Pharmaceuticals and Medical Devices Safety Information

No. 274 November 2010

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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 (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers.
The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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

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

[Outline of Information]

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

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi," a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

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Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the Precautions section of package inserts of drugs that have been revised in accordance with the Notification dated September 28, 2010.

[Brand name]: Major product names are showed.

1 **Adalimumab** (Genetical Recombination)

Brand Name (name of company)	HUMIRA Subcutaneous Injection 40 mg Syringe 0.8 mL (Abbott Japan Co., Ltd.)
Therapeutic Category	Miscellaneous metabolism agents - Miscellaneous
Indications	The diseases shown below which are not adequately responsive to conventional therapies Rheumatoid arthritis Psoriasis vulgaris, psoriasis arthropathy Ankylosing spondylitis Remission induction or maintenance therapy for moderate or severe active Crohn's disease (limited to the cases in which conventional therapy is not sufficiently effective)

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Fulminant hepatitis, hepatic dysfunction, jaundice, hepatic failure: Fulminant hepatitis, hepatic dysfunction with marked increase in AST (GOT), ALT (GPT), etc., jaundice or hepatic failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. Some of these symptoms were caused by reactivation of the hepatitis B virus.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 2 years (from initial marketing to August 17, 2010)

- Hepatic dysfunction, jaundice: 6 cases (no fatal cases)
- Hepatic failure: 2 cases (2 fatal cases)
- Fulminant hepatitis: 2 cases (2 fatal cases)

The number of patients prescribed this drug per year estimated by marketing authorization holder (MAH):
Approximately 69,000 (September 2009 to August 2010)
Marketed in Japan in: June 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Rheumatoid arthritis (Osteoporosis, gastrointestinal	40 mg/ 2 weeks for 15 days	**Abnormal hepatic function** Before administration: The patient had been treated with etanercept (genetical recombination), methotrexate, prednisolone,

		disorder, hypertension, obstructive arteriosclerosis of lower extremities, insomnia, constipation, migraine)		salazosulfapyridine, penicillamine, and leflunomide for rheumatoid arthritis. Day 1 of administration: Administration of adalimumab (genetical recombination) was initiated at 40 mg/2 weeks. Day 15 of administration: Last day of administration of adalimumab. AST (GOT) 35 IU/L (normal range: 13-33 IU/L), ALT (GPT) 25 IU/L (normal range: 8-42 IU/L). Day 27 of administration (day of onset): Blood test was performed because the patient complained of nausea, gastralgia, numbness of fingers, chills, headache, etc. lasting for approximately a week. Elevations of AST (GOT) to 662 IU/L, ALT (GPT) to 419 IU/L, LDH to 663 IU/L, Al-P to 1088 IU/L and γ-GTP to 532 IU/L were noted, and the patient was admitted to the hospital. Methotrexate was discontinued, and fluid replacement was performed (for 7 days). Day 8 of onset: Liver function was gradually stabilized. AST (GOT) 116 IU/L, ALT (GPT) 136 IU/L. Day 16 of onset: The patient was discharged from the hospital. Treatment was resumed with methotrexate 8 mg/week. No increase in liver function was noted.
	Concomitant medications: methotrexate 8 mg/week (suspected drug), prednisolone, etodolac, alendronate sodium hydrate, alfacalcidol, ticlopidine hydrochloride, ecabet sodium, sennoside, zolpidem tartrate, isoniazid, acetaminophen, triazolam, etizolam			

Laboratory Examination

	5 days before administration	Day 15 of administration	Day 27 of administration (day of onset)	Day 8 of onset	Day 15 of onset	Day 29 of onset	Day 85 of onset
LDH (IU/L)	251	260	663	-	236	256	-
AST (GOT) (IU/L)	35	35	662	116	86	57	30
ALT (GPT) (IU/L)	26	25	419	136	78	45	20
Total bilirubin (mg/dL)	0.6	0.5	0.9	-	0.6	0.6	-
Al-P (IU/L)	390	405	1088	-	612	521	-
γ-GTP (IU/L)	40	72	532	-	319	174	-

LDH: Lactate dehydrogenase, AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), Al-P: Alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Rheumatoid arthritis (None)	40 mg/ 2 weeks for 323 days	**Fulminant hepatitis, hepatic failure, hepatitis B reactivation** 5 years before administration: The patient underwent HBs antigen qualitative test and the results were negative. At another hospital, however, assessment for HBs antigen quantitative test was withheld because of low titer. 1 year and 1 month before administration: Administration of infliximab (genetical recombination), methotrexate and prednisolone was started. Results of tests

				conducted before administration of infliximab (genetical recombination) showed normal ALT (GPT), HBs antigen negative, and HBs antibody positive. Day 1 of administration: Administration of adalimumab (genetical recombination) was initiated at 40 mg/2 weeks. AST (GOT) 32 IU/L (normal range: 8-38 IU/L), ALT (GPT) 21 IU/L (normal range: 4-44 IU/L). Day 59 of administration: AST (GOT) 29 IU/L, ALT (GPT) 22 IU/L. Day 127 of administration: AST (GOT) 49 IU/L, ALT (GPT) 47 IU/L. Day 225 of administration: AST (GOT) 68 IU/L, ALT (GPT) 65 IU/L. Month 10 of administration: The patient gradually began to have a feeling of general malaise. Day 323 of administration (day of onset): General malaise further worsened. A blood test showed increased hepatobiliary enzymes (AST [GOT]563 IU/L, ALT [GPT] 361 IU/L), and drug-induced hepatic disorder was suspected. Administration of adalimumab was thus discontinued. The dose of prednisolone was increased to 5 mg/day. Glycyrrhizin/glycine/cysteine was administered. Day 16 of onset: The patient was fully conscious. Marked jaundice, markedly increased transaminases and, decreased platelet and PT (by 10%) were noted. Acute severe hepatitis was suspected, and the patient was transferred to another hospital. Results of tests conducted at admission were: positive for HBs antigen and HBc antibody and negative for HBs antibody and IgM-HBc antibody. Blood HBV-DNA was 10^9 copies/mL, and the patient was diagnosed with reactivation of latently infected HBV. As liver synthetic capacity was markedly reduced, treatment with plasma exchange and dialysis filtration, interferon beta and entecavir hydrate was started. Day 18 of onset: Steroid pulse therapy with methylprednisolone 1 g/day was started. Day 22 of onset: Encephalopathy was not noted. SpO_2 began to decrease in the evening. Atrial fibrillation and tachycardia occurred. Continuous administration of a diuretic and diltiazem hydrochloride was started, but respiratory discomfort did not improve. Day 23 of onset: SpO_2 was controlled at 90% level. Urine output began to markedly decrease in the early evening. Despite transfusion loading and administration of a diuretic, there was no improvement in the urine output, and renal failure and metabolic acidosis occurred. The patient had delirium with grade III hepatic coma. Day 24 of onset: The patient's condition became aggravated. Oxygenation was maintained with administration of oxygen using a reservoir mask, but anuria persisted, shallow breathing gradually appeared, and the patient eventually died.

	Concomitant medications: methotrexate 10 mg/week (suspected drug), prednisolone 2.5 mg/day (suspected drug), folic acid 5 mg/day, brotizolam, teprenone, famotidine, alfacalcidol

Laboratory Examination

	5 years before administration	Day 1 of administration	Day 59 of administration	Day 127 of administration	Day 225 of administration	Day 323 of administration (day of onset)	Day 16 of onset	Day 17 of onset	Day 24 of onset
LDH (IU/L)	-	-	-	-	-	374	554	365	1689
AST (GOT) (IU/L)	-	32	29	49	68	563	1390	586	1552
ALT (GPT) (IU/L)	-	21	22	47	65	361	645	289	568
Total bilirubin (mg/dL)	-	-	-	-	-	0.6	15.5	10.9	8.9
ChE (IU/L)	-	-	-	-	-	148.0	-	-	-
NH_3 (μg/dL)	-	-	-	-	-	-	-	121.0	-
HBc-Ab	-	-	-	-	-	-	-	12.7	-
HBe-Ab	-	-	-	-	-	-	-	96.6	57.3
HBe-Ag	-	-	-	-	-	-	-	0.1	0.0
HBs-Ab	-	-	-	-	-	-	-	2.1	0.8
HBs-Ag	(+/-)	-	-	-	-	-	2000	2000	2000
HCV-Ab	-	-	-	-	-	-	-	0.3	-

LDH: Lactate dehydrogenase, AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), ChE: Cholinesterase

2 Erlotinib Hydrochloride

Brand Name (name of company)	TARCEVA Tablet 25 mg, 100 mg, 150 mg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Recurrent or advanced, unresectable non-small cell lung cancer that has progressed after chemotherapy

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Acute renal failure: Serious renal impairment including acute renal failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing treatment, should be taken.

Gastrointestinal perforation, gastrointestinal ulcer, gastrointestinal haemorrhage: Gastrointestinal perforation, gastrointestinal ulcer or gastrointestinal haemorrhage may occur. Patients should be carefully monitored and, if any abnormalities are observed, necessary examinations including endoscopy, abdominal X-ray or CT scans should be performed and appropriate measures, such as discontinuing administration of this drug, should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 2 and a half years (from initial marketing to May 17, 2010)

- Renal impairment including renal failure: 7 cases (3 fatal cases)
- Gastrointestinal ulcer: 6 cases (no fatal cases)
- Gastrointestinal haemorrhage: 10 cases (no fatal cases)
- Gastrointestinal ulcer and haemorrhage: 7 cases (1 fatal case)

The number of patients prescribed this drug per year estimated by MAH:
Approximately 5,500 (FY 2009)
Marketed in Japan in: December 2007

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Non-small cell lung cancer [squamous cell carcinoma] (Congestive cardiac failure, constipation, dysuria, pneumonia)	150 mg for 15 days	**Acute renal failure** Primary lesion, none; Metastatic sites, lung, liver; Stage, IV 245 days before administration: The patient was diagnosed with non-small cell lung cancer (squamous cell carcinoma) for the first time. Right pneumonectomy and lymph node excision were performed. 209 days before administration: Postoperative adjuvant chemotherapy (cisplatin and vinorelbine ditartrate) was performed. 99 days before administration: Recurrence of non-small cell lung cancer (squamous cell carcinoma) was confirmed. 93 days before administration: Abdominal CT was performed and showed no abnormalities in the kidney and no ascites. 91 days before administration: Primary chemotherapy (docetaxel hydrate) was performed. 45 days before administration: Pneumonia developed, and the patient was admitted to the hospital. Tazobactam sodium/piperacillin sodiumwas administered. Day 1 of administration: Administration of erlotinib hydrochloride was initiated at 150 mg/day. PS: 1. The patient had pyrexia of 38.7°C. Administration of tazobactam sodium/piperacillin sodium was initiated due to the risk of potential relapse of pneumonia. Investigation of the pathogenic bacteria was not performed. Day 2 of administration: Brain MRI showed no apparent metastasis. Day 5 of administration: The patient experienced diarrhoea (watery stools), with 3 bowel movements per day. Day 6 of administration: Abdominal CT was performed and showed metastases to liver and no abnormalities in the abdomen and kidney. Day 7 of administration: The condition of diarrhoea remitted to loose stools with 1 bowel movement per day. Day 14 of administration: The patient had stomatitis and dermatitis. The patient visited oral surgical clinic and dermatology clinic. Urine output was not measured. Day 15 of administration (day of discontinuation): Renal failure occurred. Treatment: the patient treated with dialysis. Creatinine (Cr) increased in G2. CT test was performed and showed slight ascites in the pelvis but showed no evidence of hydronephrosis. Urine output was not measured. No severe dehydration was noted. Urine analysis findings: UNa 59 mEq/L, UCl 36 mEq/L, UK 4.58 mEq/L, urine UN 291mg/dL, UCr 104.3 mg/dL, UUA 36.2 mg/dL, urine protein 54 mg/dL, urine protein excretion rate 0.13, urine sugar 36

				mg/dL, urine sugar excretion rate 0.07, FENa 1.08%, %TRP not calculated, urine protein/UCr ratio 0.52. 1 day after discontinuation: Urine output was 400 mL/day. 2 days after discontinuation: Cr increased in G3. There was a possible sign of cardiac failure. The patient consulted with a physician at the department of cardiovascular medicine, and administration of carperitide (genetical recombination) (2V/day) was initiated. Urine output was 80 mL/12 hours and 400 mL/day. The patient responded poorly to furosemide. He consulted with a physician at the nephrology department and received emergency dialysis. Transfusion of approximately 1500 mL/day and furosemide 2A were prescribed. 3 days after discontinuation: Urine output was 30 mL/day. 4 days after discontinuation: Extracorporeal Ultrafiltration Method (ECUM) was performed, and urine output was 30 mL/day. 5 days after discontinuation: Transfusion of 1000 mL/day was given, and urine output was 5 mL/day. 6 days after discontinuation: Administration of digoxin and nicergoline were discontinued. The dose of transfusion was reduced to 500 mL/day. Urine output was 5 mL/day. 7 days after discontinuation: Urine output was 0 mL/day. 8 days after discontinuation: Marked hepatic disorder was noted, and administration of all oral medications were discontinued. 9 days after discontinuation: Disturbed consciousness occurred early in the morning, with immeasurable blood pressure. The dose of transfusion was increased to 1000 mL/day, and administration of dopamine hydrochloride was initiated. The patient died. There was no progression of the disease.
	Concomitant medications: loxoprofen sodium, tazobactam sodium/piperacillin sodium, triazolam, carbocisteine, rebamipide, digoxin, magnesium oxide, valsartan, clotiazepam, propiverine hydrochloride, dexamethasone, bifidobacterium preparation, furosemide, isosorbide dinitrate			

Laboratory Examination

	1 day before administration	Day 5 of administration	Day 8 of administration	Day 12 of administration	Day 15 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	4 days after discontinuation	6 days after discontinuation	8 days after discontinuation
BUN (mg/dL)	16.1	12.0	14.7	24.3	44.3	53.9	60.2	53.5	54.8	58.7
Cr (mg/dL)	0.71	0.77	0.77	0.93	1.55	2.66	3.65	5.18	6.96	7.94
K (mEq/L)	4.9	4.7	4.3	4.4	4.1	4.1	3.8	3.8	3.6	4.0
Na (mEq/L)	138	141	139	139	139	139	133	133	133	135
Cl (mEq/L)	101	106	104	105	107	106	104	99	98	99

BUN: Blood urea nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Non-small cell lung cancer [adenocarcinoma] (Diabetic nephropathy, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, insomnia, hyperlipidaemia, cerebral infarction, constipation)	150 mg for 26 days	**Gastrointestinal ulcer** Primary lesion, right upper lobe; Metastatic sites, lymph node, brain; Stage, IV 1 year before administration: The patient received gamma knife surgery. He was diagnosed with non-small cell lung cancer for the first time. Bronchoscopy was performed. Primary chemotherapy (paclitaxel) was performed. 5 months before administration: Gamma knife surgery was performed. Secondary chemotherapy (cisplatin, gemcitabine hydrochloride) was performed. Day 1 of administration: Administration of erlotinib hydrochloride was initiated at 150 mg/day (continued until Day 18 of administration). PS: 1. Day 14 of administration: Radiotherapy was performed (continued until Day 16 of administration, cranial irradiation, total dose: 9 Gy). Day 18 of administration: Diarrhoea developed (no serious). Administration of erlotinib hydrochloride was discontinued. Day 19 of administration: Progression of the disease was confirmed. The patient recovered from diarrhoea. Day 20 of administration: Administration of erlotinib hydrochloride was resumed at 150 mg/day (continued until Day 22 of administration). Day 22 of administration: Diarrhoea developed (no serious). Administration of erlotinib hydrochloride was discontinued. Day 23 of administration: The patient recovered from diarrhoea. Day 24 of administration: Administration of erlotinib hydrochloride was resumed at 150 mg/day (continued until Day 28 of administration). Day 28 of administration (day of discontinuation): Day 28 of administration of erlotinib hydrochloride. 1 day after discontinuation: Midnight: Haematemesis suddenly occurred without any sign. Blood pressure was temporarily decreased, and decreased haemoglobin was noted at testing. Emergent upper gastrointestinal tract endoscopy was performed by a gastroenterological physician on duty, and gastric ulcer haemorrhage was found. Treatment: Transfusion (4 MAP units) was given, and endoscopic haemostasis was performed with clips and a drug (omeprazole injection). 2 days after discontinuation: Repeated gastrointestinal endoscopy was performed, and haemostasis was performed again with clips. 5 days after discontinuation: Repeated gastrointestinal endoscopy was performed and no haemorrhage from gastric ulcer was noted. Progression of the

				disease was confirmed. 6 days after discontinuation: Gastric ulcer haemorrhage remitted.
	Concomitant medications: dexamethasone, dexamethasone sodium phosphate, aspirin, sennoside, bisacodyl, amlodipine besilate, imidapril hydrochloride, tiotropium bromide hydrate, brotizolam, flurazepam hydrochloride, simvastatin, trazodone hydrochloride, glimepiride, ranitidine hydrochloride, insulin human (genetical recombination), metoclopramide, glucose-electrolyte solution, acetic acid maintenance solution, thiamine monophosphate disulfide/B_6/B_{12}, acetic acid maintenance solution (glucose-added)			

Laboratory Examination

	1 day before administration	Day 2 of administration	Day 8 of administration	Day 13 of administration	Day 19 of administration	Day 22 of administration	Day 28 of administration (day of discontinuation)	1 day after discontinuation		2 days after discontinuation	3 days after discontinuation	5 days after discontinuation
Hemoglobin (g/dL)	11.1	11.1	10.9	10.6	11.0	11.2	9.9	6.8	10.2	9.3	8.5	7.9
PLT ($\times 10^4/mm^3$)	18.6	19.6	17.3	15.8	14.6	16.3	12.6	13.7	9.0	6.4	7.5	5.7
BUN (mg/dL)	13.1	17.1	21.7	23.5	28.0	32.5	38.0	-		46.7	39.1	33.0
Serum creatinine (mg/dL)	1.10	1.21	1.22	1.15	1.36	1.28	1.38	-		1.47	1.28	1.08

PLT: Platelet, BUN: Blood urea nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 50s	Non-small cell lung cancer [adenocarcinoma] (None)	150 mg for 23 days	**Gastrointestinal haemorrhage** Primary lesion: left lower lobe; Metastatic sites: lung, bone, brain; Stage: IV 4 years and 7 months before administration: The patient was diagnosed with non-small cell lung cancer (adenocarcinoma) for the first time. Primary chemotherapy (carboplatin, paclitaxel) was performed. 3 years and 11 months before administration: Secondary chemotherapy (gefitinib) was performed. 3 years and 6 months before administration: Third chemotherapy (vinorelbine ditartrate, gemcitabine hydrochloride) was performed. 2 years and 9 months before administration: Gamma knife surgery was performed for the brain tumors. 2 years and 7 months before administration: Fourth chemotherapy (carboplatin, gemcitabine hydrochloride) was performed. 1 year and 11 months before administration: Fifth chemotherapy (tegafur/gimeracil/oteracil potassium) was performed. 1 year and 6 months before administration: Sixth chemotherapy (carboplatin, paclitaxel) was performed. 1 year and 2 months before administration: Seventh chemotherapy (vinorelbine ditartrate, gemcitabine hydrochloride) was performed. 5 months before administration: Eighth chemotherapy (docetaxel hydrate) was performed.

				Day 1 of administration: Non-small cell lung cancer (adenocarcinoma); PS, 2; oral administration of erlotinib hydrochloride was initiated at 150 mg/day (9-day administration followed by 15-day drug withdrawal). Day 25 of administration: Oral administration of erlotinib hydrochloride was resumed at 150 mg/day. Day 31 of administration: Progression of the disease was confirmed. Day 33 of administration: Melaena developed. Day 35 of administration: Anaemia developed. Day 38 of administration (day of discontinuation): Colonoscopy was performed: colonic diverticulitis. Progression of the disease: Present. Administration of erlotinib hydrochloride was discontinued. 4 days after discontinuation: Gastroscopy was performed: duodenal ulcer. 10 days after discontinuation: Gastroscopy was performed: duodenal ulcer. Melaena remitted. 14 days after discontinuation: Anaemia remitted. 301 days after discontinuation: The patient died (death from primary cancer).
	Concomitant medications: ranitidine hydrochloride, furosemide, spironolactone, clotiazepam, etizolam, isosorbide, mosapride citrate hydrate, moxifloxacin hydrochloride			

Laboratory Examination

	2 days before administration	Day 33 of administration	Day 35 of administration	Day 37 of administration	3 days after discontinuation	6 days after discontinuation	14 days after discontinuation
RBC ($\times 10^4/mm^3$)	-	342	279	265	251	302	342
Hemoglobin (g/dL)	12.7	11.3	9.2	8.7	8.0	9.9	11.1
Hematocrit (%)	-	34.9	28.2	27.0	25.8	31.2	35.5
PLT ($\times 10^4/mm^3$)	10.0	5.9	7.5	9.8	13.2	16.2	15.1
BUN (mg/dL)	9.1	30.5	11.6	10.2	10.0	10.1	10.3
Serum creatinine (mg/dL)	0.7	0.7	0.7	0.7	0.6	0.6	0.6

RBC: Red blood cell count, PLT: Platelet, BUN: Blood urea nitrogen

3 Gefitinib

Brand Name (name of company)	Iressa Tablets 250 (AstraZeneca K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Inoperable or recurrent non-small cell lung cancer

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Gastrointestinal perforation, gastrointestinal ulcer, gastrointestinal haemorrhage: Gastrointestinal perforation, gastrointestinal ulcer or gastrointestinal haemorrhage may occur. Patients should be carefully monitored and, if any abnormalities are observed, necessary examinations including endoscopy, abdominal

X-ray or CT scans should be performed and appropriate measures, such as discontinuing administration of this drug, should be taken.

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration of this drug, should be taken.

Hepatitis, hepatic dysfunction, jaundice, hepatic failure: Hepatitis, hepatic dysfunction with elevated AST (GOT), ALT (GPT), LDH, γ-GTP, Al-P and bilirubin, or jaundice may occur, resulting in hepatic failure in some cases. During administration of this drug, patients should be carefully monitored by performing hepatic function tests every one or two months, or according to the patients' condition. If any significant changes in liver function test are observed, appropriate measures, such as discontinuing administration of this drug, should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to July 27, 2010)

- Gastrointestinal perforation: 2 cases (no fatal cases)
- Gastrointestinal ulcer: 3 cases (no fatal cases)
- Gastrointestinal haemorrhage: 2 cases (no fatal cases)
- Oculomucocutaneous syndrome: 1 case (no fatal cases)
- Hepatic failure: 3 cases (1 fatal case)

The number of patients prescribed this drug per year estimated by MAH:
Approximately 16,000 (2009)

Marketed in Japan in: July 2002

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Non-small cell lung cancer (Hypertension)	250 mg for 11 days	**Perforative peritonitis** Medical history: sigmoidectomy, cataract Approximately 3 years and 2 months before administration: The patient had a detailed examination for lung cancer (adenocarcinoma) in the left lung field, and surgery was performed. Because dissemination in the thoracic cavity was noted, HCT (nedaplatin 50 mg and distilled water 500 mL) was performed, but treatment ended with test thoracotomy with cT4N0M0. Approximately 3 years and 1 month before administration: Two courses of chemotherapy (carboplatin and paclitaxel) was performed, but resulted in NC. Thereafter, the patient was followed up on an outpatient basis. Approximately 3 months before administration: Pleurodesis was performed for carcinomatous pleurisy. Day 1 of administration: Administration of gefitinib was started. Day 8 of administration: The patient visited an outpatient department. She had a diarrhoea-like symptom. Discontinuation of concomitant use of sennoside was instructed. The patient was instructed to take a bifidobacterium preparation if diarrhoea did not remit. Day 11 of administration (day of discontinuation): Watery diarrhoea and pyrexia of 38°C developed. She quit the medication on her own judgment.

				5 days after discontinuation: Diarrhoea persisted. She was unable to take meals and therefore unable to develop muscle. 6 days after discontinuation: According to her family member, the patient's consciousness was normal at midnight. Marked cold sweat on hands and feet had been noted since early morning. In the morning, her family member noticed that she was slow to respond, and she was transferred to the hospital by an ambulance. Disturbances in consciousness, decreased blood pressure and hypoxaemia were noted. She was immediately admitted to the hospital. In the afternoon, abdominal CT revealed intestinal perforation. Surgery was performed. Transverse and descending colectomy was performed, and an artificial anus was established. Perforation was noted in the descending colon. Purulent effusion was found in the abdominal cavity. She had shock during the surgery and remained to have postoperative shock. After surgery, whole-body management was continued with artificial ventilation, and her condition improved. She was weaned from artificial ventilation, although surgical wound infection causing an open wound was present. She underwent rehabilitation. Approximately 3 months after discontinuation: Perforative peritonitis remitted.
	Concomitant medications: nifedipine, arotinolol hydrochloride, sennoside, brotizolam, tegafur/uracil, diclofenac sodium, misoprostol, morphine sulfate hydrate, prochlorperazine maleate			

Laboratory Examination

	49 days after administration	6 days after discontinuation	8 days after discontinuation	46 days after discontinuation
WBC (/mm^3)	6200	14700	21400	8200
RBC (×10^4/mm^3)	408	441	427	314
Hemoglobin (g/dL)	12.4	13.1	12.9	10.3
Hematocrit (%)	37.7	39.4	38.9	31.6
PLT (×10^4/mm^3)	35.0	30.9	10.7	38.1
PT (seconds)	-	18.8	-	-
Total protein (g/dL)	7.4	5.1	4.8	-
Albumin (g/dL)	4.4	2.2	2.7	2.9
AST (GOT) (IU/L)	19	33	73	16
ALT (GPT) (IU/L)	7	20	55	11
LDH (IU/L)	197	229	261	167
Al-P (IU/L)	298	377	355	353
γ-GTP (IU/L)	13	22	22	44
Total bilirubin (mg/dL)	0.6	0.7	1.4	0.3
Direct bilirubin (mg/dL)	67	86	86	67
Total cholesterol (mg/dL)	230	52	66	149
BUN (mg/dL)	21.2	46.7	42.3	16.7
Serum creatinine (mg/dL)	0.7	1.9	0.9	0.4
Blood uric acid (mg/dL)	4.6	9.9	8.6	2.7
Na (mEq/L)	143	139	146	136
K (mEq/L)	4.5	5.0	3.4	3.9
Cl (mEq/L)	105	104	104	101

Ca (mEq/L)	-	7.9	7.2	-
CRP (mg/dL)	<0.2	43.0	28.0	<0.2

WBC: White blood cell count, RBC: Red blood cell count, PLT: Platelet, PT: Prothrombin Time, AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), LDH: Lactate dehydrogenase, Al-P: Alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, BUN: Blood urea nitrogen, CRP: C-reactive protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Lung adenocarcinoma (Interstitial pneumonia, hypertension)	250 mg for 15 days	**Gastrointestinal perforation** Medical history: pneumonia Day 1 of administration: The patient started receiving gefitinib. Day 5 of administration: Vomiting and diarrhoea developed, and the patient quit the medication on her own judgment. Day 15 of administration (day of discontinuation): At the time of the follow-up visit, administration of gefitinib was discontinued. The patient received symptomatic therapy but the symptoms did not improve significantly. 13 days after discontinuation: She had no appetite and was admitted to the hospital. She frequently had brown watery stools with abdominal tenderness (2+). 16 days after discontinuation: Abdominal pain developed in the evening. 17 days after discontinuation: Abdominal pain worsened. Muscle guarding also developed. X-ray showed the presence of free gas (+) in the abdominal cavity. Gastroscopy showed no abnormalities. Because the patient did not want to undergo surgery, she received conservative treatment with antibiotics. 18 days after discontinuation: Symptoms slowly remitted. 25 days after administration: The symptoms nearly disappeared, but she had bloody stool (+). Outcome: unknown
	Concomitant medications: codeine phosphate hydrate			

Laboratory Examination

	9 months before administration	8 days after discontinuation	13 days after discontinuation	17 days after discontinuation	21 days after discontinuation	28 days after discontinuation
WBC (/mm^3)	7820	8390	4650	1010	3680	6130
RBC (×10^4/mm^3)	-	400	354	318	333	323
Hemoglobin (g/dL)	12.6	11.3	9.5	8.7	9.1	8.8
Hematocrit (%)	-	33.3	29.4	26.3	27.5	26.8
PLT (×10^4/mm^3)	40.1	32.6	24.4	16.7	28.9	54.2
PT (%)	-	-	-	48.1	56	-
Total protein (g/dL)	8.7	-	5.5	4.9	4.8	6.6
AST (GOT) (IU/L)	24	-	7	7	95	38
ALT (GPT) (IU/L)	15	-	9	4	75	34
LDH (IU/L)	601	-	194	164	206	260

Al-P (IU/L)	-	-	225	137	536	474
γ-GTP (IU/L)	-	-	32	24	204	128
Total bilirubin (mg/dL)	-	-	0.4	0.7	0.7	0.5
Direct bilirubin (mg/dL)	-	-	0.3	0.4	0.5	0.3
BUN (mg/dL)	-	19.9	16.6	15.9	7.2	9.7
Serum creatinine (mg/dL)	-	1.0	0.7	0.7	0.5	0.6
Blood uric acid (mg/dL)	-	9.2	4.3	3.4	2.5	2.1
Na (mEq/L)	-	139	136	135	134	136
K (mEq/L)	-	4.0	3.9	3.9	3.9	5.7
Cl (mEq/L)	-	107	101	97	101	96
CRP (mg/dL)	9.59	-	-	27.96	6.42	3.55

WBC: White blood cell count, RBC: Red blood cell count, PLT: Platelet, PT: Prothrombin Time, AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), LDH: Lactate dehydrogenase, Al-P: Alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, BUN: Blood urea nitrogen, CRP: C-reactive protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 80s	Lung adenocarcinoma (Metastases to brain, metastases to bone, cellulitis of leg)	250 mg for 161 days	**Stevens-Johnson syndrome** Medical history: osteoporosis Day 1 of administration: Administration of gefitinib was initiated. Day 153 of administration: White blood cell count 10400/mm^3, CRP 14.8 mg/dL, body temperature 36.4°C. Treatment with ampicillin sodium/cloxacillin sodium hydrate (2 g/day) was initiated for cellulitis. Day 158 of administration: Rash appeared on the face and body. Maceration of the lip and scab attachment were noted, and multiple target-type erythema with no itching appeared on the body trunk and extremities, including the face. Drug eruption was suspected, and administration of ampicillin sodium/cloxacillin sodium hydrate was discontinued. Day 160 of administration: Oral administration of prednisolone (50 mg/day) was initiated. Pyrexia and bulbar conjunctival hyperaemia were also noted, and rash was accompanied by blisters and erosion. Based on these findings, the patient was diagnosed with Stevens-Johnson syndrome. Day 161 of administration (day of discontinuation): Administration of gefitinib and phenobarbital were discontinued. Oral treatment was continued only with prednisolone and famotidine. 1 day after discontinuation: Steroid pulse therapy (methylprednisolone sodium succinate 1000 mg/day × 3 days) was initiated. An ointment containing dimethyl isopropylazulene was used for whole-body treatment. Cefazolin sodium hydrate (2 g/day) was administered. 4 days after discontinuation:

				Albumin was decreased, and the area of erosions accounted for more than 30% of the whole area. The patient was diagnosed with Lyell syndrome. Administration of steroid was discontinued. Human normal immunoglobulin and albumin were administered. Cefazolin sodium hydrate was switched to meropenem hydrate. 6 days after discontinuation: Platelet count decreased. Gabexate mesilate (1000 mg/day) was administered. 11 days after discontinuation: Administration of human normal immunoglobulin was discontinued. 14 days after discontinuation: Gabexate mesilate was switched to dalteparin sodium (2500 units/day). The patient was transferred to the internal medicine ward. 16 days after discontinuation: Chest X-ray also showed pleural effusion. Despite treatment with a diuretic and other drugs, respiratory failure suddenly occurred, and the patient died.
	Concomitant medications: phenobarbital, ampicillin sodium/cloxacillin sodium hydrate, ursodeoxycholic acid, famotidine, hochuekkito, sodium risedronate hydrate, alfacalcidol, heparinoid, alprostadil alfadex			

Laboratory Examination

	Day 153 of administration
Body temperature (°C)	36.4
WBC (/mm^3)	10400
CRP (mg/dL)	14.8

WBC: White blood cell count, CRP: C-reactive protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 80s	Non-small cell lung cancer (Prostate cancer, renal cell carcinoma)	250 mg for 13 days	**Hepatic failure** Medical history: old myocardial infarction Approximately 8 months before administration: The patient was diagnosed with non-small cell lung cancer. Radiotherapy of the chest was performed (total dose, 66 Gy; continued until approximately 6 months before administration). Approximately 6 months before administration: Chemotherapy with carboplatin and paclitaxel was initiated (2 cycles in total). Approximately 3 months before administration: Chemotherapy with gemcitabine hydrochloride alone was initiated (2 cycles in total). Day 1 of administration: Administration of gefitinib was started. Day 4 of administration: Gastrointestinal symptoms (impaired appetite, diarrhoea) occurred. Day 13 of administration: Fluid replacement was initiated due to worsening of impaired appetite. Day 14 of administration (day of discontinuation): Hepatic failure occurred. Steroid infusion was administered for general malaise and pain. Administration of gefitinib was discontinued.

				1 day after discontinuation: Disturbance in consciousness, hepatic failure and multi-organ failure was noted. Ulinastatin, gabexate mesilate, a steroid and platelet transfusion were administered. 2 days after discontinuation: The patient died. Cause of death: Acute hepatic failure was suspected. Autopsy was not performed.
	Concomitant medications: carbocisteine, ambroxol hydrochloride, tranexamic acid, prednisolone, naproxen, roxatidine acetate hydrochloride, bifidobacterium, albumin tannate, isosorbide dinitrate, pravastatin sodium, ferrous fumarate, digoxin			

Laboratory Examination

	1 day before administration	Day 3 of administration	Day 6 of administration	On day 9 of administration	Day 13 of administration	1 day after discontinuation
WBC (/mm^3)	14000	14300	12800	14600	19500	13600
RBC ($\times10^4$/mm^3)	312	295	279	299	339	367
Hemoglobin (g/dL)	9.2	8.8	8.3	8.9	10.0	10.9
Hematocrit (%)	29.6	27.9	26.3	28	32.0	33.1
PLT ($\times10^4$/mm^3)	14.9	13.1	13.6	14.2	13.7	1.3
Total protein (g/dL)	5.4	-	5.0	-	5.4	-
AST (GOT) (IU/L)	87	66	72	67	74	370
ALT (GPT) (IU/L)	95	71	78	83	102	192
LDH (IU/L)	1252	908	1285	955	1049	3480
Al-P (IU/L)	973	1065	1120	1435	2074	1769
γ-GTP (IU/L)	349	362	367	452	636	549
Total bilirubin (mg/dL)	1.1	0.9	1.0	1.4	-	12.4
Serum creatinine (mg/dL)	0.6	0.7	0.7	0.8	0.8	1.6
BUN (mg/dL)	16.4	21.2	20.8	25.5	33.9	64.9
Na (mEq/L)	140.9	138.3	138.9	138.6	138.0	132.1
K (mEq/L)	4.9	5.2	5.2	4.8	5.1	6.5
Cl (mEq/L)	104.3	105.0	102.6	102.0	101.1	97.8
Ca (mEq/L)	9.4	-	-	-	-	10.9
CRP (mg/dL)	13.17	12.2	12.5	10.0	11.44	11.31

WBC: White blood cell count, RBC: Red blood cell count, PLT: Platelet, AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), LDH: Lactate dehydrogenase, Al-P: Alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, BUN: Blood urea nitrogen, CRP: C-reactive protein

4 Goserelin Acetate

(1) Goserelin Acetate (1.8 mg)

Brand Name (name of company)	Zoladex 1.8 mg depot (AstraZeneca K.K.)
Therapeutic Category	Hormones-Miscellaneous
Indications	Endometriosis

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Thromboembolism: Thromboembolism such as myocardial infarction, cerebral infarction, venous thrombosis, and pulmonary embolism may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as, discontinuing administration of the drug should be taken.

(2) Goserelin Acetate (3.6 mg)

Brand Name (name of company)	Zoladex 3.6 mg depot (AstraZeneca K.K.)
Therapeutic Category	Hormones-Miscellaneous
Indications	Prostate cancer Premenopausal breast cancer

≪PRECAUTIONS (underlined parts arerevised)≫

[Adverse Reactions (clinically significant adverse reactions)]

<Prostate cancer>

Cardiac failure: Cardiac failure may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

Thromboembolism: Thromboembolism such as myocardial infarction, cerebral infarction, venous thrombosis, and pulmonary embolism may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

<Premenopausal breast cancer>

Thromboembolism: Thromboembolism such as myocardial infarction, cerebral infarction, venous thrombosis and pulmonary embolism may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

(3) Goserelin Acetate (10.8 mg)

Brand Name (name of company)	Zoladex LA 10.8 mg depot (AstraZeneca K.K.)
Therapeutic Category	Hormones-Miscellaneous
Indications	Prostate cancer

≪PRECAUTIONS (underlined parts arerevised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Cardiac failure: Cardiac failure may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Thromboembolism: Thromboembolism such as myocardial infarction, cerebral infarction, venous thrombosis, and pulmonary embolism may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to July 28, 2010)

(For men)

- Cardiac failure: 1 case (no fatal cases)
- Myocardial infarction: 1 case (no fatal cases)

The number of patients prescribed this drug per year estimated by MAH:
Approximately 89,000 (2009)

Marketed in Japan in: September 1991 (3.6 mg)
October 2000 (1.8 mg)
April 2002 (10.8 mg)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Prostate cancer (Metastases to bone, old myocardial infarction)	3.6 mg/ 4 weeks administered once	**Cardiac failure** Date unknown: The patient had pain in the left buttock for a year. 50 days before administration: The patient visited the department of orthopedics of the hospital. He was admitted to the hospital due to a metastatic bone tumor. He was diagnosed with prostate cancer based on detailed examination. 13 days before administration: Administration of bicalutamide was initiated for prostate cancer. Day 1 of administration: Administration of goserelin acetate was started. 18 days after administration: Occasional difficulty in breathing developed. 21 days after administration: Administration of tegafur/uracil was initiated. 29 days after administration: Chest X-ray was performed due to marked lower leg oedema. Cardiothoracic ratio (CTR) was 65%, and he was admitted to the hospital for cardiac failure. After admission, atrial fibrillation (Af) occurred and deslanoside (0.4 mg, iv) and furosemide injection was administered. Administration of goserelin acetate, bicalutamide and tegafur/uracil were discontinued. 31 days after administration: The patient had ventricular fibrillation (Vf) and lost consciousness. He received direct-current (DC) shock 5 times. He also received lidocaine hydrochloride (50 mg, 2 times), verapamil hydrochloride (5 mg), sodium bicarbonate injection and midazolam injection while being intubated. Then, the Vf turned into Af, and his condition became stable. He was extubated in the early evening. Amiodarone hydrochloride (800 mg) and mexiletine hydrochloride (div) were administered. 32 days after administration: Amiodarone hydrochloride (400 mg) was administered. 36 days after administration: Echocardiography showed left ventricular ejection fraction (LVEF) of 15% and finding of diffuse left ventricular hypokinesia. 37 days after administration: Cardiac failure improved to NYHA III, but Vf was present. 39 days after administration: Ventricular tachycardia (VT) occurred, and administration of mexiletine hydrochloride was resumed. Cardiac failure had not resolved.
	Concomitant medications: bicalutamide (suspected drug), tegafur/uracil (suspected drug), magnesium oxide			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Prostate cancer (Cholelithiasis, hypertension)	10.8 mg/ 12 weeks continued	**Myocardial infarction** 5 years before administration: The patient underwent varicose vein operation. 48 days before administration: A definitive diagnosis of prostate cancer was made. 42 days before administration: Administration of chlormadinone acetate was initiated. Day 1 of administration: Administration of goserelin acetate was started. 23 days after administration: The patient lost consciousness at home. Myocardial infarction developed. He was transferred to another hospital. He was admitted to the hospital for treatment. His condition improved with medical treatment. 42 days after administration: He was temporarily discharged from the hospital. 43 days after administration: Administration of chlormadinone acetate was discontinued. Approximately 1 and a half months after administration: He was admitted to the hospital again. Coronary artery bypass was performed. Approximately 2 months after administration: Administration of aspirin 100 mg/day, nicorandil 3 tablets/day and nitroglycerin 25 mg 1 sheet/day was initiated for myocardial infarction. His postoperative course was favorable, and he was discharged from the hospital. Approximately 2 and a half months after administration: The second administration of goserelin acetate was performed. Approximately 5 and a half months after administration: Administration of amlodipine besilate 5 mg/day and furosemide 20 mg/day was initiated for myocardial infarction. Goserelin acetate was administered for a third time. Approximately 8 and a half months after administration: Investigation showed no abnormalities, and he was followed at a nearby hospital. Approximately 9 and a half months after administration: The patient recovered from myocardial infarction.
	Concomitant medications: chlormadinone acetate (suspected drug), naftopidil			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Prostate cancer (Hyperphosphataemia, urinary incontinence)	10.8 mg/ 12 weeks continued	**Cerebral infarction** 8 months before administration: The patient was diagnosed with prostate cancer. 6 months before administration: Administration of bicalutamide 80 mg/day was initiated. 4 months before administration: Administration of propiverine hydrochloride was initiated at 10 mg/day. Day 1 of administration: Administration of goserelin acetate was started.

				Approximately 2 weeks after administration: The dose of propiverine hydrochloride was changed to 30 mg/day. 3 months after administration: Administration of imipramine hydrochloride was initiated at 25 mg/day. Approximately 4 months after administration: Gait disturbance developed. Brain CT showed multiple cerebral infarctions, and the patient was diagnosed with arteriosclerotic Parkinson's disease. Amantadine hydrochloride 100 mg/day was administered. Approximately 5 months after administration: Symptoms did not remit, and the patient was transferred to the department of neurology of another hospital. Approximately 6 months after administration: Multiple cerebral infarction and Parkinson's disease remitted.
	Concomitant medications: bicalutamide (suspected drug), propiverine hydrochloride (suspected drug), imipramine hydrochloride (suspected drug)			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 70s	Prostate cancer (None)	3.6 mg/ 4 weeks for 33 months	**Pulmonary thrombosis** Before administration: The patient developed lower back pain. He visited a nearby hospital, where chest abnormal opacity was noticed, and he was referred to this hospital. The patient was diagnosed with prostate cancer was, and osaterone acetate[1)] 2.5 mg/day was administered for 16 weeks. Day 1 of administration: Administration of goserelin acetate and chlormadinone acetate 100 mg/day was initiated. 2 years and 9 months after administration: He experienced a sudden onset of chest pain and dyspnoea and was transferred to an emergency and critical care center. Upon arrival, decreased blood pressure and hypoxaemia were noted, and chest X-ray showed increased CTR and marked dilatation of bilateral pulmonary arteries. The patient was admitted to ICU and received intensive care, but died 4 hours after arrival. Autopsy showed a mold-shaped thrombosis in the main trunk of the bilateral pulmonary arteries and his death was found to have been caused by pulmonary thrombosis.
	Concomitant medications: chlormadinone acetate (suspected drug)			

Osaterone acetate[1)] :unapproved in Japan

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Male 70s	Prostate cancer (Hypertension)	3.6 mg/ 4 weeks continued	**Pulmonary infarction** The patient had pulmonary tuberculosis and a drug allergy. Before administration: The patient was diagnosed with prostate cancer based on biopsy.

				Administration of fosfestrol[2)] was initiated for treatment of prostate cancer. Administration of fosfestrol was discontinued. Administration of chlormadinone acetate was initiated. Day 1 of administration: Administration of goserelin acetate was started for treatment of prostate cancer. 7 months after administration: Pulmonary infarction developed. The patient had no symptoms, but a chest X-ray showed dilatation of the pulmonary artery, and he was admitted to the hospital. Lung perfusion scintigraphy showed a shadow defect. TAT (thrombin-antithrombin III complex) was elevated to 8.2. Administration of goserelin acetate was continued. Administration of chlormadinone acetate was discontinued one day after the onset of pulmonary infarction. Administration of flutamide was initiated. Date unknown: Since he had no symptoms or signs, such as hypoxaemia, fibrinolytic therapy was not performed, and he was just followed on an outpatient basis. 8 months after administration: No change occurred.
	Concomitant medications: chlormadinone acetate (suspected drug), flutamide			

Fosfestrol[2)]: marketing discontinued

5 Solifenacin Succinate

Brand Name (name of company)	Vesicare Tablets 2.5 mg, 5 mg (Astellas Pharma Inc.)
Therapeutic Category	Urogenital and anal organ agents - Miscellaneous
Indications	Overactive bladder with symptoms of micturition urgency, pollakiuria, and urge incontinence

≪PRECAUTIONS (underlined parts arerevised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Prolonged QT, ventricular tachycardia, atrioventricular block, sick sinus syndrome, severe bradycardia: Prolonged QT, ventricular tachycardia (including torsades de pointes), atrioventricular block, sick sinus syndrome, severe bradycardia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to August 30, 2010)

- Prolonged QT: 2 cases (no fatal cases)
- Ventricular tachycardia: 2 cases (no fatal cases)
- Atrioventricular block: 1 case (no fatal cases)
- Sick sinus syndrome: 1 case (no fatal cases)
- Bradycardia: 3 cases (no fatal cases)

The number of patients prescribed this drug per year estimated by MAH:
Approximately 870,000 (FY 2009)

Marketed in Japan in: June 2006

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 90s	Neurogenic bladder, overactive bladder (Hypertension, oedema)	2.5 mg for 15 days ↓ 5 mg for 42 days	**Complete atrioventricular block** 43 days before administration: The patient visited Hospital A. Administration of gentamicin sulfate and an antibacterial was initiated for vulvitis. (administered for 4 days) 41 days before administration: She visited Hospital B for the first time at the request of herself and her family member. Day 1 of administration: Blood pressure was 130/80 mmHg. Propiverine hydrochloride was switched to solifenacin succinate 2.5 mg. Thereafter, she visited Hospital B every two weeks. Day 16 of administration: The dose of solifenacin succinate was increased to 5 mg at the request of herself and her family member. Day 43 of administration: Administration of candesartan cilexetil 8 mg and ubidecarenone 30 mg was initiated because blood pressure of 160/80 mmHg and oedema were noted. Day 55 of administration: She experienced abdominal pain around this time. Day 56 of administration: She visited Hospital B, and was found to have no problems. Day 57 of administration (day of discontinuation): Tachypnoea and decreased level of consciousness were observed in the morning. The patient visited Hospital B in the afternoon. At the time of visit, arrhythmia (no ECG record) and hand tremor were noted, with Japan Coma Scale (JCS)-III 200 and pulse rate 30-40/min. Within 10-20 minutes, she became unconscious, and she was transferred to Hospital C by an ambulance 55 minutes after the visit. Electrocardiogram: Complete atrioventricular block Blood test: Decreased hepatic and renal function were noted, and the patient was diagnosed with acute circulatory failure. Chest X-ray: Marked pleural effusion and pulmonary congestion were noted. Brain CT: No abnormalities. Blood pressure 160/90 mmHg. JCS slightly improved. Because she refused pacemaker implantation, she was admitted to the hospital for detailed examination and additional treatment. She was admitted to the cardiovascular medicine of Hospital C 1 hour and 45 minutes after the visit. Electrocardiogram showed repeated episodes of ventricular tachycardia and sinus arrest approximately 3 hours and 30 minutes after the visit. Sinus arrest occurred 4 hours after the visit. Death was confirmed 4 hours and 10 minutes after the visit. Cause of death: complete atrioventricular block. She had no concurrent ischaemic heart disease or diabetes mellitus. Both Hospital A and Hospital B had no ECG record and chest

				X-ray images. Arrhythmia was noticed at another hospital that she had visited before visiting Hospital A, but arrhythmia and cardiac murmur, etc. were not noted at Hospital B.
	Concomitant medications: candesartan cilexetil, ubidecarenone			

Laboratory Examination

	Day 1 of administration	Day 43 of administration	Day 57 of administration (day of discontinuation)
AST (GOT) (IU/L)	-	19	65
ALT (GPT) (IU/L)	-	9	65
Al-P (IU/L)	-	185	-
LDH (IU/L)	-	210	580
CK (CPK) (IU/L)	-	-	651
BUN (mg/dL)	-	15.9	105.2
Creatinine (mg/dL)	-	0.72	1.82
CRP (mg/dL)	-	-	0.64
Na (mEq/L)	-	148	154
K (mEq/L)	-	3.2	4.4
Cl (mEq/L)	-	108	124
Systolic blood pressure (mmHg)	130	160	160
Diastolic blood pressure (mmHg)	80	80	90
Pulse rate (/min)	-	-	30-40

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), Al-P: Alkaline phosphatase, LDH: Lactate dehydrogenase, CK (CPK): Creatine kinase (Creatine phosphokinase), BUN: Blood urea nitrogen, CRP: C-reactive protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Overactive bladder (Hypertension, sequelae of cerebral infarction)	5 mg for 27 days	**Sick sinus syndrome** Approximately 7 years before administration: The patient experienced sinus bradyarrhythmia with a minimum heart rate of 31/min when he had orally taken diltiazem hydrochloride. 10 days before administration: Administration of doxazosin mesilate and telmisartan was initiated. Blood pressure 192/116 mmHg, pulse rate 59/min. Day 1 of administration: The patient visited the outpatient department in the morning. Blood pressure 114/80 mmHg. He complained of a tense feeling of the shoulder, staggering gait, unstable home blood pressure and pollakiuria with a frequency of urination of 3 to 4 times during the night. Administration of solifenacin succinate was started at 5 mg. Day 15 of administration: The patient visited the outpatient department in the morning. Blood pressure 136/68 mmHg. He complained of shoulder muscle stiffness and heart rate of 30/min level, which was occasionally noted while measuring home blood pressure. He was instructed to visit this hospital as

				needed because a follow-up observation was considered appropriate, and returned home. Day 22 of administration: He experienced shortness of breath, yawning and a staggering gait from around this time. Day 27 of administration (day of discontinuation): The patient visited the outpatient department in the morning. Blood pressure 110/74 mmHg, SpO_2 97%. He told that he had experienced severe shortness of breath for the last 4 to 5 days and was unable to walk to the house of his child in his neighborhood. Chest X-ray showed no abnormalities. Electrocardiogram showed bradycardia of 35/min. A referral letter was prepared. He visited the department of cardiology medicine of another hospital in the early evening. Administration of solifenacin succinate was withdrawn. 2 days after discontinuation: Holter monitoring showed sinus arrest for 5.5 seconds. 6 days after discontinuation: He was admitted to the department of cardiology medicine of another hospital. Electrocardiogram monitoring showed sinus arrest for 7 seconds or longer and faintness. The patient was diagnosed with sick sinus syndrome. 7 days after discontinuation: DDD pacemaker implantation was performed. 10 days after discontinuation: He was discharged from the hospital. 15 days after discontinuation: He recovered.
	Concomitant medications: telmisartan, aspirin, doxazosin mesilate			

Laboratory Examination

	10 days before administration	Day 1 of administration	Day 15 of administration	Day 27 of administration
Systolic blood pressure (mmHg)	192	114	136	110
Diastolic blood pressure (mmHg)	116	80	68	74
Heart rate (/min)	-	-	30 level	35
Pulse rate (/min)	59	-	-	-
SpO_2 (%)	-	-	-	97

SpO_2: Oxygen saturation

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 80s	Overactive bladder (Atrial fibrillation, chronic cardiac failure, hypertension, prostate cancer, hepatic	2.5 mg for 415 days	**Polymorphic ventricular tachycardia, drug-induced long QT syndrome** Day 1 of administration: The patient started receiving solifenacin succinate at 2.5 mg. Date unknown: Administration of azosemide was initiated at 60 mg. Date unknown: Drug-induced long QT syndrome developed. Day 411 of administration: The patient was referred and admitted to this hospital from another hospital due to abnormal electrocardiogram findings

		function disorder)		including prolonged QT and negative T wave. Findings at admission: RR interval, irregular; PR interval, atrial fibrillation; QRS interval 102 msec; QTc interval 527 msec; heart rate 91-99/min; AST (GOT) 115 IU/L; ALT (GPT) 53 IU/L; LDH 217 IU/L; CRP 2.77 mg/dL; K 3.0 mEq/L. Hepatic disorder was noted at the time of admission. Inflammatory reaction was also noted, and drip infusion of sulbactam sodium/ampicillin sodium was initiated for bronchopneumonia. Day 412 of administration: Blood test at admission showed hypokalaemia. Oral administration of spironolactone was initiated, and correction was started. Day 414 of administration: RR interval, irregular; PR interval, atrial fibrillation; QRS interval 104 msec; QTc interval 535 msec; heart rate 80-90/min. Day 415 of administration (day of discontinuation): He lost consciousness in the morning. Respiratory arrest occurred, but he recovered spontaneously with artificial ventilation. Approximately 20 minutes later, RR interval 880 msec; PR interval 218 msec; QRS interval 110 msec; QTc interval 567 msec; heart rate 68/min. CRP 1.30 mg/dL, K 3.0 mEq/L. Approximately an hour later, polymorphic ventricular tachycardia was detected by electrocardiogram monitoring. It stopped spontaneously. Approximately 1 hour and 10 minutes later, K 3.3 mEq/L. 1 hour and 25 minutes later, loss of consciousness and convulsion occurred again. He spontaneously recovered with cardiac massage. 2 hours and 50 minutes later, he was admitted to the intensive care unit (ICU). Two episodes and one episode of polymorphic ventricular tachycardia occurred during emergency coronary angiography and after return to the ICU, respectively. Polymorphic ventricular tachycardia occurred at a frequent interval of once every 30 minutes in the evening from around this time. Approximately 10 minutes later, the first DC shock was performed. Administration of all the oral medications, including solifenacin succinate, was temporarily discontinued. 1 day after discontinuation: Polymorphic ventricular tachycardia occurred at a more frequent interval of once every 10 minutes in the very early morning. He repeatedly lost consciousness and DC shocks were repeated. In the early morning, K was corrected to 4.2 mEq/L with treatment. From early to late morning, the frequency of polymorphic ventricular tachycardia and persistent ventricular tachycardia decreased to approximately once every 2 hours. In the early morning, RR interval 1032 msec; PR interval 226 msec; QRS interval 102 msec; QTc interval 515 msec; heart rate 58/min. In the early evening, RR interval 1032 msec; PR interval 228 msec; QRS interval 98 msec; QTc interval 523 msec; heart rate 58/min.

				During the clinical course shown above, approximately 50 episodes of persistent ventricular tachycardia occurred, 17 of which required DC shocks. Polymorphic ventricular tachycardia disappeared, but prolonged QT persisted. (Polymorphic ventricular tachycardia resolved.) QT was gradually shortened after the washout of solifenacin succinate. 7 days after discontinuation: RR interval 1148 msec; PR interval 208 msec; QRS interval 94 msec; QTc interval 403 msec; heart rate 52/min. 18 days after discontinuation: AST (GOT) 48 IU/L; ALT (GPT) 39 IU/L; LDH 190 IU/L; CRP 0.37 mg/dL. 21 days after discontinuation: Electrocardiogram showed normalization of prolonged QT. (Drug-induced long QT syndrome resolved.) RR interval 996 msec; PR interval 216 msec; QRS interval 88 msec; QTc interval 421 msec;, heart rate 59/min. 22 days after discontinuation: He was discharged from the hospital. Hepatic disorder improved at the time of discharge.
	Concomitant medications: azosemide, ethinylestradiol, silodosin, aspirin, allopurinol, magnesium oxide, kallidinogenase, azulen sodium sulfonate hydrate/L-glutamine, combination drug containing pancreatic digestive enzyme, *Clostridium butyricum* preparation, spironolactone, sulbactam sodium/ampicillin sodium, leuprorelin acetate			

Laboratory Examination

	Day 1 of administration	Day 393 of administration	Day 411 of administration	Day 414 of administration	Day 415 of administration (day of discontinuation)	1 day after discontinuation		7 days after discontinuation	18 days after discontinuation	21 days after discontinuation
						Early morning	Early evening			
AST (GOT) (IU/L)	23	47	115	-	125	-	-	-	48	-
ALT (GPT) (IU/L)	11	32	53	-	72	-	-	-	39	-
LDH (IU/L)	215	158	217	-	209	-	-	-	190	-
Serum K (mEq/L)	-	4.2	3.0	-	3.0	4.2	-	-	4.7	-
CRP (mg/dL)	-	-	2.77	-	1.30	-	-	-	0.37	-
Pulse rate (/min)	-	-	98	-	64	62	-	-	60	-
RR interval (msec)	-	-	-	-	880	1032	1032	1148	-	996
PR interval (msec)	-	-	-	-	218	226	228	208	-	216
QRS interval (msec)	-	-	102	104	110	102	98	94	-	88
QTc interval (msec)	-	-	527	535	567	515	523	403	-	421
Heart rate (/min)	-	-	91-99	80-90	68	58	58	52	-	59

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), LDH: Lactate dehydrogenase, CRP: C-reactive protein

6 Bicalutamide, Flutamide

Brand Name (name of company)	**Bicalutamide** Casodex Tablet 80 mg (AstraZeneca K.K.) **Flutamide** Odyne Tab. 125 mg (Nippon Kayaku Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Prostate cancer

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Cardiac failure, myocardial infarction: Cardiac failure or myocardial infarction may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to July 28, 2010)

- Cardiac failure: 2 cases (no fatal cases)

The number of patients prescribed these drugs for a year estimated by MAHs:
For bicalutamide, approximately 114,000 (2009)
For flutamide, approximately 20,000 (2009)

Marketed in Japan in: December 1994 (flutamide)
May 1999 (bicalutamide)

Case Summary
< Bicalutamide >

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Prostate cancer (None)	80 mg for approx. 10 months	**Cardiac failure** Day 1 of administration: The patient started receiving bicalutamide for treatment of prostate cancer. Approximately month 9 of administration: Wheezing developed at night. Although dextromethorphan hydrobromide hydrate and theophylline were prescribed by another hospital, the patient did not recover. Approximately month 10of administration: On 23 days after onset, cardiac failure was suspected, and echocardiography was performed. Diffuse left cardiac function decreased (EF 30%). On 26 days after onset, he was admitted to the hospital with diagnoses of congestive cardiac failure and cardiac asthma. His general conditions gradually improved with symptomatic therapy for cardiac failure. During the course, non-persistent ventricular tachycardia occasionally occurred, but did not relapse after concomitant administration of mexiletine hydrochloride 300 mg/day (started on 28 days after onset). (Day of discontinuation): On 29 days after onset, administration of bicalutamide was discontinued. 10 days after discontinuation: His general conditions improved. According to the New York

				Heart Association (NYHA) classification, his Stages of Heart Failure improved from IV to II. Chest X-ray showed decreased CTR and the disappearance of pulmonary congestion and pleural effusion. Weight decreased from 66 kg to 61 kg. However, echocardiogram showed no improvement with EF of 30%. 21 days after discontinuation: Congestive cardiac failure remitted.
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 90s	Prostate cancer (Constipation, gastric ulcer)	80 mg for 109 days	**Myocardial infarction** Day 1 of administration: The patient started receiving goserelin acetate 3.6 mg and bicalutamide for treatment of prostate cancer. Approximately month 3.5of administration: Disturbance in consciousness suddenly developed. The patient's consciousness recovered in a few minutes, but he was urgently transferred to the hospital. Upon arrival, he had sense of oppression in the chest, and electrocardiogram showed elevated ST in II, III and aVf. Myocardial infarction was suspected, and he was admitted to ICU. After admission, bradycardia, decreased blood pressure and atrioventricular block were noted. Cardiac catheterization was performed, and a stent was implanted. Thereafter, he had a favorable course. He was discharged from the hospital on 6 days after onset. Myocardial infarction remitted.
	Concomitant medications: goserelin acetate, famotidine, magnesium oxide			

7 Pemetrexed Sodium Hydrate

Brand Name (name of company)	Alimta Injection 100mg, 500mg (Eli Lilly Japan K.K.)
Therapeutic Category	Antimetabolites
Indications	Malignant pleural mesothelioma, advanced or recurrent non-small cell lung cancer which is unresectable

≪PRECAUTIONS (underlined parts arerevised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Infection: Serious infections including sepsis and pneumonia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome): Serious skin disorders such as toxic epidermal necrolysis or oculomucocutaneous syndrome may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to May 31, 2010)

- Infectious disease: 35 cases (3 fatal cases)
- Oculomucocutaneous syndrome (Stevens-Johnson syndrome): 2 cases (no fatal cases)

The number of patients prescribed this drug per year estimated by MAH:
Approximately 20,000 (September 2009 to August 2010)

Marketed in Japan in: January 2007

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Malignant pleural mesothelioma (Metastases to lymph nodes, pleural effusion, asbestosis, interstitial lung disease, chronic obstructive pulmonary disease)	940 mg in every five weeks for 2 courses	**Infection (pneumonia)** [Medical history] smoking history (40 cigarettes/day for 20 years), history of asbestos exposure 8 days before administration: The patient started receiving folic acid preparation. 7 days before administration: Administration of a vitamin B_{12} preparation was initiated. 3 days before administration: Auscultation: Abnormality was found. 1 day before administration: SpO_2 97%, and finding of interstitial lung disease was present before administration of pemetrexed sodium hydrate. Day 1 of administration: PS: 1. Administration of pemetrexed sodium hydrate 940 mg/body and cisplatin 140 mg/body was initiated. 12 days after first administration: Bacterial pleurisy developed. The patient had pyrexia (38.0°C). X-ray and CT showed an increased pleural effusion. Despite administration of an antibiotic, the symptom did not remit (cefozopran hydrochloride 4 g/day for 16 days). 15 days after first administration: Left thoracic cavity drainage (paracentesis drainage) was performed. The type of pleural effusion was a bloody pleural effusion with predominant neutrophils. Pyrexia gradually remitted after drainage. 26 days after first administration: The drain tube was removed. 34 days after first administration: The patient recovered from bacterial pleurisy. 36 days after first administration: Pemetrexed sodium hydrate and cisplatin were administered (second course). 47 days after first administration (day of onset): Pneumonia developed. He had pyrexia (38.0°C). 49 days after first administration (2 days after onset): An X-ray showed concurrent right pneumonia. He gradually improved with administration of antibiotics (cefozopran hydrochloride 2 g/day for 4 days followed by 4 g/day for 7 days, prulifloxacin 400 mg/day for 11 days). 66 days after first administration (19 days after onset): The patient recovered from pneumonia. Administration of antibiotics was discontinued. Administration of pemetrexed sodium hydrate was continued.
	Concomitant medications: cisplatin (suspected drug), retinol/calciferol, mecobalamin, loxoprofen sodium, rebamipide, tiotropium bromide hydrate, rilmazafone hydrochloride hydrate			

Laboratory Examination

	1 day before administration	12 days after administration	47 days after administration (day of onset)	49 days after administration (2 days after onset)	67 days after administration (20 days after onset)	70 days after administration (23 days after onset)
Body temperature (°C)	36.3	38.0	38.0	-	-	36.7
WBC (/mm^3)	6900	-	-	9300	-	10900
Neutrophil count (/mm^3)	4400	-	-	7700	-	8900
CRP (mg/dL)	2.36	-	-	16.25	4.21	-
SpO_2 (%)	97	-	-	-	-	-

WBC: White blood cell count, CRP: C-reactive protein, SpO_2: Oxygen saturation

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Recurrent large cell lung cancer (Metastases to liver, to lung, to central nervous system, and to lymph nodes, pleural effusion, chronic obstructive pulmonary disease)	810 mg administered once	**Infection (carinii pneumonia)** [Medical history] gastric ulcer, smoking history (14 cigarettes/day for 40 years) 191 days before administration: The patient underwent left S6 pulmonary segmentectomy, and partial resection of the upper lobe and lymph node excision were performed. He was diagnosed with large cell lung cancer (Stage IV) based on histological examination. Slight pleural effusion was present. Intrapulmonary metastasis, metastasis to brain and metastases to mediastinal lymph nodes were confirmed. 155 days before administration: After surgery, 4 courses of chemotherapy (paclitaxel + carboplatin) were performed. 37 days before administration: Gamma knife surgery was performed for metastasis to the brain. 21 days before administration: Gamma knife surgery was performed for metastasis to the brain. Then, administration of prednisolone was initiated at 20 mg. 14 days before administration: Chest X-ray and CT: No abnormalities were found in the lung field. 7 days before administration: Administration of a folic acid preparation and vitamin B_{12} preparation was initiated. Day 1 of administration: Monotherapy of pemetrexed sodium hydrate was initiated at 500 mg/m^2 (810 mg/body) for postoperative recurrence of S6 lung cancer. PS was 0-1 before administration of pemetrexed sodium hydrate. 2 days after administration: Blood sodium decreased. 6 days after administration: Chest X-ray: No abnormalities were found in the lung field. 8 days after administration: Lymphocytes, white blood cell, and platelets decreased.

				10 days before administration: Administration of ceftazidime hydrate was initiated for pyrexia of 38°C range (for 7 days). SpO_2 94% (room air). Chest X-ray: No abnormalities were found in the lung field. Pleural effusion was noted. 11 days after administration (day of onset): Administration of oxygen was initiated at 2 L/min for decreased SpO_2 of 89%. Blood culture: negative. 12 days after administration (1 day after onset): SpO_2 94% (O_2 5 L/min). Thereafter, the patient's respiratory status worsened with SpO_2 of 85% (O_2 10 L/min). Chest X-ray and CT: Extensive infiltrates were found in the right lung. Metastasis to liver were confirmed. Administration of methylprednisolone was initiated at 500 mg for 3 days. KL-6 486 U/mL; SP-D 89.1 ng/mL. Administration of sulfamethoxazole/trimethoprim 9 g/day was initiated due to elevated β-D glucan of 3630 pg/mL. 13 days after administration (2 days after onset): Chest X-ray: Abnormalities were found. Opacity distribution: right lung. SpO_2 ranged 80-90% (O_2 18 L/min) and did not improve. 15 days after administration (4 days after onset): Administration of methylprednisolone 80 mg/day was continued. Pentamidine isetionate was administered for 2 days. 16 days after administration (5 days after onset): He died. This patient was clinically diagnosed with carinii pneumonia based on an elevated β-D glucan and unresponsiveness to steroids.
	Concomitant medications: cyanocobalamin, retinol/calciferol, prednisolone, dexamethasone sodium phosphate, etodolac, lansoprazole			

Laboratory Examination

	Day 1 of administration	2 days after administration	8 days after administration	11 days after administration (day of onset)	12 days after administration (1 day after onset)	14 days after administration (3 days after onset)
WBC (/mm^3)	7500	9200	2200	-	4600	5700
Neutrophil count (/mm^3)	6075	8188	1885	-	4301	5340
Lymphocyte count (/mm^3)	562	734	244	-	197	159
PLT ($\times 10^4$/mm^3)	16.3	19.1	9.1	-	5.9	6.2
Na (mEq/L)	131	129	121	130	135	145
CRP (mg/dL)	0.3	-	1.1	-	19.7	9.1
β-D-glucan (pg/mL)	-	-	-	-	3630	-
KL-6 (U/mL)	-	-	-	-	486	-
SpO_2 (%)	-	-	-	89	85	-

WBC: White blood cell count, PLT: Platelet, CRP: C-reactive protein, KL-6: Sialylated carbohydrate antigen KL-6, SpO_2: Oxygen saturation

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 70s	Lung adenocarcinoma stage IV (Gastritis, osteoporosis, insomnia)	400 mg/m^2 administered once	**Stevens-Johnson syndrome** 105 days before administration: Sputum cytology revealed adenocarcinoma. The patient was diagnosed with lung adenocarcinoma (T4N3M1, Stage IV). 75 days before administration: First-line chemotherapy (gemcitabine hydrochloride 1000 mg/m^2 + tegafur/gimeracil/oteracil potassium 60 mg/day/2 weeks) was performed. 74 days before administration: Skin eruption (Grade 3) appeared on the body trunk, and treatment was discontinued. 65 days before administration: The first course of second-line chemotherapy (docetaxel hydrate 60 mg/m^2) was performed. Grade 4 neutropenia + pyrexia developed 7 days later. Her condition was improved with administration of cefepime dihydrochloride + filgrastim (genetical recombination). 43 days before administration: The second course of docetaxel hydrate (50 mg/m^2) was administered. Grade 4 decreased neutrophil count and pyrexia developed 8 days later. Her condition was improved with administration of cefepime dihydrochloride + filgrastim (genetical recombination). 7 days before administration: Administration of a folic acid preparation and vitamin B12 preparation was initiated. Day 1 of administration: Administration of pemetrexed sodium hydrate as third-line chemotherapy was initiated at 400 mg/m^2. PS: 2. 4 days after administration (day of onset): She had erythema multiforme and pyrexia. Type of skin eruption: erythema, mucosal lesion. Skin color: vivid red. Morphology of individual rash: 2 to 4 cm in diameter, multiple, with residual healthy skin. Area of onset: whole body. Symptoms: itching, pyrexia. She did not wear any jewelry and did not use any over-the-counter products including herbs and supplements before onset of the event. 6 days after administration (2 days after onset): Epinastine hydrochloride 10 mg/day was administered for erythema (for 18 days). 7 days after administration (3 days after onset): Cefepime dihydrochloride 4 g/day was administered (for 6 days). 10 days after administration (6 days after onset): The patient was diagnosed with Stevens-Johnson syndrome, and she improved with oral prednisolone 30 mg/day for 7 days. DLST, patch test, scratch test, intracutaneous test, rechallenge test, skin biopsy and autoimmune disease screening test were not performed. 19 days after administration (15 days after onset): Stevens-Johnson syndrome remitted. Pyrexia developed, and dyspnoea worsened. Interstitial pneumonia developed.

				52 days after administration (48 days after onset): She died of lung cancer and interstitial pneumonia.
	Concomitant medications: retinol/calciferol, cyanocobalamin, gemcitabine hydrochloride, tegafur/gimeracil/oteracil potassium, docetaxel hydrate, raloxifene hydrochloride, alfacalcidol, teprenone, zolpidem tartrate			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 60s	Large cell lung cancer stage IV (Metastases to liver, to bone, to central nervous system, and to lung)	500 mg/m^2 administered once	**Stevens-Johnson syndrome** Approximately 1 year and 5 months before administration: The patient took first-line chemotherapy (gemcitabine hydrochloride + cisplatin) (for approximately 3 months). Bone marrow depression induced by gemcitabine hydrochloride developed in the same month. Approximately 1 year and 1 month before administration: Second-line chemotherapy (gemcitabine hydrochloride alone) was performed (for approximately 1 year). 25 days before administration: Administration of phenytoin was initiated at 100 mg three times daily. 21 days before administration: Administration of folic acid and vitamin B_{12} formulation was initiated. Day 1 of administration: Third-line chemotherapy with pemetrexed sodium hydrate was initiated at 500 mg/m^2. White blood cell count 3900/mm^3, neutrophils 65%, lymphocytes 17%. 2 days after administration (day of onset): Skin eruption and itching developed mainly in the precordial region. The patient was diagnosed with Stevens-Johnson syndrome. Administration of pemetrexed sodium hydrate was discontinued. [Symptoms] Type of skin eruption: oedematous erythema. Skin color: vivid red. Area of onset: whole body. Symptoms: itching. Morphology of individual rash: myriad, with residual healthy skin. 4 days after administration (2 days after onset): Slightly reticular mild erythema was seen all over the body. Olopatadine hydrochloride 10 mg/day was orally administered (for 10 days). 6 days after administration (4 days after onset): Skin eruption was noted all over the body and enanthema with white necrosis attached on lips and in the mouth were confirmed. Administration of oral prednisolone was initiated at 10 mg/day. 7 days after administration (5 days after onset): Dark red purple erythema was noted on the body trunk, and enanthema in the mouth remained unchanged. The dose of prednisolone was increased to 20 mg/day. 10 days after administration (8 days after onset): Erythema on the body trunk was disappearing. Enanthema in the mouth also substantially improved. The dose of prednisolone was decreased to 10 mg/day. Decreased neutrophil count was noted. White blood cell count 2000/mm^3, neutrophils 24%, lymphocytes 59%.

				13 days after administration (11 days after onset): Erythema on the body trunk and enanthema in the mouth disappeared. The patient recovered from Stevens-Johnson syndrome. The dose of prednisolone was decreased to 5 mg/day (until 4 days later). White blood cell count 18000/mm^3, neutrophils 86%, lymphocytes 6%. Decreased neutrophil count resolved. Pemetrexed sodium hydrate was not readministerd to the patient.
	Concomitant medications: folic acid, cyanocobalamin, cisplatin, phenytoin (suspected drug), ecabet sodium, lafutidine, etizolam, maprotiline hydrochloride, nitrazepam, zolpidem tartrate, tulobuterol, over-the-counter products including herbs and supplements			

8 Leuprorelin Acetate

Brand Name (name of company)	LEUPLIN FOR INJECTION 1.88 (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Hormones-Miscellaneous
Indications	**LEUPLIN FOR INJECTION 1.88** Endometriosis Shrinkage of uterine fibroids in patients with symptoms such as menorrhagia, lower abdominal pain, lower back pain and anaemia, and improvement of these symptoms Central precocious puberty **LEUPLIN FOR INJECTION 3.75** Endometriosis Shrinkage of uterine fibroids in patients with symptoms such as menorrhagia, lower abdominal pain, lower back pain and anaemia, and improvement of these symptoms Premenopausal breast cancer Prostate cancer Central precocious puberty **LEUPLIN FOR INJECTION KIT 1.88** Endometriosis Shrinkage of uterine fibroids in patients with symptoms such as menorrhagia, lower abdominal pain, lower back pain and anaemia, and improvement of these symptoms **LEUPLIN FOR INJECTION KIT 3.75** Endometriosis Shrinkage of uterine fibroids in patients with symptoms such as menorrhagia, lower abdominal pain, lower back pain and anaemia, and improvement of these symptoms Premenopausal breast cancer Prostate cancer **LEUPLIN SR FOR INJECTION KIT 11.25** Prostate cancer Premenopausal breast cancer

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

<For all indications>

Thromboembolism: Thromboembolism such as myocardial infarction, cerebral infarction, venous thrombosis and pulmonary embolism may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

<For postate cancer>
Cardiac failure: Cardiac failure may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to July 28, 2010)
(For men)
- Cardiac failure: 3 cases (no fatal cases)
- Myocardial infarction: 2 cases (no fatal cases)
- Cerebral infarction: 3 cases (no fatal cases)
- Thromboembolism: 2 cases (no fatal cases)

(For women)
- Myocardial infarction: 3 cases (no fatal cases)
- Cerebral infarction: 2 cases (no fatal cases)
- Thromboembolism: 2 cases (no fatal cases)

The number of patients prescribed this drug per year estimated by MAH:
Approximately 336,000 (August 2009 to July 2010)
Marketed in Japan in: September 1992

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Adenomyosis uteri (Anaemia, shortness of breath)	1.88 mg for approx. 1 month*	**Pulmonary embolism, acute myocardial infarction** Day 1 of administration: The patient started receiving leuprorelin acetate for adenomyosis uteri (second course). 4 days after administration: Exertional dyspnoea worsened. 6 days after administration: Fibrinogen degradation products (FDP) (41.3 μg/mL; normal range, 0.0-5.0), D-dimer (8.5 μg/mL; normal range, 0.0-1.0), anti-cardiolipin antibody (<8). A contrast CT image revealed thrombosis in the pulmonary artery and thus, the patient was diagnosed with pulmonary embolism. After admission to the hospital, anticoagulant therapy (warfarin potassium) and fibrinolytic therapy (urokinase) were performed. 8 days after administration: Genital haemorrhage was noted. Urokinase was switched to heparin. Ultrasonography of leg vein showed deep vein thrombosis of the right leg and superficial venous thrombosis of the left lower leg. Acute myocardial infarction developed. The patient had left shoulder pain. Electrocardiogram: elevated ST in V_{5-6}. Q wave was normal. Pain remitted within approximately 1 hour after intravenous administration of morphine hydrochloride hydrate. Spasm was suspected. 9 days after administration: Blood test in the morning showed CK (CPK) 709 IU/L and troponin T (+). Ultrasoundcardiography (UCG): no change. Lung perfusion scintigraphy showed multiple blood flow defects. Administration of pills was initiated for haemostasis of genital haemorrhage. 10 days after administration: She had left shoulder pain. Electrocardiogram: elevated ST in

				II, III and aV_F. No abnormal Q waves were noted. Acute myocardial infarction relapsed. Sublingual nitroglycerin, intravenous morphine hydrochloride hydrate and nicorandil tablets were administered, and pain remitted within 3 hours. 11 days after administration: Because genital haemorrhage remitted, administration of urokinase was resumed. CK (CPK) 2904 IU/L, troponin T (+). UCG: severe inferior wall hypokinesis. 16 days after administration: Administration of warfarin potassium was initiated. Administration of heparin and urokinase were gradually discontinued. 27 days after administration: A CT image showed residual thrombosis in the pulmonary artery (a part of thrombosis was shrank). 28 days after administration: Lung perfusion scintigraphy showed an improvement in blood flow defects. 31 days after administration: MRI: adenomyosis uteri 169 × 125 mm. 41 days after administration: UCG: inferior wall hypokinesis. 52 days after administration: She was discharged from the hospital with home oxygen therapy and continuously received warfarin potassium. 69 days after administration: Pulmonary embolism remitted. Acute myocardial infarction resolved with sequelae.
	Concomitant medications: none			

*: Including the period during which the therapeutic effect continued.

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Prostate cancer (Atrial fibrillation, gastrointestinal disorder, metastasis to bone, respiratory disorder, chronic obstructive pulmonary disease)	3.75 mg for 56 days ↓ 11.25 mg for approx. 13 months*	**Cardiac failure** 21 days before administration: The patient was diagnosed with prostate cancer. Day 1 of administration: Administration of leuprorelin acetate (3.75 mg) was initiated. Day 57 of administration: Treatment was switched to leuprorelin acetate (11.25 mg). Day 235 of administration: The patient had cardiac failure. Day 237 of administration: Administration of furosemide (40 mg/day) was initiated (duration unknown). Day 278 of administration: Cardiac failure remitted. 13 months after administration: Final administration of leuprorelin acetate was performed. 15 months after administration: The patient died of intestinal obstruction.
	Concomitant medications: aspirin, digoxin, ubidecarenone, verapamil hydrochloride, mosapride citrate hydrate, ranitidine hydrochloride			

*: Including the period during which the therapeutic effect continued.

2

Revision of Precautions (No. 220)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated September 28, 2010 (excluding those presented in "1. Important Safety Information" of this Bulletin).

[Brand name]: Major products names are showed.

1

< Enzyme preparations >

Alglucosidase Alfa (Genetical Recombination)

[Brand Name]

MYOZYME for Intravenous Infusion 50 mg (Genzyme Japan K.K.)

[WARNING]

WARNING

Anaphylactic reaction included in infusion associated reaction (IAR) may occur in association with administration of this drug. This drug should be administered to patients only after appropriate emergency measures are prepared, and patients should be carefully monitored after administration. If serious infusion associated reactions are observed, administration of this drug should be immediately discontinued, and appropriate measures should be taken. In addition, reactions (immune mediated reaction) that are thought to be mediated by immune complexes have been reported during treatment with this drug.

[Adverse Reactions (clinically significant adverse reactions)]

Immune mediated reaction: During treatment with this drug, symptoms such as skin necrosis, skin ulcer, arthralgia, joint swelling, proteinuria or haematuria may occur due to reaction that is thought to be mediated by immune complexes. If these symptoms are observed, discontinuation of administration should be considered, and appropriate measures should be taken.

2

< Hypnotics and sedatives, anxiolytics >

Alprazolam
Diazepam (oral dosage form)
Nitrazepam
Haloxazolam

[Brand Name]

CONSTAN 0.4mg. TABLETS (Takeda Pharmaceutical Company Limited), Solanax Tablets 0.4 mg (Pfizer Japan Inc)
2 mg. CERCINE TABLETS (Takeda Pharmaceutical Company Limited), Horizon Tablets 2 mg (Astellas Pharma Inc.)
NELBON TABLETS 5 mg (Daiichi Sankyo Co., Ltd.), Benzalin Tablet 2 (Shionogi & Co., Ltd.)
SOMELIN FINE GRANULES 1% (Daiichi Sankyo Company Limited)

[Use in Pregnant, Parturient And Nursing Women]

Women in their third trimester of pregnancy should be administered this drug only if the potential benefits outweigh the risks. [It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association

with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.]
It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

3

< Hypnotics and sedatives, anxiolytics >

Estazolam
Nimetazepam
Brotizolam
Lorazepam

[Brand Name]

EURODIN 1 mg. TABLETS (Takeda Pharmaceutical Company Limited)
Erimin Tablet 3 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Lendormin Tablets 0.25mg (Nippon Boehringer Ingelheim Co., Ltd.)
WYPAX TABLETS 0.5 (Pfizer Japan Inc.)

[Use in Pregnant, Parturient And Nursing Women]

It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.
It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

4

< Hypnotics and sedatives, anxiolytics, psychotropics >

Oxazolam
Quazepam
Cloxazolam
Clorazepate Dipotassium
Chlordiazepoxide
Tofisopam
Triazolam
Prazepam
Fludiazepam
Flutazolam
Flutoprazepam
Flurazepam Hydrochloride
Mexazolam
Medazepam
Rilmazafone Hydrochloride
Hydrate
Lormetazepam
Clotiazepam

[Brand Name]

SERENAL TABLETS 5 (Daiichi Sankyo Co., Ltd.)
DORAL TABLETS 15 (Hisamitsu Pharmaceutical Co., Inc.)
SEPAZON TABLETS 1 (Daiichi Sankyo Company Limited)
Mendon Capsule 7.5 mg (Abbott Japan Co., Ltd.)
5 mg. CONTOL TABLETS (Takeda Pharmaceutical Company Limited),
Balance Tablets 5 mg (Astellas Pharma Inc.)
GRANDAXIN Tab. 50 (Mochida Pharmaceutical Co., Ltd.)
Halcion Tablets 0.125 mg (Pfizer Japan Inc.)
SEDAPRAN KOWA TAB. 5 (Kowa Co, Ltd.)
Erispan Tablet 0.25 mg (Dainippon Sumitomo Pharma Co., Ltd.)
COREMINAL Tab. 4 mg (Sawai Pharmaceutical Co., Ltd.)
RESTAS Tablets 2 mg (MSD K.K.)
BENOZIL Capsules 10 (Kyowa Hakko Kirin Co., Ltd.)

MELEX TABLETS 0.5 mg (Daiichi Sankyo Co., Ltd.)
Resmit Tablet 2 (Shionogi & Co., Ltd.)
Rhythmy Tablet 1 mg (Shionogi & Co., Ltd.)
Evamyl Tablet 1.0 (Bayer Yakuhin, Ltd.), LORAMET TABLETS 1.0 (Pfizer Japan Inc.)
RIZE TABLETS 5 mg (Mitsubishi Tanabe Pharma Corporation)

[Use in Pregnant, Parturient And Nursing Women]

Women in their third trimester of pregnancy should be administered this drug only if the potential benefits outweigh the risks. [It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.
It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

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5 **< Hypnotics and sedatives, anxiolytics >**

Diazepam (injectable dosage form)

[Brand Name]

CERCINE INJECTION 5 mg. (Takeda Pharmaceutical Company Limited), Horizon Injection 10mg (Astellas Pharma Inc.)

[Use in Pregnant, Parturient And Nursing Women]

Women in their third trimester of pregnancy should be administered this drug only if the potential benefits outweigh the risks. [It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines. In addition, sleeping baby has been reported in cases where this drug was intravenously injected during delivery.]
It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

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6 **< Hypnotics and sedatives, anxiolytics >**

Flunitrazepam

[Brand Name]

Silece Tablets 1 mg (Eisai Co., Ltd.), ROHYPNOL Tablet 1 (Chugai Pharmaceutical Co., Ltd.)

[Use in Pregnant, Parturient And Nursing Women]

It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.
It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

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7 **< Hypnotics and sedatives, anxiolytics >**

Bromazepam

[Brand Name]	Lexotan Tablets 1 (Chugai Pharmaceutical Co., Ltd.), Seniran Suppositories 3 mg (Sandoz K.K.)
[Use in Pregnant, Parturient And Nursing Women]	Women in their third trimester of pregnancy should be administered this drug only if the potential benefits outweigh the risks. [It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.] It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

8 **<Hypnotics and sedatives, anxiolytics>**

Midazolam

[Brand Name]	Dormicum Injection 10 mg (Astellas Pharma Inc.)
[Use in Pregnant, Parturient And Nursing Women]	It has been reported that irregular heart rate occurred in fetuses, and hypotension, feeding difficulty, hypothermia and respiratory depression occurred in neonates when this drug was administered to women in their third trimester of pregnancy or to patients during delivery at a high dose. It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines. It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

9 **< Hypnotics and sedatives, anxiolytics >**

Ethyl Loflazepate

[Brand Name]	MEILAX TABLETS 1 mg, 2 mg, MEILAX FINE GRANULES 1% (Meiji Seika Kaisha, Ltd.)
[Use in Pregnant, Parturient And Nursing Women]	Women in their third trimester of pregnancy should be administered this drug only if the potential benefits outweigh the risks. [It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.] It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

10 < Antiepileptics >

Clonazepam

[Brand Name]

Landsen Tablet 0.5 mg (Dainippon Sumitomo Pharma Co., Ltd.), RIVOTRIL Tablet 0.5 mg (Chugai Pharmaceutical Co., Ltd.)

[Use in Pregnant, Parturient And Nursing Women]

It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.

It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

11 < Antiepileptics >

Clobazam

[Brand Name]

MYSTAN Tablet 5 mg, 10 mg, MYSTAN Fine Granule 1% (Dainippon Sumitomo Pharma Co., Ltd.)

[Use in Pregnant, Parturient And Nursing Women]

It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines.

It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

12 < Psychotropics >

Etizolam

[Brand Name]

DEPAS TABLETS 0.5 mg, 1 mg, DEPAS FINE GRANULES 1% (Mitsubishi Tanabe Pharma Corporation)

[Use in Pregnant, Parturient And Nursing Women]

Women in their third trimester of pregnancy should be administered this drug only if the potential benefits outweigh the risks. [It has been reported that symptoms such as feeding difficulty, vomiting, decreased activity, hypotonia, hypertonicity, lethargy, somnolence, respiratory depression/apnoea, cyanosis, irritability, nervousness, tremor, hypothermia, tachycardia occurred in neonates in association with benzodiazepines. These symptoms may be reported as withdrawal symptoms or neonatal asphyxia. Aggravated jaundice in neonates has been also reported in association with benzodiazepines. Increased serum CK (CPK) may occur in neonates whose mothers who have been continuously treated with this drug in their third trimester of pregnancy.]

It has been reported that withdrawal symptoms occurred in neonates whose mother had been continuously treated with benzodiazepines before delivery.

13

< Antiarrhythmic agents >

Landiolol Hydrochloride

[Brand Name] ONOACT 50 for Injection (Ono Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Cardiac arrest, complete atrioventricular block, sinus arrest, severe bradycardia**: Cardiac arrest, complete atrioventricular block, sinus arrest or severe bradycardia may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

14

< Digestive organ agents-Miscellaneous >

Infliximab (Genetical Recombination)

[Brand Name] REMICADE for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corp.)

[Important Precautions] It has been reported that demyelinating disease of the central nerve system (e.g., multiple sclerosis, optic neuritis, transverse myelitis) and of the peripheral nerve system (e.g., Guillain-Barre syndrome) occurred or worsened during anti-TNF therapy including this drug. Therefore, this drug should not be administered to patients who currently have or have had demyelinating disease. Patients with suspected demyelinating disease should be investigated by neurological assessment and/or imaging diagnosis in order that the adequacy of treatment with this drug should be carefully evaluated based on the potential risks and benefits. Patients should be carefully monitored after administration.

[Adverse Reactions (clinically significant adverse reactions)] **Demyelinating diseases**: Demyelinating diseases (e.g., multiple sclerosis, optic neuritis, transverse myelitis, Guillain-Barre syndrome) may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

15

< Pituitary hormone preparations >

Somatropin (Genetical Recombination)

[Brand Name] Growject for Injection 1.33 mg (JCR Pharmaceuticals Co., Ltd.), Saizen 1.33 mg Injection, Serostim Injection 5 mg (Merck Serono Co., Ltd.), Genotropin TC Inj. 5.3 mg (Pfizer Japan Inc.), NORDITROPIN S Injection 10 mg (Novo Nordisk Pharma Ltd.), Humatrope Injection 6 mg (Eli Lilly Japan K.K.)

[Other Precautions] It is reported that administration of human growth hormone may increase a risk for secondary tumor in patients with a history of childhood cancer.

16

< Antidiabetic agents >

Sitagliptin Phosphate Hydrate

[Brand Name] GLACTIV Tablets 25 mg (Ono Pharmaceutical Co., Ltd.), JANUVIA Tablets 25mg (MSD K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic dysfunction, jaundice**: Hepatic dysfunction with marked elevations of AST (GOT), ALT (GPT), etc. or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
Acute renal failure: Acute renal failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

17 **< Miscellaneous metabolism agents - Miscellaneous >**

Adalimumab (Genetical Recombination)

[Brand Name] HUMIRA Subcutaneous Injection 40 mg Syringe 0.8 mL (Abbott Japan Co., Ltd.)

[Important Precautions] It has been reported that demyelinating disease of the central nerve system (e.g., multiple sclerosis, optic neuritis, myelitis transverse) and of the peripheral nerve system (e.g., Guillain-Barre syndrome) occurred or worsened during anti-TNF therapy including this drug. Therefore, this drug should not be administered to patients who currently have or have had demyelinating disease. Patients with suspected demyelinating disease should be investigated by neurological assessment and/or imaging diagnosis in order that the adequacy of treatment with this drug should be carefully evaluated based on the potential risks and benefits. Patients should be carefully monitored after administration.

[Adverse Reactions (clinically significant adverse reactions)] **Demyelinating diseases**: It is reported that demyelinating diseases (e.g., multiple sclerosis, optic neuritis, transverse myelitis, Guillain-Barre syndrome) may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

18 **< Miscellaneous metabolism agents-Miscellaneous >**

Etanercept (Genetical Recombination)

[Brand Name] ENBREL 10 mg for S.C. Injection (Pfizer Japan Inc.)

[Important Precautions] It has been reported that demyelinating disease of the central nerve system (e.g., multiple sclerosis, optic neuritis, myelitis transverse) and of the peripheral nerve system (e.g., Guillain-Barre syndrome) occurred or worsened during anti-TNF therapy including this drug. Therefore, this drug should not be administered to patients who currently have or have had demyelinating disease. Patients with suspected demyelinating disease should be investigated by neurological assessment and/or imaging diagnosis in order that the adequacy of treatment with this drug should be carefully evaluated based on the potential risks and benefits. Patients should be carefully monitored after administration.

[Adverse Reactions (clinically significant adverse reactions)] **Demyelinating diseases**: Demyelinating diseases (e.g., multiple sclerosis, optic neuritis, transverse myelitis, Guillain-Barre syndrome) may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

19 **< Antineoplastics-Plant extract preparations >**

Irinotecan Hydrochloride Hydrate

[Brand Name] CAMPTO 40 mg for I.V. infusion (Yakult Honsha Co., Ltd.), TOPOTECIN INTRAVENOUS DRIP INFUSION 40 mg (Daiichi Sankyo Co., Ltd.)

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

20 **< Antineoplastics-Miscellaneous >**

Miriplatin Hydrate

[Brand Name] MIRIPLA for Intra-arterial Injection 70 mg (Dainippon Sumitomo Pharma Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic dysfunction, hepatic failure: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), bilirubin, Al-P and/or γ-GTP may occur immediately after administration of this drug, and some of the cases may result in hepatic failure. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

Hepatobiliary disorders: Hepatobiliary disorders such as biloma may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

21

< Antineoplastics-Miscellaneous >

Rituximab (Genetical Recombination)

[Brand Name]

RITUXAN Injection 10 mg/mL (Zenyaku Kogyo Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Cranial nerve symptoms such as reversible posterior leukoencephalopathy syndrome: Reversible posterior leukoencephalopathy syndrome (symptoms include convulsive seizure, headache, psychiatric symptom, vision disturbance, hypertension, etc.) may occur. In addition, visual and hearing disorders such as blindness and deafness, and cranial nerve disorders such as sensory disturbance and facial palsy have been reported within 6 months after the treatment with this drug. Patients should be carefully monitored, and if such symptoms occur, administration should be discontinued, and appropriate measures should be taken.

22

< Various functional testing reagents >

Glucagon
Glucagon (Genetical Recombination)

[Brand Name]

GLUCAGON for Inj. 1 unit "ITO" (ILS Inc.)
Glucagon G Novo 1mg (Novo Nordisk Pharma Ltd.)

[Careful Administration]

Patients with type I diabetes mellitus

[Important Precautions]

It is reported that blood lactic acid increased in patients with type I diabetes mellitus after administration of this drug, leading to lactic acidosis and requiring emergency treatment. When administering this drug, patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken. During a test for hepatic glycogenosis, special attention should be paid for the occurrence of lactic acidosis.

23

< Non-main therapeutic purpose agents-Miscellaneous >

Iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil (MIRIPLA suspension vehicle)

[Brand Name]

MIRIPLA suspension vehicle 4 mL (Dainippon Sumitomo Pharma Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic dysfunction, hepatic failure: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), bilirubin, Al-P and/or γ-GTP may occur immediately after administration of miriplatin suspension, and some of the cases may result in hepatic failure. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

Hepatobiliary disorders: Hepatobiliary disorders such as biloma may occur after administration of miriplatin suspension. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

3

List of products subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of November 1, 2010)

Nonproprietary name Brand name on	Name of the marketing authorization holder	Date of EPPV initiate
Metformin Hydrochloride Metgluco Tablets 250 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 10, 2010
Thalidomide THALED capsule 50	Fujimoto Pharmaceutical Corporation	May 25, 2010
Epoetin Kappa (Genetical Recombinant) [Epoetin Alfa Biosimilar 1] Epoetin Alfa BS Injection 750 syringe [JCR], Epoetin Alfa BS Injection 1500 syringe [JCR], Epoetin Alfa Injection 3000 syringe [JCR], Epoetin Alfa BS Injection 750 [JCR], 1500 [JCR], 3000 [JCR]	JCR Pharmaceuticals Co., Ltd.	May 27, 2010
Travoprost/Timolol Maleate DuoTrav Combination Ophthalmic Solution	Alcon Japan Ltd.	June 11, 2010
Dorzolamide Hydrochloride/Timolol Maleate COSOPT Ophtalmic Solution	Banyu Pharmaceutical Co., Ltd.	June 11, 2010
Eculizumab (Genetical Recombination) Soliris Intravenous Drip Infusion 300 mg	Alexion Pharmaceuticals, Inc.	June 14, 2010
Alogliptin Benzoate NESINA Tablets 6.25 mg., 12.5 mg., 25 mg.	Takeda Pharmaceutical Company Limited	June 15, 2010
Candesartan Cilexetil/Amlodipine Besilate UNISIA Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 15, 2010
Panitumumab (Genetical Recombination) Vectibix Intravenous Drip Infusion 100 mg	Takeda Pharmaceutical Company Limited	June 15, 2010
Pregabalin Lyrica Capsules 25 mg, 75 mg, 150 mg	Pfizer Japan Inc.	June 22, 2010 October 27, 2010*1
Fentanyl Citrate Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	June 24, 2010
Metformin Hydrochloride/Pioglitazone Hydrochloride METACT Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	July 6, 2010
Ramelteon ROZEREM Tablets 8 mg	Takeda Pharmaceutical Company Limited	July 6, 2010

Lenalidomide Hydrate	Celgene K.K.	July 20, 2010*[2]
Revlimid Capsules 5 mg		August 20, 2010*[3]
Olopatadine Hydrochloride	Kyowa Hakko Kirin Co., Ltd.	July 23, 2010
ALLELOCK Tablets 2.5, 5*[4]		
Pazufloxacin Mesilate	Toyama Chemical Co., Ltd.	July 23, 2010
PASIL INTRAVENOUS DRIP INFUSION 300 mg, 500 mg*[5]		
Pazufloxacin Mesilate	Mitsubishi Tanabe Pharma Corporation	July 23, 2010
Pazucross INJECTION 300, 500*[5]		
Budesonide	AstraZeneca K.K.	July 23, 2010
Pulmicort 100 μg Turbuhaler 112 doses, Pulmicort 200 μg Turbuhaler 56, 112 doses*[6]		
Lansoprazole	Takeda Pharmaceutical Company Limited	July 23, 2010*[7]
Takepron capsules 15, Takepron OD Tablets 15		August 20, 2010*[8]
Darbepoetin Alfa (Genetical Recombination)	Kyowa Hakko Kirin Co., Ltd.	August 26, 2010
NESP INJECTION 10 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 15 μg/1 mL PLASTIC SYRINGE, NESP 20 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 30 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 40 μg/1 mL PLASTIC SYRINGE, NESP INJECTION 60 μg/0.6 mL PLASTIC SYRINGE, NESP 120 μg/0.6 mL PLASTIC SYRINGE, NESP INJECTION 180 μg/0.9 mL PLASTIC SYRINGE		
Ambrisentan	GlaxoSmithKline K.K.	September 17, 2010
Volibris Tablets 2.5 mg		
Tramadol Hydrochloride	Nippon Shinyaku Co., Ltd.	September 17, 2010
Tramal Capsules 25 mg, 50 mg		
Levetiracetam	UCB Japan Co., Ltd.	September 17, 2010
E Keppra Tablets 250 mg, 500 mg		
Abatacept (Genetical Recombination)	Bristol-Myers K.K.	September 21, 2010
ORENCIA FOR I.V. INFUSION 250 mg		
Temsirolimus	Pfizer Japan Inc.	September 22, 2010
TORISEL Injection 25 mg		
Paclitaxel	Taiho Pharmaceutical Co., Ltd.	September 24, 2010
Abraxane I.V. Infusion 100 mg		
Teriparatide (Genetical Recombination)	Eli Lilly Japan K.K.	October 1, 2010
FORTEO s.c. injection kit 600 μg		
Telmisartan/Amlodipine Besilate	Nippon Boehringer Ingelheim Co., Ltd.	October 7, 2010
Micamlo Combination Tablets AP		
Pazufloxacin Mesilate	Toyama Chemical Co., Ltd.	October 13, 2010
PASIL INTRAVENOUS DRIP INFUSION 1000 mg		
Pazufloxacin Mesilate	Mitsubishi Tanabe Pharma Corporation	October 13, 2010
Pazucross INJECTION 1000 mg		
Bazedoxifene Acetate	Pfizer Japan Inc.	October 13, 2010
Viviant Tablets 20 mg		
Laninamivir Octanoate Hydrate	Daiichi Sankyo Company, Limited	October 19, 2010
INAVIR DRY POWDER INHALER 20 mg		
Botulinum Toxin Type A	GlaxoSmithKline K.K.	October 27, 2010
BOTOX for injection 50 Unit, 100 Unit*[9]		

Adalimumab (Genetical Recombination) HUMIRA Subcutaneous Injection 40 mg Syringe 0.8 mL *10	Abbott Japan Co., Ltd.	October 27, 2010
Olanzapine Zyprexa Tablet 2.5 mg, 5 mg, 10 mg, Zyprexa Fine Granule 1 %, Zyprexa Zydis Tablet 5 mg, 10 mg *11	Eli Lilly Japan K.K.	October 27, 2010
Peramivir Hydrate RAPIACTA Bag for Intravenous Drip Infusion 300 mg, RAPIACTA Vial for Intravenous Drip Infusion 150 mg * 6	Shionogi & Co., Ltd.	October 27, 2010

*1 An additional indication for "treatment of patients with peripheral neuropathic pain"

*2 The originally approved indication for “treatment of patients with relapsed or refractory multiple myeloma”

*3 An additional indication for “treatment of patients with myelodysplastic syndrome associated with a chromosome 5q deletion”

*4 An additional administration for “pediatrics (aged 7 and older)”

*5 An additional indication for “treatment of patients with sepsis, applicable microorganism; *Streptococcus pneumonia*”

*6 An additional administration for “pediatrics”

*7 An additional indication for “treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of low-dose aspirin”

*8 An additional indication for “treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of non-steroidal anti-inflammatory drugs”

*9 An additional indication for "treatment of patients with upper limb spasms or lower limb spasms"

*10 An additional indication for "remission induction or maintenance therapy for moderate or severe active Crohn's disease (limited to patients who are not adequately responsive to conventional therapy)"

*11 An additional indication for "treatment of manic symptoms in patients with bipolar disorder"