, Salazopyrin Suppositories (Pfizer Japan Inc.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Hypersensitivity syndrome, infectious mononucleosis-like symptoms:** Hypersensitivity syndrome and infectious mononucleosis-like symptoms may occur. Patients should be carefully monitored. If the following symptoms are observed, discontinue administration and take appropriate measures.

Rash, pyrexia, and cold-like symptoms are observed as initial symptoms, and may be followed by serious delayed hypersensitive symptoms accompanied by swollen lymph nodes, hepatic function disorder, hepatauxe, white blood cell increased, eosinophilia, and development of atypical lymphocytes etc.

Moreover, caution should be exercised as these symptoms may recur or become protracted even if drug administration is discontinued.

<Reference Information> Company report

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List of products subject to Early Post-marketing Phase Vigilance

(As of July 1, 2005)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Fosamprenavir Calcium Hydrate / Lexiva Tablets 700	GlaxoSmithKline K.K.	January 7, 2005
Beclometasone Dipropionate / Qvar Aerosol 50 and 100*[1]	Dainippon Pharmaceutical Co., Ltd.	January 19, 2005
Zoledronic Acid Hydrate / Zometa Injection 4 mg	Nihon Ciba-Geigy K.K.	January 21, 2005
Pralmorelin Hydrochloride / Ghrp Kaken 100 for Injection	Kaken Pharmaceutical Co., Ltd.	February 25, 2005
Aluminum Potassium Sulfate/Tannic Acid / Zione Injection/Lidocaine, Zione Injection	Mitsubishi Pharma Corporation	March 15, 2005
Epinastine Hydrochloride / Alesion Dry Syrup 1%	Nippon Boehringer Ingelheim Co., Ltd.	March 23, 2005
Etanercept (Genetical recombination) / Enbrel 25 mg for s.c. Injection	Wyeth K.K.	March 30, 2005
Oxaliplatin / Elplat for Injection 100 mg	Yakult Honsha Co., Ltd.	April 6, 2005
Tacrolimus Hydrate / Prograf Capsules 0.5 mg and 1 mg*[2]	Astellas Pharma Inc.	April 11, 2005
Emtricitabine / Emtriva Capsules 200 mg	Japan Tobacco Inc.	April 19, 2005
Emtricitabine/Tenofovir Disoproxil Fumarate / Truvada Tablets	Japan Tobacco Inc.	April 19, 2005
Rosuvastatin Calcium / Crestor Tablets 2.5 mg and 5 mg	AstraZeneca K.K.	April 27, 2005
Bosentan Hydrate / Tracleer Tablets 62.5 mg	Actelion Pharmaceuticals Japan Ltd.	June 10, 2005
Tamibarotene / Amnolake Tablets 2 mg	Toko Pharmaceutical Industrial Co., Ltd.	June 13, 2005
Tocilizumab (Genetical recombination) / Actemra for Intravenous Infusion 200	Chugai Pharmaceutical Co., Ltd.	June 13, 2005
Adenosine / Adenoscan Injection 60 mg	Daiichi Suntory Pharma Co., Ltd.	June 21, 2005
Voriconazole / Vfend Tablets 50 mg and 200 mg, Vfend 200 mg for Intravenous Use	Pfizer Japan Inc.	June 27, 2005

Note) Subject to additional indication etc.

*1: Additional indications of pediatric dosage "In children, 50 μg of the drug is generally inhaled into the mouth twice a day. Moreover, although the dosage may be increased/decreased as needed according to age and symptoms, the maximum daily dosage is 800 μg in adults and 200 μg in children. (underlined parts are additions)"

*2: An additional indication for “Rheumatoid arthritis (only for cases which are not adequately responsive to conventional therapies”