Pharmaceuticals and Medical Devices Safety Information

No. 204 August 2004

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This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

1

Important Safety Information

This section presents contents of revisions, reference materials, and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 203).

1 Argatroban

Brand Name (name of company)	Argaron Injection (Nichi-iko Pharmaceutical Co., Ltd.) Slovastan Injection 10 mg (Sawai Pharmaceutical Co., Ltd.) Slonnon Injection (Daiichi Pharmaceutical Co., Ltd.) Novastan Inj. (Mitsubishi Pharma Corporation)
Therapeutic Category	Cardiovascular agents-Miscellaneous
Indications	① Improvement of neurological abnormalities (motor paralysis) and activities of daily living (ADL) disabilities (ADL includes walking, standing, sustaining the sitting position, and eating) associated with the following disease - Acute cerebral thrombosis within 48 hours after the onset of symptoms (excluding lacunar type) ② Improvement of ulcers of extremities, pain at rest, and cold extremities associated with chronic arterial occlusion (Buerger's disease and arteriosclerosis obliterans) ③ Prevention of blood coagulation in extracorporeal circuit in the following patients (during haemodialysis) - Patients with congenital antithrombin III deficiency - Patients with decreased antithrombin III (in whom antithrombin III activities have decreased to 70% or less of normal, and sodium heparin or calcium heparin is judged not to prevent coagulation (residual blood) in the extracorporeal circuit.) (② is applicable only for Argaron Injection and Slovastan Injection 10 mg)

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

[Adverse Reactions (clinically significant adverse reactions)]	**Fulminant hepatitis, hepatic function disorder and jaundice:** Serious hepatitis such as fulminant hepatitis and jaundice may occur.Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.
<Reference Information>	Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 80s	Cerebral embolism (hypertension, chronic cardiac failure)	60 mg 2 days ↓ 20 mg 4 days	**Hepatitis fulminant** On day 1 of administration: The patient was hospitalized due to diagnosis of cerebral embolism. Administration of this drug was started after hospitalization. Administration of diltiazem hydrochloride, which was administered before hospitalization, was discontinued. No abnormalities were found in hepatic function at the hospitalization. On day 2 of administration: Both HBs antibody and HCV antibody were negative. On day 6 of administration (day of discontinuation): Since aspiration pneumonia developed in the evening, a blood test was conducted. The result showed advanced hepatic function disorder and administration of this drug was discontinued. Administration of piperacillin sodium, fosfomycin sodium, imipenem/cilastatin sodium, isepamicin sulfate, glycyrrhizin/glycine/cysteine was started. 1 day after discontinuation: Administration of liver extract/flavin adenine dinucleotide was started (3 days). 2 days after discontinuation: Administration of 10 μg of alprostadil was started (3 days). Hepatitis viral markers (IgM-HA antibody, IgM-HBc antibody, qualitative HCV-RNA) were negative. 3 days after discontinuation: Complications (increased FDP, decreased AT-III) with DIC (disseminated intravascular coagulation) were confirmed, and administration of lyophilized human antithrombin III concentrate, nafamostat mesilate and heparin sodium was started. 4 days after discontinuation: Administration of 500 ml of amino acid preparation for hepatic failure (1) was started. 6 days after discontinuation: Whereas there was a decreasing trend in AST (GOT) and ALT (GPT), total bilirubin was increased. Prothrombin time (PT) was running at approximately 20%, and it was thought that hepatic failure was progressing due to decreasing trends in cholinesterase and albumin levels. The patient was diagnosed with hepatitis fulminant based on coma hepatic of grade III to IV and PT etc. 7 days after discontinuation: Administration of 1 g of methylprednisolone sodium succinate was started (2 days). 8 days after discontinuation: Abdominal CT showed atrophy of entire liver. 10 days after discontinuation: Glucagon-insulin therapy was started. 20 days after discontinuation: The patient died (cause of death: multi-organ failure). There were no autopsy findings.	Company report

	Concomitant medications: diltiazem hydrochloride, thiamine monophosphate disulfide/B_6/B_{12}, ascorbic acid, dopamine hydrochloride

Clinical Laboratory Values

	On day 1 of admin.	On day 2 of admin.	On day 6 of admin. (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	5 days after discontinuation	9 days after discontinuation	12 days after discontinuation	18 days after discontinuation
PLT ($\times 10^4$/mm^3)	26.8	--	25.8	18.5	14.7	--	19.4	--	18.3
PT (%)	--	--	--	28.4	35.5	--	25.1	--	19.2
AST (GOT) (IU/L)	19	--	1498	1910	517	--	280	--	65
ALT (GPT) (IU/L)	17	--	1480	2080	1499	--	344	--	45
Al-P (IU/L)	274	--	280	237	273	--	292	--	568
LDH (IU/L)	291	--	2652	2280	1217	--	1672	--	777
γ-GTP (IU/L)	--	--	--	68	--	--	--	--	--
Total bilirubin (mg/dL)	0.3	--	2.4	2.3	2.9	--	13.7	--	26.1
Direct bilirubin (mg/dL)							10		
BUN (mg/dL)	18	--	42	49	54	--	43	--	26
Ammonia (μg/dL)	--	--	88	--	56	--	--	--	--
AT-III (%)	--	--	--	65	27	--	97	--	33
FDP (μg/mL)	--	--	--	8.6	181.5	--	18.4	--	7.3
Albumin (g/dL)	--	4.7	--	--	--	2.7	2.4	--	--
Cholinesterase (IU/L)	--	243	--	172	--	125	--	56	--

PLT: Platelet
PT: Prothrombin Time
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
BUN: Blood Urea Nitrogen
AT-III: Antithrombin III
FDP: Fibrinogen/Fibrin Degradation Products

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	Arterioscerlosis obliterans (cerebral infarction, arrhythmia)	20 mg 10 days	**Acute hepatitis** 4 days before administration: AST (GOT), ALT (GPT), Al-P, and total bilirubin were 29 IU/L, 41 IU/L, 395 IU/L, and 0.7 mg/dL, respectively. On day 3 of administration: The nonionic contrast medium ioversol was administered for CT test. On day 10 of administration (day of discontinuation): Increases in AST (GOT) and ALT (GPT) were confirmed in tests conducted before the patient was discharged. AST (GOT), ALT (GPT), Al-P, and total bilirubin were 186 IU/L, 418 IU/L, 701 IU/L, and 0.5 mg/dL, respectively.	Company report

				Administration of this drug was discontinued, and treatment for hepatitis (prednisolone sodium succinate for injection, protoporphyrin disodium and ursodeoxycholic acid) was started. 5 days after discontinuation: AST (GOT), ALT (GPT), and Al-P were 39 IU/L, 147 IU/L, and 464 IU/L, respectively. Total bilirubin was not measured. 17 days after discontinuation**:** The patient recovered. AST (GOT), ALT (GPT), Al-P, and total bilirubin were 25 IU/L, 56 IU/L, 435 IU/L,and 0.5 mg/dL.	
	Concomitant medications: isosorbide dinitrate, verapamil hydrochloride, bifemelane hydrochloride, dihydroergotoxine mesilate, tizanidine hydrochloride, maprotiline hydrochloride, ioversol				

Clinical Laboratory Values

	4 days before admin.	On day 10 of admin. (day of discontinuation)	2 days after discontinuation	4 days after discontinuation	5 days after discontinuation	6 days after discontinuation	7 days after discontinuation	15 days after discontinuation	17 days after discontinuation
AST (GOT) (IU/L)	29	186	76	49	39	42	32	26	25
ALT (GPT) (IU/L)	41	418	261	180	147	147	124	72	56
Al-P (IU/L)	395	701	574	479	464	474	443	439	435
LDH (IU/L)	412	450	289	295	289	304	293	306	299
γ-GTP (IU/L)	140	169	160	143	140	149	142	132	136
Total bilirubin (mg/dL)	0.7	0.5	--	--	--	--	--	0.4	0.5

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase

2 Mosapride Citrate

Brand Name (name of company)	Gasmotin Powder, Gasmotin Tablets 2.5 mg and 5 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Digestive organ agents-Miscellaneous
Indications	Gastrointestinal symptoms accompanying chronic gastritis (heartburn, nausea/vomiting)

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis fulminant, hepatic function disorder, jaundice: Hepatitis fulminant, serious hepatic function disorder accompanied with marked elevations of AST (GOT), ALT (GPT) and γ-GTP, etc. and jaundice may occur resulting in death in some cases. Patient should be carefully monitored and if abnormalities are observed, discontinue administration immediately and appropriate measures should be taken.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 20s	Depression (none)	15 mg 217 days	**Hepatitis fulminant** On day 1 of administration: The patient was diagnosed with depression at Hospital A, and oral administration of fludiazepam, milnacipran hydrochloride, trazodone hydrochloride, rilmazafone hydrochloride, and this drug was started. Hepatic function was normal. On day 57 of administration: Medication was changed to oral administration of paroxetine hydrochloride hydrate at 20 mg, oxazolam, rilmazafone hydrochloride, mianserin hydrochloride, and this drug. On day 78 of administration: Dosage of paroxetine hydrochloride hydrate was increased to 40 mg. On day 141 of administration: Blood test showed hepatic disorder [AST (GOT), ALT (GPT), and γ-GTP were 127 IU/L, 304 IU/L, and 98 IU/L, respectively]. On day 169 of administration: Dosage of paroxetine hydrochloride hydrate was decreased to 20 mg. Administration of oxazolam and this drug was continued. On day 197 of administration: Administration of paroxetine hydrochloride hydrate and this drug was continued. Malaise, queasy, and vomiting were developed around this time. On day 217 of administration (day of discontinuation): Administration of this drug was discontinued. 1 day after discontinuation: The patient was examined at Hospital B due to significant general malaise, and was indicated by doctor as having hepatic disorder. The patient was hospitalized [total bilirubin, AST (GOT), ALT (GPT), and PT were 6.4 mg/dL, 1350 IU/L, 2039 IU/L, and 40.8%, respectively]. 5 days after discontinuation: Since PT worsened to 23.2%, steroid pulse therapy was started. Antiammonia measures and administration of lyophilized human antithrombin III concentrate was implemented. 7 days after discontinuation: The patient was transferred to this hospital. Based on grade II hepatic encephalopathy and PT of 20.8%, the patient was diagnosed with hepatitis fulminant. Intensive care such as plasma exchange was started. 8 days after discontinuation: Hepatic encephalopathy was worsened to grade III. The patient was admitted to ICU, and plasma exchange was performed. 10 days after discontinuation: Hepatic encephalopathy was worsened to grade IV. High-flux haemodiafiltration and plasma exchange were performed under artificial respiration.	Company report

				13 days after discontinuation: Since encephalopathy continued, plasma exchange and haemodialysis were performed. 18 days after discontinuation: Hepatic encephalopathy was improved to grade II. High-flux haemodiafiltration was performed. 22 days after discontinuation: Ultrafiltration was performed. Hepatic encephalopathy was worsened to grade III. 23 days after discontinuation: The patient was discharged from ICU, transferred to a private room in general ward. 27 days after discontinuation: Hepatic encephalopathy was worsened to grade IV. 31 days after discontinuation: The patient died.	
	Concomitant medications: paroxetine hydrochloride hydrate, fludiazepam, milnacipran hydrochloride, trazodone hydrochloride, rilmazafone hydrochloride, oxazolam, mianserin hydrochloride				

Clinical Laboratory Values

	On day 1 of admin.	On day 141 of admin.	1 day after discontinuation	5 days after discontinuation	7 days after discontinuation	10 days after discontinuation	13 days after discontinuation	18 days after discontinuation	23 days after discontinuation
AST (GOT) (IU/L)	18	127	1350	708	276	84	65	130	88
ALT (GPT) (IU/L)	35	304	2039	1181	916	81	27	61	11
LDH (IU/L)	203	236	1080	714	645	407	--	--	--
γ-GTP (IU/L)	13	98	128	103	107	28	--	--	--
Al-P (IU/L)	--	--	427	418	375	264	--	--	--
Total bilirubin (mg/dL)	--	0.4	6.4	10.4	17.2	16.8	5.5	11.9	19.7
Albumin (g/dL)	--	--	3.7	3.1	3.4	3.1	--	3.2	--
PT (%)			40.8	23.2	20.8	41.5	80	27.6	19.5

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

3 Salicylamide/Acetaminophen/Anhydrous Caffeine/Promethazine Methylenedisalicylate

Brand Name (name of company)	Salazac Granules (Taiyo Yakuhin Co., Ltd.) etc.
Therapeutic Category	Common cold drugs
Indications	Improvement and alleviation of the following symptoms accompanying common cold or upper respiratory inflammation Nasal secretion, congested nose, pharyngalgia/laryngodynia, headache, arthralgia, myalgia, pyrexia

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

[Adverse Reactions (clinically significant adverse reactions)]	**Glaucoma:** Glaucoma attacks may occur. If visual acuity reduced and eye pain etc. are observed, administration of this drug should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	Common cold (none)	3 g 2 days	**Glaucoma** Medical history: none 2 days before administration: The patient took over-the-counter cold medicine (containing acetaminophen/ethenzamide/diphenylpyraline/anhydrous caffeine/riboflavin/oriental bezoar/ginseng/hesperidin) for 2 days for cold-like symptoms (dosage was unclear). On day 1 of administration: As symptoms did not improve, administration of 3 g of this drug, 200 mg of minocycline hydrochloride, 75 mg of diclofenac sodium and 60 mg of benproperine phosphate was started at another hospital. Around this time, visual impairment developed. On day 2 of administration (day of discontinuation): The patient took first medical examination at the ophthalmologic department of this hospital, and was diagnosed with acute glaucoma attacks in both eyes. Intraocular pressure for right eye: 80 mmHg, intraocular pressure for left eye: 26 mmHg. Treatment with ocular instillations of pilocarpine hydrochloride 2% 12 times every 5 minutes (right eye), carteolol hydrochloride 2% once (right eye), 250 mg of acetazolamide, 600 mg of potassium L-aspartate potassium, and 200 mL of concentrated glycerin/fructose (drip infusion) did not improve the symptons. Laser iridotomy in right eye was performed. Symptoms were improved after operation. 1 day after discontinuation: Intraocular pressure for both eyes returned to within a normal range, and vision was good. 7 days after discontinuation: Laser iridotomy in left eye was performed. Afterwards, although intraocular pressure was controlled through ocular instillation, the patient was thought to have chronic comditon. Opinion of prescribing doctor: Although it cannot be confirmed because the patient had not received diagnosis before development of glaucoma, the patient may have already had narrow-angle glaucoma (possibility of chronic narrow-angle glaucoma).	Company report

				In addition to physical deconditioning from cold-like symptoms, since the patient was susceptive to antihistaminic, it can be imagined that glaucoma attacks occurred due to the diphenylpyraline contained in the over-the-counter cold medicine and the promethazine methylenedisalicylate contained in this drug.	
	Concomitant medications: minocycline hydrochloride, diclofenac sodium, benproperine phosphate				

4 Concentrated Glycerin/Fructose

Brand Name (name of company)	Glyceol Injection (Otsuka Pharmaceutical Factory, Inc.) etc.
Therapeutic Category	Cardiovascular agents-Miscellaneous
Indications	○ Treatment of increased intracranial pressure and intracranial oedema ○ Improvement of consciousness disorder, neurological disorder, and subjective symptoms accompanying the following diseases caused by improvements of intracranial pressure and intracranial oedema Cerebral infarction (cerebral thrombosis, cerebral embolism), intracerebral haemorrhage, subarachnoid haemorrhage, head trauma, brain tumour, encephalomeningitis ○ Post-treatment after brain surgery ○ Decrease in cranial capacity during brain surgery ○ When decrease in intraocular pressure is necessary ○ Decrease in ocular volume during eye surgery

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

[Contraindications]	Patients with adult-onset type II citrullinemia
[Important Precautions]	There have been reports of death resulting from aggravation of pathological conditions after administration of this drug for treatment of brain oedema in patients with adult-onset type II citrullinemia. This drug should not be used in patient with suspected adult-onset type II citrullinemia (disease where blood citrulline is increased; characterized by abnormal behaviour and consciousness disturbed, etc. resulting from repeated hyperammonaemia).
<Reference Information>	Yazaki Masahide et al.: The 45th annual meeting of the Japanese Society of Neurology Program/Abstracts: 229 (2004) (In Japanese)

The 45th annual meeting of the Japanese Society of Neurology (May 11 to 14, 2004)
P-1-R-1
Risk of administering glycerol for brain oedema in patients with adult-onset citrullinemia (CTLN2)

[Purpose] To study the risk of administration of glycerol and the efficacy of single administration of mannitol for treatment of brain oedema in patients with CTLN2, from the therapeutic experiences of 3 patients with CTLN2.

[Method] Therapeutic experiences in relation to brain oedema of 3 patients with CTLN2 (Patient 1: female aged 40, Patient 2: male aged 31, Patient 3: male aged 40) were reviewed. Administration of glycerol followed by the additional administration of mannitol was conducted for Patients 1 and 2 after they developed brain oedema. Single administration of mannitol was conducted for Patient 3 after the patient developed brain oedema.

[Results] For Patients 1 and 2, even after additional administration of mannitol was conducted after administration of glycerol, brain oedema did not improve and both patients died. For Patient 3, after administration of mannitol, clear improvements in the brain oedema were confirmed and the patient survived.

[Consideration] It is possible that mannitol is more effective than glycerol in treatment of brain oedema in patients with CTLN2. On the mitochondrial membrane, citrin possesses the function of transferring cytoplasmic NADH within the mitochondria. However, it is also possible that the pathological conditions of CTLN2 are aggravated further through the promotion of accumulation of cytoplasmic NADH due to the metabolism of glycerol itself.

2

Revision of PRECAUTIONS

(No. 158)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 203) (excluding those presented in "1. Important Safety Information" of this Bulletin.), together with reference materials.

1 <Antiparkinsonian agents> Cabergoline

[Brand Name]	Cabaser Tab. 0.25 mg and 1.0 mg (Pfizer Japan Inc.)
[Adverse Reactions (clinically significant adverse reactions)]	**Neuroleptic malignant syndrome (Syndrome malin):** Hyperthermia, consciousness disturbed, advanced muscle stiffness, movements involuntary, increase in serum CK (CPK) may occur due to discontinuation or sudden decrease in the dosage of this drug in treatment for Parkinson's disease. Dosage should be gradually decreased after readministration of this drug, and appropriate measures such as cooling of the body and hydration, etc. should be taken in such cases. The same symptoms may occur during continued administration of this drug.
<Reference Information>	Company report

2 <Psychotropics> Fluvoxamine Maleate

[Brand Name]	Depromel Tablets 25 and 50 (Meiji Seika Kaisha Ltd.), Luvox Tablets 25 and 50 (Solvay Seiyaku K.K.)
[Contraindications]	Patients receiving thioridazine and tizanidine hydrochloride
[Interactions (contraindications for concomitant use)]	Tizanidine hydrochloride
<Reference Information>	Company report

3 <Central nervous system agents-Miscellaneous> Edaravone

[Brand Name]	Radicut Inj. 30 mg (Mitsubishi Pharma Corporation)
[Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms (urticaria, blood pressure decreased, and dyspnoea, etc.) may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>	Company report

4 <Antispasmodics> Tizanidine Hydrochloride

[Brand Name]	Ternelin Granules 0.2%, Ternelin Tablets 1 mg (Nihon Ciba-Geigy K.K.), and others
[Contraindications]	Patients receiving fluvoxamine maleate
[Interactions (contraindications for concomitant use)]	Fluvoxamine maleate
<Reference Information>	Company report

5 <Hyperlipidaemia agents> Pitavastatin Calcium

[Brand Name]	Livalo Tablets 1 mg and 2 mg (Kowa Company, Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder with significant elevations of AST (GOT) and ALT (GPT), etc. and jaundice may occur. Patients should be carefully monitored through periodic hepatic function tests, etc., and if abnormalities are observed, discontinue administration and take appropriate measures.
<Reference Information>	Company report

6 <Urogenital and anal organ agents-Miscellaneous> Flavoxate Hydrochloride

[Brand Name]	Bladderon Granules, Bladderon Tablets (Nippon Shinyaku Co., Ltd.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if abnormalities such as urticaria, cold sweat, dyspnoea, laryngeal oedema, and blood pressure decreased etc. are observed, administration should be immediately discontinued and appropriate measures should be taken.
<Reference Information>	Company report

7 <Epidermides-Miscellaneous, Leprostatics> Diaphenylsulfone

[Brand Name]	Protogen Tablets 25 mg, Lectisol Tablets 25 mg (Mitsubishi Pharma Corporation)
[Adverse Reactions (clinically significant adverse reactions)]	**Eosinophilic pneumonia:** Eosinophilic pneumonia may occur. If respiratory symptoms such as pyrexia, cough, and dyspnoea are observed, discontinue administration, perform chest X-ray and blood tests, etc., immediately, and take appropriate measures.
<Reference Information>	Company report

8 <Epidermides-Miscellaneous> Maxacalcitol (topical dosage form)

[Brand Name] Oxarol Ointment (Chugai Pharmaceutical Co., Ltd.)

[Careful Administration] Patients with decreased hepatic functions

[Important Precautions] Since this drug is an activated vitamin D_3 derivative drug, serum calcium levels may become increased. In addition, since there have been reports of acute renal failure accompanied with hypercalcemia, patients should be monitored through periodic tests on serum calcium level and renal function (serum creatinine, BUN, etc.) (once 2 to 4 weeks after initiation of use, accordingly thereafter) when using this drug. If normal ranges are exceeded, reduce the dosage or discontinue administration.
In patients who have skin eruptions over broad areas, or who have highly severe skin eruptions and it is possible that percutaneous absorption of this drug increases due to a decline in the skin barrier function, hypercalcemia develops easily and may result in acute renal failure. Administration of this drug should be started at small doses. Patients should be carefully monitored, and periodic tests on serum calcium and renal function should be conducted.

<Reference Information> Company report
Iwata Yohei, et al.: The Japanese Journal of Dermatology, 113 (3): 271-279 (2003) (In Japanese)

9 <Miscellaneous metabolism agents> Epalrestat

[Brand Name] Kinedak Tablets (Ono Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatitis fulminant, hepatic function disorder, jaundice or hepatic failure**: Hepatitis fulminant, hepatic function disorder with significant elevation of AST (GOT), ALT (GPT), etc., jaundice or hepatic failure may occur. Patients should be carefully monitored. If such symptoms are observed, administration should be discontinued, and appropriate measures should be taken.

<Reference Information> Company report

10 <Miscellaneous metabolism agents> Sodium Hyaluronate (injectable dosage form)

(drug products with the indication for gonalgia from chronic rheumatoid arthritis)

[Brand Name] Suvenyl Dispo, Suvenyl Vial (Chugai Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Shock:** Shock symptom may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

11 <Acting mainly on mold> Micafungin Sodium

[Brand Name]	Funguard 50 mg and 75 mg for Infusion (Toyama Fujisawa Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Blood disorder:** Neutropenia, platelets decreased, and haemolytic anaemia may occur. Patients should be carefully monitored through periodic tests, etc. and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Shock, anaphylactoid symptom:** Shock and anaphylactoid symptom may occur. Patients should be carefully monitored and if abnormalities such as blood pressure decreased, oral cavity discomfort, dyspnoea, generalised flushing, angioedema, and urticaria are observed, administration should be discontinued, an air passage should be secured as necessary, and appropriate measures such as administration of adrenaline, steroids, antihistamines, etc. should be taken.
<Reference Information>	Company report

12 <Antivirals> Abacavir Sulfate

[Brand Name]	Ziagen Tablets 100 (GlaxoSmithKline K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	Severe hepatomegaly (hepatic steatosis) due to lactic acidosis and fat deposit
<Reference Information>	Company report

13 <Synthetic narcotics> Fentanyl Citrate

[Brand Name]	Fentanest (Sankyo Co., Ltd.)
[Precautions of Dosage and Administration]	Administration should be carefully conducted while monitoring patient's condition (respiratory depression, etc.). Particularly in cases where this drug is administered additionally or a change is made from a different opioid drug to this drug, take the dosage of the previously administered drug and the duration of analgesic effect into consideration, and adjust the dosage accordingly while paying attention to onset of adverse reactions (refer to the guidelines). If intravenous injection as an opioid drug for the first time in patients with cancer pain, consider starting with a dosage lower than usual (refer to the guidelines), based on individual differences. Dosage should be adjusted while monitoring the conditions of analgesic effects and onset of adverse reactions.
<Reference Information>	Company report Japanese Society of Anesthesiologists — Usage Guidelines for Anesthetics and Drugs Related to Anesthetics 2nd Revision: 14 (2004) (In Japanese)