Pharmaceuticals and Medical Devices Safety Information

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

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Important Safety Information

This section presents details of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification after the issue before previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 199), together with reference materials.

1 Clofedanol Hydrochloride

Brand Name (name of company)	Coldrin Granules, Coldrin Tablets (Nippon Shinyaku Co., Ltd.)
Therapeutic Category	Antitussives
Indications	Cough accompanying the following diseases Acute bronchitis, acute upper respiratory tract inflammation

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

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme exudativum: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme exudativum may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 20s	Antitussive (none)	75 mg 8 days	**Drug rash (erythema multiforme exudativum)** 3 days before administration: Acute sinusitis, acute pharyngitis (moderate) developed. On day 1 of administration: Administration of this drug was started at Hospital A (prescribing doctor). On day 8 of administration (day of discontinuation): Administration of this drug was discontinued. 1 day after discontinuation: Exanthema generalised occurred. 2 days after discontinuation: The patient received consultation at Hospital B. 3 days after discontinuation: The patient received consultation at Hospital C (doctor for treating adverse reactions), and hospitalized the same day. Administration of 30 mg prednisolone (oral administration) was started. 9 days after discontinuation: The symptoms improved and the patient was discharged from the hospital. Administration of prednisolone was discontinued.	Company report

				18 days after discontinuation: 20 mg of prednisolone was readministrated (oral administration) for persisted skin rash on the femoral region. 32 days after discontinuation: As the symptoms improved to a mild degree, prednisolone was switched to betamethasone valerate (external application). 60 days after discontinuation: Administration of 20 mg prednisolone was restarted (oral administration) due to remaining pigmentation. Administration of betamethasone valerate was completed. 74 days after discontinuation: Prednisolone was discontinued. 96 days after discontinuation: The results of DLST were all negative (this drug, clarithromycin, sanactase, carbocisteine and ibuprofen). 117 days after discontinuation: Although mild skin rash persisted, final diagnosis was given by internist. Outcome: The patient recovered with sequelae (sequelae: pigmentation in the femoral region).	
	Concomitant medications: povidone-iodine, betamethasone sodium phosphate, clarithromycin, sanactase, carbocisteine, ibuprofen				

Clinical Laboratory Values

	3 days after discontinuation	7 days after discontinuation
WBC (/mm^3)	7000	8500
Eosinophils (%)	9	2
CRP (mg/dL)	3.74	<0.3

WBC: White Blood Cell CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 50s	Cough (herpes labialis)	75 mg 4 days ↓ (no treatment for 4 days) ↓ 75 mg 2 days	**Drug eruption Stevens-Johnson syndrome type** 3 days before administration: Acute bronchitis developed. On day 1 of administration: Diffuse erythema edematous developed in the femoral regions after the first administration of this drug. On day 2 of administration: At first, it was thought to be a drug rash caused by cherry bark extract/codeine phosphate. Administration of cherry bark extract/codeine phosphate was discontinued, and treatment with steroids was given. On day 4 of administration (day of completion): Administration of this drug was completed. 3 days after completion: Skin rash improved. 5 days after completion (on day 1 of readministration): Bronchitis relapsed. Readministration of this drug was conducted. On day 2 of readministration (day of discontinuation): Administration of this drug was discontinued.	Company report

				Administration of lomefloxacin hydrochloride, fenoterol hydrobromide, and tipepidine hibenzate was started. 1 day after discontinuation: Drug eruption Stevens-Johnson syndrome type developed. (Mouth ulcer, oral pain, and generalised diffuse erythema edematous developed.) 3 days after discontinuation: Intravenous drip infusion of methylprednisolone (from 3 days after discontinuation to 6 days after discontinuation) and oral administration of betamethasone (from 8 days after discontinuation to 10 days after discontinuation) were carried out as the treatment. 11 days after discontinuation: The patient recovered. No drug was administered for herpes labialis.	
	Concomitant medications: cefotiam hydrochloride, sulpyrine, clarithromycin, cherry bark extract/codeine phosphate, lomefloxacin hydrochloride, fenoterol hydrobromide, tipepidine hibenzate				

Clinical Laboratory Values

	3 days after discontinuation
AST (GOT) (IU/L)	15
ALT（GPT）(IU/L)	12
γ-GTP （IU/L）	8
LAP (IU/L)	133
LDH (IU/L)	396
Total bilirubin (mg/dL)	0.5
Al-P （IU/L）	7.3
BUN (mg/dL)	13.8
Creatinine (mg/dL)	1.3
RBC ($\times 10^4/mm^3$)	458
WBC ($/mm^3$)	7700

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
γ-GTP: γ-Glutamyltranspeptidase
LAP: Leucine Aminopeptidase
LDH: Lactate Dehydrogenase
Al-P: Alkaline Phosphatase
BUN: Blood Urea Nitrogen
RBC: Red Blood Cell
WBC: White Blood Cell

2 Flavoxate Hydrochloride

Brand Name (name of company)	Apolakeat Tablets (Towa Pharmaceutical Co., Ltd.) etc.
Therapeutic Category	Urogenital and anal organ agents-Miscellaneous
Indications	Pollakiuria and feeling of residual urine accompanying the following diseases. Nervous pollakisuria, chronic prostatitis, and chronic cystitis

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice (initial symptoms: general malaise, anorexia, pyrexia, itching, yellow ocular colouring, etc.): Hepatic function disorder with significant increase in AST (GOT), ALT (GPT), γ-GTP, Al-P, and bilirubin, and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 80s	Pollakiuria (hypertension)	400 mg 47 days	**Cholestatic liver disorder** Approx. 18 years before administration: Moderate hypertension developed. Approx. 7 years before administration: Severe chronic renal failure developed. On day 1 of administration: Administration of this drug was started. On day 43 of administration: Cholestatic liver disorder developed. AST (GOT), ALT (GPT), direct bilirubin and indirect bilirubin were increased to 149 IU/L, 184 IU/L, 1.7 mg/dL and 0.7 mg/dL, respectively. Jaundice and itchy skin developed. On day 47 of administration (day of discontinuation): Oral administrations of this drug, which had been administrated since on day 1 of administration, and administration of valsartan, which had been administrated since on day 29 of administration, were discontinued. 3 days after discontinuation: AST (GOT) and ALT (GPT) were decreased to 75 IU/L and 105 IU/L, respectively. Direct bilirubin and indirect bilirubin were decreased to 3.5 mg/dL and 2.6 mg/dL, respectively. Jaundice and itchy skin persisted. 14 days after discontinuation: The patient was hospitalized internal medicine (reporting doctor) for a detailed examination on drug-induced hepatitis. Administration of 300 mg ursodeoxycholic acid (oral administration) was started. 25 days after discontinuation: The patient was recovered from cholestatic liver disorder.	Company report
	Concomitant medications: triazolam, sulpiride, valsartan, famotidine				

Clinical Laboratory Values

	On day 8 of administration	On day 43 of administration	3 days after discontinuation	9 days after discontinuation	16 days after discontinuation
Neutrophils (%)	78.9	77.2	70.3	—	—
Eosinophils (%)	2.7	4.4	9.1	8.0	6.0
Basophils (%)	0.5	0.8	0.6	0.0	2.0
Monocytes (%)	5.6	6.4	7.7	2.0	6.0
Lymphocytes (%)	12.3	11.2	11.7	23.0	9.0
AST (GOT) (IU/L)	15	149	75	56	53
ALT (GPT) (IU/L)	9	184	105	82	74
Al-P (IU/L)	214	1866	1862	2165	2287
γ-GTP (IU/L)	38	520	583	677	608
LDH (IU/L)	206	319	273	261	255
Total bilirubin (mg/dL)	0.4	2.4	6.1	8.2	11.8
BUN (mg/dL)	68	46	33	43.2	41.6
Creatinine (mg/dL)	8.64	8.12	7.30	6.79	7.34

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 80s	Pollakiuria (gastric ulcer)	400 mg 121 days	**Hepatic function enzyme elevation** 46 days before administration: Gastrointestinal endoscopy was conducted due to black stools. As gastric ulcer was indicated, administration of famotidine, rebamipide, ecabet sodium, aluminum hydroxide gel/magnesium hydroxide was started. On day 1 of administration: As the patient complained pollakiuria, administration of this drug was started. Frequency of urination was decreased by the efficacy of this drug. On day 98 of administration: In a liver function test conducted as a precautionary measure due to the complaint of heartburn from the patient, increase tendency in AST (GOT) and ALT (GPT) were found. On day 105 of administration: Although another gastrointestinal endoscopy could not be performed, since black stools were (-), the gastric ulcer was considered to have been cured, and the administration of all drugs for gastric ulcer was discontinued. On day 119 of administration: As the result of retesting hepatic function, further increases in AST (GOT) and ALT (GPT) were found Abdominal echo showed no abnormalities. There were also no diseases related to a hepatic function enzyme elevation found even in the abdominal CT, and the symptom was judged as drug-induced.	Company report

				On day 121 of administration (day of discontinuation): Hepatic function was normalized by discontinuation of this drug. 29 days after discontinuation: Hepatic function enzyme was restored. Therapeutic drug: Drip infusion of maintenance fluid	
	Concomitant medications: famotidine, rebamipide, ecabet sodium, aluminum hydroxide gel/magnesium hydroxide				

Clinical Laboratory Values

	55 days before administration	On day 98 of administration	On day11 9 of administration	On day 121 of administration (day of discontinuation)	6 days after discontinuation	29 days after discontinuation
AST (GOT) (IU/L)	16	180	517	470	144	42
ALT (GPT) (IU/L)	10	163	389	367	190	34
Total bilirubin (mg/dL)	0.91	0.93	2.45	1.91	1.63	0.98
LDH (IU/L)	—	505	638	612	361	374

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase

3 Vinorelbine Ditartrate

Brand Name (name of company)	Navelbine Injection 10 and 40 (Kyowa Hakko Kogyo Co., Ltd.)
Therapeutic Category	Antineoplastics plant extract preparations
Indications	Non-small cell lung cancer

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

[Adverse Reactions (clinically significant adverse reactions)]

Acute pancreatitis may occur. Patients should be carefully monitored and if abdominalities such as pain or serum amylase increased etc., are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 50s	Non-small cell lung cancer, stage IV (none)	20 mg/m^2 (once a week) twice	**Acute pancreatitis** 14 days before administration: Fourth chemotherapy with gemcitabine hydrochloride was conducted as pretreatment. On day 1 of administration: Chemotherapy with this drug for the non-small cell lung cancer was started. On day 8 of administration (day of completion): Second administration of this drug was performed. 2 days after completion: Stools were slightly hard. Abdominal pain developed after fully ingesting breakfast. Small amount of hard stools, in addition to cold sweat were observed. There was heavy feeling in epigastric region, similar to a time 20 years ago when the patient had gastroduodenal ulcer. Abdominal area was soft, and there was no tenderness. Tumor mass was not palpated. Intravenous injection of 20 mg of scopolamine butylbromide was conducted. The patient had nausea, vomiting, and stabbing abdominal pain. Intramuscular administration of 7.5 pentazocine and fluid replacement were started. 25 mg of diclofenac sodium suppository was administered. Intramuscular administration of 15 mg pentazocine was conducted. Abdominal pain was slightly improved. Gastroduodenal ulcer was confirmed by gastrointestinal endoscopy (H2 + S2). Based on serum amylase of 2081 IU/L and white blood cell increased, the patient was considered to have acute pancreatitis, and administration of 400 mg gabexate mesilate, 4 g flomoxef sodium, and 40 mg omeprazole was started. Afterwards, 3 intravenous injections of 15 mg of pentazocine were conducted for abdominal pain. 3 days after completion: Pyrexia of 37.8°C and swollen abdomen developed. Abdominal ultrasound was conducted. There was no pancreatic enlargement, but echo-poor was confirmed. Main pancreatic duct was mildly dilated. Fluid replacement and gabexate mesilate were increased. Constipation was noted. 6 days after completion: Intestinal obstruction was suspected due to high-pitched intestinal murmur. Colonoscope was conducted, but no intestinal obstruction was found. Watery stools occurred 8 to 9 times. Abdominal pain was slightly alleviated. Serum amylase was decreased to 267 IU/L. 10 days after completion: The patient had loose stools. Abdominal pain	Company report

				was mild, and swollen abdomen was alleviated. Periumbilical region was slightly hard, and the patient had mild tenderness. In an abdominal CT, localized ascites in the periumbilical region, small amount of left pleural effusion, mild spleen enlarged, dilation of main pancreatic duct, some obscurity in pancreatic contour, and dilation of the transverse colon were confirmed. 13 days after completion: Abdominal pain was alleviated. The patient had several times of paste-like diarrhoea. Elimination of ascites was confirmed by abdominal ultrasound. There were no abnormalities in pancreas other than prominence of dilation of main pancreatic duct. 16 days after completion: The patient had sooty stools twice. Liquid diet was started, but there was no increase in abdominal pain. Pyrexia of the low 37°C persisted. 18 days after completion: Abdominal pain in upper right side was noted, but there was no irradiation of pain to back. The patient had somewhat black diarrhoea stool once. There were some tympanic resonance in abdominal area and high-pitched increased bowel sounds. The patient ate more than half of meals.	
	Concomitant medications: ramosetron hydrochloride, betamethasone sodium phosphate				

Clinical Laboratory Values

	On day 8 of admin. (day of completion of admin.)	2 days after completion	6 days after completion	7 days after completion	9 days after completion	13 days after completion	17 days after completion
Serum amylase (IU/L)	—	2081	267	—	269	283	227
Urine amylase (IU/L)	—	31440	—	—	373	—	—
WBC (/mm^3)	5400	11800	2900	3400	4500	5600	5100
RBC ($\times 10^4/mm^3$)	368	436	309	313	324	352	340
Haemoglobin (g/dL)	11.8	13.9	9.7	10.1	10.2	11.2	10.5
Haematocrit (%)	34.5	41.4	29.0	29.5	30.4	32.8	31.3
AST (GOT) (IU/L)	30	32	28	28	—	27	22
ALT (GPT) (IU/L)	31	42	33	29		26	16
LDH (IU/L)	186	194	448	412	—	287	214
Blood glucose (mg/dL)	—	—	—	106	—	113	—

WBC: White Blood Cell
RBC: Red Blood Cell
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 70s	Non-small cell lung cancer, stage IV (none)	25 mg/m^2 (once a week) 4 times	**Acute pancreatitis** On 1 day of administration: Chemotherapy with this drug and gemcitabine hydrochloride for non-small cell lung cancer was started. On day 28 of administration (day of completion): Fourth administration of this drug and gemcitabine hydrochloride was conducted. 1 day after completion: (day after last day of administration) The patient had epigastric pain since before breakfast. She ate nearly a full breakfast, but vomited large amounts of the breakfast afterwards. Abdominal pain was intensified. Chills and shivering were observed. As there was oxygen saturation decreased, oxygen inhalation was started. Chills disappeared gradually through fluid replacement and administration of diclofenac sodium suppositories, but severe abdominal pain and back pain were intensified again in the evening. Although the patient was treated with pentazocine, flurbiprofen axetil, scopolamine butylbromide, diclofenac sodium suppositories, etc., the abdominal pain hardly improved. 2 days after completion: As acute pancreatitis was suspected in a blood biochemistry test, administration of fluid replacement, gabexate mesilate, panipenem/betamipron was started under fasting conditions. 3 days after completion: Abdominal pain was alleviated. 6 days after completion: Back pain disappeared, only heaviness in epigastric region remained. 8 days after completion: There were no more complaints of abdominal pain. 10 days after completion: Liquid diet was started. 14 days after completion: The patient had sufficient bowel movements.	Company report
	Concomitant medications: gemcitabine hydrochloride, betamethasone sodium phosphate				

Clinical Laboratory Values

	On day 20 of administration	2 days after completion	3 days after completion	6 days after completion	9 days after completion	14 days after completion
Serum amylase (IU/L)	—	746	194	62	34	102
Urine amylase (IU/L)	—	3006	879	105	—	—
WBC (/mm^3)	6900	12300	5200	5600	7300	9800
RBC (×10^4/mm^3)	388	348	320	328	322	370
Haemoglobin (g/dL)	11.6	10.4	9.5	9.8	9.6	10.9
Haematocrit (%)	33.6	30.2	27.6	27.7	27.5	32.2
AST (GOT) (IU/L)	11	227	72	35	24	13
ALT (GPT) (IU/L)	9	171	101	45	24	11
LDH (IU/L)	209	410	156	184	—	254

WBC: White Blood Cell
RBC: Red Blood Cell
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase

4 Phtharal

Brand Name (name of company)	Disopa Solution 0.55% (Johnson & Johnson K.K.)
Therapeutic Category	Germicides and disinfectants
Indications	Chemical disinfection and sanitization of medical devices

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

[PRECAUTIONS of Indications]

Since bullous keratopathy etc. has been reported in patients who had used surgical instruments during ultrasonic cataract surgery that were sanitized with this solution, this solution should not be used for surgical instruments used for ultrasonic cataract surgery.

[Precautions of Dosage and Administration]

Promptly wash medical devices, etc. thoroughly after use, dry them and sanitize them with this solution. [If medical devices etc. are immersed directly in this solution without washing them first, it may become difficult to remove living organisms and secretions.]
Thoroughly rinse medical devices after sanitizing them with this solution and dry them off (Refer to "Important Precautions").
Caution should be exercised for decrease in concentration resulting from cleaning water mixing in. [Use the devices after confirming that the phtharal concentration is 0.3% and more with Disopa test strips, etc. In addition, do not use devices if over 14 days have passed.]

[Important Precautions]

Caution should be exercised for the following points when handling this solution.
1)This solution should not be handled by person with a history of hypersensitivity to this solution or phtharal.
2)Since this solution has protein-binding properties, do not handle this solution with bare hands. In addition, caution should be exercised so that this solution does not directly come in contact with human bodies. When handling this solution, wear protective apparel such as rubber gloves, goggles, and gowns.
3)If this solution comes in contact with the skin, wash the skin with water immediately. If this solution enters into the eyes, wash the affected eye immediately with running water for 15 minutes and more and seek treatment from a specialist. If wearing contact lenses, remove the contact lens, wash the affected eye thoroughly, and seek treatment from a specialist. The removed contact lens should not be reused.
This solution should not be used on human bodies.
Since it has been reported that symptoms such as anaphylactic shock, esophageal/gastric mucosal damage, chemical burn, coloring of the oral cavity, etc. have been observed in patients on which medical devices such as flexible

cystoscopes and transoesophageal echocardiography (TEE) probes that were sanitized with this solution were used, caution should be exercised for the followings.

1) After sanitizing, rinse this solution off of the device using a large amount of water.
2) Extra caution should be exercised for the devices with complex structures, such as those with fine pores, etc., as such devices may not sufficiently washed.
3) The medical devices that were sanitized using this solution should not be used in patients with a history of hypersensitivity to this solution or phtharal.

<Reference Information> Company report

Case Summary

No.	Patient		Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)	Clinical course and therapeutic measures	
1	Female 70s	Disinfection and sanitization of for surgical instruments used for ultrasonic cataract surgery (none)	**Bullous keratopathy** 7 days before use: Surgical instruments such as handpieces, chips, sleeves, etc. used for ultrasonic cataract surgery were disinfected and sanitized with this solution. After washing the apparatuses, they were dried for 1 day in a sterilizing room. 6 days before use: The apparatuses disinfected in the above process were sterilized in an autoclave. On day 1 of use: An ultrasonic cataract surgery was performed using the apparatuses sterilized in the above process. 1 day after use: Bullous keratopathy developed. Intraocular pressure: 12 mmHg Visual acuity: hand-motion Number of corneal endothelial cells: could not be measured (1664 cells/mm^2 before operation)	Company report
	Drugs used during operation: sodium hyaluronate, cefmenoxime hydrochloride, bromfenac sodium, intraocular perfusion/washing fluid			

No.	Patient		Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)	Clinical course and therapeutic measures	
2	Male 60s	Disinfection/ sanitization of flexible cystoscope (none)	**Anaphylactic shock** On day 1 of use: The patient was examined with a flexible cystoscope that was disinfected and sanitized using this solution. He complained of general malaise and rashes after returning home. General rashes, flushing, slight syanosis of lip developed. Blood pressure was 90 mmHg. Blood vessel secured immediately, transfusion, and oxygen inhalations were performed. Blood pressure was increased without using a vasopressor. After performing intravenous injection of hydrocortisone sodium phosphate, blood pressure was stabilized (140 mmHg range). Urethral anesthetic and sanitizing agent for flexible cystoscope were suspected but the cause was unclear.	Company report
	Drugs used during examination: lidocaine hydrochloride, benzalkonium chloride			

No.	Patient		Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)	Clinical course and therapeutic measures	
3	Female 70s	Disinfection and sterilization of transoesophageal ecoprobe (none)	**Oral coloring, damage to the mucosal membrane of the esophagus, etc.** On day 1 of use: Emergent coronary artery bypass surgery was performed for unstable angina. Due to insufficient evaluation of the cardiac function before the surgery, and with the purpose of monitoring cardiac function during the surgery, a transoesophageal echo probe that was disinfected and sterilized using this solution was inserted into the patient after general anesthesia. At the end of the surgery (duration of surgery: 6 hours and 5 minutes, duration of anesthesia: 8 hours and 25 minutes), black coloring on the patient's lip and inside the mouth was confirmed. 1 day after use: After awakening from the anesthetic the day after the surgery, the patient complained of pharyngeal difficulties, as well as of difficulties ingesting food and drinking fluids. Black coloring remained on the lip and inside the mouth. Pharyngeal and upper gastrointestinal tract endoscopy revealed several ulcerative lesions on the hypopharynx and esophageal wall.	Company report
	Drugs used during examination: unknown			

5 Fluorouracil (injectable dosage form)

Brand Name (name of company)	5-FU Injection 250 Kyowa (Kyowa Hakko Kogyo Co., Ltd.)
Therapeutic Category	Antimetabolites
Indications	Remission of subjective and objective symptoms of the following diseases: Gastric cancer, liver carcinoma, colonic cancer, rectal cancer, breast cancer, pancreatic carcinoma, cancer of the uterine cervix, cancer of the uterine body, ovarian cancer It should be noted that this product must be used concurrently with other anti-tumour agents or radiation treatments for the following diseases: Esophageal carcinoma, lung cancer, head and neck tumour

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

[Adverse Reactions (clinically significant adverse reactions)]	**Hyperammonemia accompanying consciousness disturbed** may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 50s	Esophageal cancer (none)	1125 mg for 5 days	**Hyperammonemia** 1 month before administration: First course of chemotherapy with 1125 mg of this drug (5 days) + 113 mg of cisplatin (1 day) was implemented. On day 1 of administration: Second course of the above chemotherapy was started, together with a high-calorie infusion containing glucose, amino acids, and electrolytes and infusion of physiological saline. On day 5 of administration: General malaise was started to intensify at around noon. The patient fell into the state of unrest late at night. High blood ammonia of 452 μg/dL was confirmed in a blood sample, and in order to avoid protein loading, the high-calorie infusion was discontinued and switched to a physiological saline. Administration of this drug was continued. Intravenous injection of diazepam 1A administered, but state of unrest did not improve. On day 6 of administration (day of discontinuation): In a reexamination, blood ammonia was still high, at 448 μg/dL. Administration of this drug was discontinued and intravenous drip infusion of 1000 mL of an amino acid preparation for liver failure was started. Function kidney decreased thought to have resulted from cisplatin was confirmed (serum creatinine 1.8 mg/dL). Depressed level of consciousness (JCSII-20) was also confirmed. The level of consciousness was further depressed (JCSIII-300) around noon. Since faecal occult blood was positive and a small amount of haemorrhage was confirmed during salivary inhalation, haemorrhage in the digestive tract was suspected despite a decrease in the haemoglobin not being confirmed, and intravenous drip infusion of carbazochrome sodium sulfonate 3A and tranexamic acid 1A was started. Urine output of 300 to 400 mL/h and polyuria confirmed. Infusion of maintenance fluid was conducted while looking at the balance between in and out. Around the evening, blood ammonia decreased to 206 μg/dl and the level of consciousness also improved (JCSII-20). The patient complaint of mild abdominal pain upper. During the night, blood ammonia was normalized to 18 μg/dL. Serum creatinine was 1.7 mg/dL. Level of consciousness was JCSI-2. The patient had intermittent abdominal pain. 1 day after discontinuation: Since blood ammonia was returned to the normal range of 28 μg/dL, the patient was judged to have recovered from hyperammonemia. Consciousness level was normal. Urine output was 300 mL/h. 2 days after discontinuation: CT showed no obvious abnormalities other than oesophageal carcinoma.	Company report

				4 days after discontinuation: Radiation treatment was restarted. No haemorrhaging was observed in esophageal endoscopy. Urine output was normalized to 110 to 120 mL/h. 5 days after discontinuation: Serum creatinine was decreased to 1.5 mg/dL. 9 days after discontinuation: Serum creatinine was returned to 1.1 mg/dL.	
	Concomitant medications: cisplatin, ramosetron hydrochloride, dexamethasone sodium phosphate, maintenance fluid, high-calorie infusion liquid containing glucose, amino acids, and metabolites, physiological saline				

Clinical Laboratory Values

	Before administration	On day 1 of admin.	Late at night on day 5 of admin.	Morning on day 6 of admin.	Afternoon on day 6 of admin.	Night-time on day 6 of admin.	1 day after discontinuation	2 days after discontinuation	9 days after discontinuation
BUN (mg/dL)	7	9	28	36	42	46	40	20	11
Serum creatinine (IU/L)	0.9	0.8	1.9	1.8	1.8	1.7	1.7	1.7	1.1
AST (GOT) (IU/L)	16	19	26	22	26	20	21	24	23
ALT (GPT) (IU/L)	11	18	27	28	27	25	21	22	13
LDH (IU/L)	119	144	179	182	173	166	152	153	155
Al-P (IU/L)	182	211	187	165	160	165	168	185	213
γ-GTP (IU/L)	44	49		52				82	67
Serum sodium (mEq/L)	139	144	133	138	137	138	137	134	137
Serum potassium (mEq/L)	3.1	4.5	4.7	5.5	4.6	4.2	4.0	3.6	4.0
Serum chloride (mEq/L)	100	106	96	104	104	106	108	99	98
Blood ammonia (μg/dL)	—	—	452	448	206	18	28	42	19
Urine output (mL/day)	1896	—	—	—	—	—	7261	5746	2205

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 50s	Oropharyngeal cancer neck metastasis (none)	1400 mg 5 days	**Consciousness disturbed, hyperammonemia** 3 days before administration: Together with administration of cisplatin, hydration was carried out through a total of 2700 mL of high-calorie infusion containing glucose, amino acids, and electrolytes + physiological saline. On day 1 of administration: Chemotherapy through 24-hour continuous intravenous injection of high-calorie infusion containing glucose, amino acids, and electrolytes and 1400 mg of this drug (5 days) + 140 mg of cisplatin (1 day) was started.	Company report

				On day 5 of administration (day of discontinuation): Consciousness disturbed developed in the morning. The patient reacted to pain and stimulation, but not when addressed. Sursumvergence developed. Level of consciousness was JCSII-20. Administration of this drug was immediately discontinued. Head CT showed no clear findings. Blood test was performed around noon, The result showed high serum ammonia of 298 μg/dL,which suspected consciousness disturbed due to hyperammonemia. Based on serum creatinine at 2.79 mg/dL, findings of acute renal failure due to cisplatin were also confirmed. Administration of amino acid preparatin for liver failure was started. Level of consciousness was JCSII-10 in the evening. 1 day after discontinuation: Consciousness became clear and returned to a normal state in the morning. Blood ammonia improved to 42 μg/dL.	
	Concomitant medications: cisplatin, pentazocine, ondansetron hydrochloride				

Clinical Laboratory Values

	Before administration	On day 2 of administration	On day 5 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation
BUN (mg/dL)	16	21	54	84	99
Serum creatinine (mg/dL)	0.95	0.93	2.79	4.0	4.5
Total bilirubin (mg/dL)	0.8	0.7	0.8	0.8	0.5
AST (GOT) (IU/L)	18	26	28	26	24
ALT (GPT) (IU/L)	22	48	30	29	27
LDH (IU/L)	128	143	213	189	169
Al-P (IU/L)	322	283	245	258	255
Serum sodium (mEq/L)	138	137	130	130	128
Serum potassium (mEq/L)	4.1	3.9	3.5	3.4	3.3
Serum chloride (mEq/L)	99	100	87	88	90
Blood ammonia (μg/dL)	—	—	298	42	52

BUN: Blood Urea Nitrogen
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
Al-P: Alkaline Phosphatase

6 Doxazosin Mesilate

Brand Name (name of company)	Cardenalin Tablets 0.5 mg, 1 mg, 2 mg, and 4 mg (Pfizer Japan Inc.)
Therapeutic Category	Antihypertensives
Indications	Hypertension, hypertension due to pheochromocytoma

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis, hepatic function disorder, jaundice: Hepatitis, hepatic function disorder with significant increases in AST (GOT), ALT (GPT), and γ-GTP levels, etc. and jaundice may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 60s	Essential hypertension (liver disorder, headache)	2 mg 125 days	**Acute hepatitis** Drinking habit: yes On day 1 of administration: Although 5 mg of amlodipine besilate had been administered for hypertension, medication was changed to 2 mg of this drug due to headache. On day 116 of administration: As the patient complaint of strong fatigability, a liver function test was conducted. Since high AST (GOT) and ALT (GPT) values were confirmed, abstinence from alcohol and treatment through hospitalization were recommended but the patient refused. On day 123 of administration: Since worsening of data was found out in a reexamination, the patient was referred to another hospital for testing and hospitalization. On day 124 of administration: The patient was hospitalized due to jaundice. The result of hepatitis viral test was negative. Intravenous administration of 500 mL of a preparation containing glucose, electrolytes, and amino acids, glycyrrhizin/glycine/cysteine 1A, fursultiamine hydrochloride, liver extract/flavin adenine dinucleotide was started. On day 125 of administration (day of discontinuation): Administration of this drug was discontinued, and administration of 2 mg trichlormethiazide was started from the next day. 4 days after discontinuation: Although hepatic enzyme values tended to improve, jaundice worsened. Blood collection for DLST was performed. Intravenous administration of 500 mL of glucose acetated Ringer's solution and glycyrrhizin/glycine/cysteine 1A. 9 days after discontinuation: Intravenous administration of glycyrrhizin/glycine/cysteine 1A was conducted. Administration of 150 mg ursodeoxycholic acid was conducted for exacerbation of jaundice.	Company report

				20 days after discontinuation Acute hepatitis improved, and the patient was recovered from jaundice. 31 days after discontinuation: Recovery from hepatitis was confirmed. IgM-HA antibody, HBs antigen, HBc antibody, HCV antibody: (−) <DLST results> This drug: negative	
	Concomitant medications: amfenac sodium				

Clinical Laboratory Values

	7 months before administration	On day 116 of administration	On day 123 of administration	On day 124 of administration	3 days after discontinuation	6 days after discontinuation	31 days after discontinuation
AST (GOT) (IU/L)	27	478	1137	1080	690	350	22
ALT (GPT) (IU/L)	40	845	1571	1680	1530	967	36
γ-GTP (IU/L)	173	246	551	694	872	772	255
Al-P (IU/L)	261			542	630	550	288
LDH (IU/L)	415	—	—	—	—	298	204
Total bilirubin (mg/dL)	1.7	1.59	2.87	2.4	2.9	3.7	1.4
Direct bilirubin (mg/dL)	—	—	—	—	—	2.0	—
Total protein (g/dL)	—	6.7	—	6.7	6.6	—	—
Cholinesterase (IU/L)				4922	5180	4455	
Albumin (%)	—	—	—	66.2	60.6	—	—
Total cholesterol (mg/dL)	—	207	—	197	—	—	254

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 40s	Hypertension (hyperuricemia, hepatopathy alcoholic, hyperlipidaemia, gout)	1 mg 47 days	**Liver disorder** Drinking habit: yes Before administration: Liver disorder due to alcohol was suspected. Approx. 4 months before administration: Administration of 5 mg amlodipine besilate for hypertension, and 50 mg benzbromarone, and 6 g potassium citrate/sodium citrate for hyperuricemia were started, respectively. On day 1 of administration: 1 mg of this drug was additionally administered for hypertension. On day 46 of administration: A periodic testing showed abnormal laboratory findings in hepatic function. The patient did not have any subjective symptoms. On day 47 of administration (day of discontinuation): Administration of amlodipine besilate was continued, and administration of this drug, benzbromarone, and potassium citrate/sodium citrate were discontinued. 500 mL of glucose maintenance fluid, 40 mL of glycyrrhizin/glycine/cysteine, and liver extract/flavin adenine dinucleotide 1A were intravenously administered for 3 days.	Company report

				2 days after discontinuation: The values of liver function tests decreased. Viral infection was suspected, but since antigen-antibody tests were negative, a follow-up was conducted. 10 days after discontinuation: The values of liver function tests were markedly improved. 11 days after discontinuation: Administration of benzbromarone and potassium citrate/sodium citrate was restarted. 45 days after discontinuation: Test results were slightly high, but conditions returned to those from before. During the clinical course, there were no changes in alcohol intake. HA antibody, HBs antigen, HCV antibody: (−) DLST test: not performed	
	Concomitant medications: amlodipine besilate, benzbromarone, potassium citrate/sodium citrate				

Clinical Laboratory Values

	On day 1 of administration	On day 46 of administration	2 days after discontinuation	10 days after discontinuation	45 days after discontinuation
AST (GOT) (IU/L)	36	1523	60	35	41
ALT (GPT) (IU/L)	53	1365	349	85	66
γ-GTP (IU/L)	154	270	310	223	180
Al-P (IU/L)	—	—	231	—	—
Total bilirubin (mg/dL)	—	—	0.4	0.7	0.5
Cholinesterase (IU/L)	—	—	5476	—	—

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

7 Sodium Risedronate Hydrate

Brand Name (name of company)	Actonel Tab. 2.5 mg (Ajinomoto Co., Inc.) Benet Tablets 2.5 mg (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Miscellaneous metabolism agents
Indications	Osteoporosis

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder with significant increases in AST (GOT), ALT (GPT), and γ-GTP levels and jaundice may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 70s	Osteoperosis (hypertension, chronic gastritis, constipation)	2.5 mg 23 days	**Hepatic function disorder** 6 years before administration: Treatment for hypertension with atenolol was started. 3 years before administration: Medication was changed to enalapril maleate (due to bradycardiac tendency). Approx. 6 months before administration: The patient had distention and epigastric pain. Gastritis erosive was found in gastroscopy. Approx. 2 months before administration: Fracture of right upper arm occured. Approx. 1 month before administration: Constipation developed. On day 1 of administration: Osteoporosis was confirmed in lumbar spine XP, and administration of this drug was started. On day 8 of administration: Gastralgia was (−). On day 20 of administration: Jaundice was (−). On day 23 of administration (day of discontinuation): Upper abdominal pain developed. Administration of this drug was discontinued. Lafutidine was discontinued, and switched to sodium rabeprazole. General malaise developed. Drip infusion[*1)] was implemented. Bilirubin value was not measured during blood collection, and jaundice was not observed. 11 days after discontinuation: General malaise exacerbated. Loss of appetite was (+). Upper abdominal pain was slightly alleviated. Queasy was (+). Hepatic mass was not found in abdominal echo, but there was rough image of hepatic parenchyma. Dilation of intrahepatic bile ducts was (−), common bile duct was φ10 mm, ascites was (−), and slightly enlarged spleen. Drip infusion[*1)] was implemented. Oral administration of drugs other than enalapril maleate and magnesium oxide discontinued. Bilirubin value increased, a little bit of jaundice was observed (yellow tinge apparent). HBs antigen RPH was (–). HCV antibody LA determination was (−). 14 days after discontinuation: Drip infusion[*1)] was conducted. 15 days after discontinuation: The patient was referred to a physician at another hospital and received medical consultation. She was hospitalized. Total bilirubin value was 5.6 mg/dL, and jaundice was confirmed. 41 days after discontinuation: Decrease in values was confirmed at the hospital where the patient was referred to. Total bilirubin was 2.0 mg/dL, AST (GOT) was 62 IU/L, and ALT (GPT) was 41 IU/L.	Company report

				Autoantibody measurement: not performed Drip infusion[*1)]: 200 mL of acetic acid maintenance fluid, 20 mL of glycyrrhizin/glycine/cysteine, 200 mg of glutathione, 400 mg of methylmethionine sulfonium chloride, 4 mL of a deproteinized calf blood extract.	
	Concomitant medications: magnesium oxide, sodium rabeprazole, mosapride citrate, enalapril maleate, lafutidine				

Clinical Laboratory Values

	9 months before admin.	6 months before admin.	On day 23 of admin. (day of discontinuation)	11 days after discontinuation	15 days after discontinuation	25 days after discontinuation	41 days after discontinuation
Total bilirubin (mg/dL)	—	—	—	4.4	5.6	3.4	2.0
AST (GOT) (IU/L)	21	17	600	432	179	101	62
ALT (GPT) (IU/L)	13	12	413	299	179	71	41
Al-P (IU/L)	—	—	—	456	567	324	347
LDH (IU/L)	417	193	431	—	—	—	219
γ-GTP (IU/L)	19	17	244	242	243	187	151
CRP	(−)	(−)	(1+)	(1+)	—	—	—
WBC (/mm^3)	5800	6500	5000	3700	—	—	5100
RBC ($\times10^4$/mm^3)	373	376	403	383	—	—	347
PLT ($\times10^4$/mm^3)	19.7	18.3	11.5	9.2	8.9	8.6	13.6

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
CRP: C-Reactive Protein
WBC: White Blood Cell
RBC: Red Blood Cell
PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 60s	Osteoporosis (hypertension, anxiety neurosis, irritable bowels, dizziness, gallstones)	2.5 mg 38 days	**Hepatic function disorder** On day 1 of administration: As the patient was indicated bone mass decreased in bone mineral assay, this drug was prescribed. Administration of this drug was started. On day 38 of administration (day of discontinuation): Regular blood test showed severe hepatic function disorder [AST (GOT 1810 IU/L, ALT (GPT) 986 IU/L, γ-GTP 307 IU/L). There were no particular subjective symptoms. Administration of this drug was discontinued. 1 day after discontinuation: The patient was referred to the other hospital. She was hospitalized for a detailed examination and treatment. Unknown: In a blood test conducted after hospitalization, virus hepatitis was negative. Data gradually improved. Gallstones were confirmed in an echo, and although the possibility of these gallstones being the cause were considered, since there was an increase in the eosinophils and both AIH (autoimmune hepatitis) and PBC (primary biliary cirrhosis) were negative, the DLST that was performed in relation to this drug was positive. 12 days after discontinuation: The patient was discharged from the hospital.	Company report

				14 days after discontinuation: The patient visited this hospital. With AST (GOT) 720 IU/L, ALT (GPT) 513 IU/L, LDH 813 IU/L, Al-P 776 IU/L, and γ-GTP 626 IU/L, persisting hepatic function disorder was confirmed, but there were no particular subjective symptoms. Follow-up monitoring was carried out while patient rested. 35 days after discontinuation: Recovery to AST (GOT) 19 IU/L, ALT (GPT) 12 IU/L, LDH 236 IU/L, Al-P 236 IU/L, and γ-GTP 122 IU/L. Results of serological test (performed at the other hospital; testing date unclear) ANA (−), AMA-II (−), HBs-Ag (−), EBNA 40x, VCA-IgG 40x, HBe-AG (−), IgM-HBc (−), IgM-HA (−), HCV-Ab (−) <DLST results (performed at the other hospital; testing date unclear)> This drug: S.I. 3.3, positive (1.8 and more is positive)	
	Concomitant medications: nifedipine, etizolam, bifidobacterial preparation, betahistine mesilate				

Clinical Laboratory Values

	143 days before admin.	71 days before admin.	On day 38 of admin. (day of discontinuation)	1 day after discontinuation	4 days after discontinuation	10 days after discontinuation	14 days after discontinuation	35 days after discontinuation
AST (GOT) (IU/L)	24	19	1810	394	37	17	720	19
ALT (GPT) (IU/L)	17	13	986	637	195	37	513	12
LDH (IU/L)	—	259	—	570	261	266	813	236
Al-P (IU/L)				473	315	242	776	236
γ-GTP (IU/L)	63	36	307	296	201	121	626	122
Total bilirubin (mg/dL)	—	—	—	0.9	0.7	0.5	0.9	0.5
Direct bilirubin (mg/dL)	—	—	—	0.2	0.2	0.2	—	—
WBC (/mm^3)	6170		3700	5200	5500	5900		5640
RBC ($\times10^4$/mm^3)	491	—	484	459	427	411	—	463
PLT ($\times10^4$/mm^3)	32.9	—	27.2	21.0	20.2	20.2	—	25.5
Urea nitrogen (mg/dL)	16.5	—	13.0	11.2	10.9	10.3	—	—
Creatinine (mg/dL)	0.8	—	0.67	0.69	0.72	0.67	—	—

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
Al-P: Alkaline Phosphatase
WBC: White Blood Cell
RBC: Red Blood Cell
PLT: Platelet

2

Revision of PRECAUTIONS

(No. 155)

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 bulletin before previous one (Pharmaceuticals and Medical Devices Safety Information No. 199) (excluding those presented in "1. Important Safety Information" of this Bulletin.), together with reference materials.

1 <Antipyretics and analgesics, anti-inflammatory agents> Lornoxicam

[Brand Name]	Lorcam Tab. 2 mg and 4 mg (Taisho Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome)**: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Acute renal failure**: Since acute renal failure may occur, patients should be carefully monitored. If abnormalities (edema, oliguria, hematuria, protein urine, increased BUN, increased blood creatinine, hypoalbuminemia, etc.) are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

2 <Cardiotonics> Dobutamine Hydrochloride

[Brand Name]	Dobutrex Injection 100 mg (Mochida Pharmaceutical Co., Ltd.), and others
[Other Precautions]	Although not approved in Japan, it has been reported that life-threatening cardiac ruptures have occurred during dobutamine stress tests that were implemented at an early stage after acute myocardian infarction in foreign countries.
<Reference Information>	Company report

3 <Antiarrhythmic agent> Pilsicainide Hydrochloride

[Brand Name]	Sunrythm Capsules 25 mg and 50 mg, Sunrythm Injection 50 (Daiichi Suntory Pharma Co., Ltd.), and others
[Important Precautions]	Caution should be exercised as there have been reports of electrocardiogram changes (ST elevated of the bundle branch block right and right-sided chest leads (V_1 to V_3)) characteristic to the Brugada syndrome becoming apparent, as well as of the occurrence of ventricular fibrillation, ventricular tachycardia, and premature ventricular ectopic beats accompanying such electrocardiogram changes.
<Reference Information>	Company report

4 <Antiarrhythmic agent> Flecainide Acetate

[Brand Name] Tambocor Tablets 50 mg and 100 mg, Tambocor Injection 50 mg (Eisai Co., Ltd.)

[Important Precautions] As there have been reports of electrocardiogram changes (ST elevated of the bundle branch block right and right-sided chest leads (V_1 to V_3)) characteristic to the Brugada syndrome becoming apparent, Caution should be exercised for the occurrence of ventricular fibrillation, ventricular tachycardia, and premature ventricular ectopic beats accompanying such electrocardiogram changes.

<Reference Information> Company report

5 <Cardiovascular agents-Miscellaneous> Concentrated Glycerin/Fructose

[Brand Name] Glyceol Injection (Otsuka Pharmaceutical Factory, Inc.), and others

[Important Precautions] There have been reports of nerve damage (convulsion, tachypnoea, lethargy etc.) and death resulting from the administration of this drug for brain oedema and to prevent brain oedema induced by incomplete metabolism in neonates, infants, and young children with fructose-1,6-bisphosphatase (FBPase) deficiency.

Blood glucose level and blood lactic acid values should be measured, when administering this drug for brain oedema and unknown consciousness disturbed in neonates, etc., and the administration should be discontinued if abnormalities in the gluconeogenesis, especially FBPase deficiencies are suspected. In addition, during and after administration of this drug, confirm that there is no hypoglycemic tendency, and that neurological manifestations and brain oedema representative of consciousness disturbed have not exacerbated. If any exacerbations are observed, administration should be discontinued to such patients.

<Reference Information> Company report
Hasegawa, Y., et al.: Pediatrics International, 45 (1): 5 (2003)

6 <Peptic ulcer agent> Rebamipide

[Brand Name] Mucosta Granules 20%, Mucosta Tablets 100 (Otsuka Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid reactions**: Shock or anaphylactoid reactions may occur. Patients should be carefully monitored. If abnormalities are observed, the drug should be discontinued and appropriate measures should taken.

<Reference Information> Company report

7 <Mixed hormone preparations> Androgen and Estrogen Preparation

(indications include climacteric disturbance and osteoporosis)

[Brand Name] Primodian-Depot (Nihon Schering K.K.), Bothermon Depot 50 mg (Teikoku Hormone Medical Co., Ltd.), and others

[Contraindications] Patients with arterial thromboembolic disorders (for example, coronary heart disease, cerebral stroke) or patients with a history of such diseases.

[Precautions of Dosage and Administration] If administering this drug for "osteoporosis", the bone density should be measured 6 months to 1 year after administration and if efficacy is not confirmed, administration should be discontinued and other treatment should be considered.

[Careful Administration] Patients with endometriosis

Patients with a strong genetic predisposition of breast cancer, patients with breast nodules, patients with mastopathy, and patients with abnormalities found in breast X-ray images

Patients in a preoperative state or prolonged resting state

Patients with systemic lupus erythematosus

[Important Precautions]

As a result of a study conducted overseas, higher risk of breast cancer was reported in women with concomitant estrogen and progesterone over the long-term, compared to the control group. It was reported that this risk increased the longer the period of concomitant administration became. Physicians should adequately advise the patients of the risks and benefits of this drug, limit the use of this drug to the minimum, and avoid chronical administration over a long-term.
Medical histories including histories of diseases and genetic predisposition should be taken, and breast examination and gynecological examination should be performed before initiating therapy with this drug. After starting administration, periodic breast examinations and gynecological examinations should be performed.

[Other Precautions]

As a result of epidemiologic investigations in postmenopausal women treated with estrogen preparation over the long-term, higher risk of endometrial cancer was reported compared to women in control group. It was reported that this risk increases in proportion to the period of use and the amount of use, and that the risk is suppressed by the concomitant administration of a progesterone preparation.

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

As a result of a randomized clinical trial in postmenopausal women conducted in the United States, significantly higher risk of breast cancer was reported in the conjugated estrogen and progesterone preparation group compared to placebo (hazard ratio = 1.24). As a result of an epidemiologic investigation in the United Kingdom, significantly higher risk of breast cancer was reported in women with concomitant estrogen compared to placebo (2.00 times higher). It was reported that this risk increased the longer the period of concomitant administration became (less than 1 year: 1.45 times; 1–4 years: 1.74 times; 5–9 years: 2.17 times; more than 10 years: 2.31 times).

HRT and the risks of coronary heart disease

As a result of a randomized clinical trial in postmenopausal women conducted in the United States, higher risk of coronary heart disease was reported in the in the conjugated estrogen and progesterone preparation group compared to placebo, and that this risk was significantly high particularly after 1 year from the start of administration (hazard ratio = 1.81).

HRT and the risks of stroke

As a result of a randomized clinical trial in postmenopausal women conducted in the United States, significantly higher risk of stroke (mainly cerebral infarction) was reported in the conjugated estrogen and progesterone preparation group compared to placebo (hazard ratio = 1.31).

HRT and the risks of dementia

As a result of a randomized clinical trial in postmenopausal women over aged 65 conducted in the United States, significantly higher risk of dementia including Alzheimer's disease was reported in the in the conjugated estrogen and progesterone preparation group compared to placebo (hazard ratio = 2.05).

<Reference Information>

Company report

8 <Mixed hormone preparations>
Androgen and Estrogen Preparation

(indications include climacteric disturbance and exclude osteoporosis)

[Brand Name] Esjin Depot (Fuji Pharma Co., Ltd.), Bothermon Injection 5.0 mg (Teikoku Hormone Medical Co., Ltd.)

[Contraindications] Patients with arterial thromboembolic disorders (for example, coronary heart disease, cerebral stroke) or patients with a history of such diseases.

[Careful Administration] Patients with endometriosis

Patients with a strong genetic predisposition of breast cancer, patients with breast nodules, patients with mastopathy, and patients with abnormalities found in breast X-ray images

Patients in a preoperative state or prolonged resting state

Patients with systemic lupus erythematosus

[Important Precautions] As a result of a study conducted overseas, higher risk of breast cancer was reported in women with concomitant estrogen and progesterone over the long-term, compared to the control group. It was reported that this risk increased the longer the period of concomitant administration became. Physicians should adequately advise the patients of the risks and benefits of this drug, limit the use of this drug to the minimum, and avoid chronical administration over a long-term.
Medical histories including histories of diseases and genetic predisposition should be taken, and breast examination and gynecological examination should be performed before initiating therapy with this drug. After starting administration, periodic breast examinations and gynecological examinations should be performed.

[Other Precautions] As a result of epidemiologic investigations in postmenopausal women treated with estrogen preparation over the long-term, higher risk of endometrial cancer was reported compared to women in control group. It was reported that this risk increases in proportion to the period of use and the amount of use, and that the risk is suppressed by the concomitant administration of a progesterone preparation.

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HRT and the risks of dementia

As a result of a randomized clinical trial in postmenopausal women over aged 65 conducted in the United States, significantly higher risk of dementia including Alzheimer's disease was reported in the in the conjugated estrogen and progesterone preparation group compared to placebo (hazard ratio = 2.05).

<Reference Information> Company report

9 <Hemostatics>
Tranexamic Acid (oral dosage form)
Epsilon Aminocaproic Acid
Hemocoagulase

[Brand Name]	Transamin Powder 50%, Transamin Tablets 250 mg and 500 mg, Transamin Capsules (Daiichi Pharmaceutical Co., Ltd.), and others Epsilon Granules 98.6%, Epsilon Injection 20% (Daiichi Pharmaceutical Co., Ltd.) Reptilase-S Injection (Tobishi Pharmaceutical Co., Ltd.)
[Contraindications]	Patients receiving thrombin
[Interactions (contraindications for concomitant use)]	Thrombin
<Reference Information>	Company report

10 <Hemostatics, miscellaneous metabolism agents>
Tranexamic Acid (injectable dosage form)
Aprotinin

[Brand Name]	Transamin Injection 5% and 10% (Daiichi Pharmaceutical Co., Ltd.) Trasylol 50000 KIU (Mitsubishi Pharma Corporation)
[Contraindications]	Patients receiving thrombin
[Interactions (contraindications for concomitant use)]	Thrombin
<Reference Information>	Company report

11 <Antineoplastic antibiotics>
Mitomycin C

[Brand Name]	Mitomycin Injection 2 mg and 10 mg (Kyowa Hakko Kogyo Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Shock or anaphylactoid reaction** may occur, patients should be carefully monitored. If symptoms such as itching, rash, hot flush, sweating, dyspnoea and blood pressure decreased occur, treatment should be immediately discontinued and appropriate measures should be taken.
<Reference Information>	Company report

12 <Antineoplastic plant extract preparations>
Irinotecan Hydrochloride

[Brand Name]	CAMPTO for I. V. infusion (Yakult Honsha Co., Ltd.), Topotecin Injection (Daiichi Pharmaceutical Co., Ltd.)
[Warning]	**WARNING** In clinical studies for this drug, cases of death considered to be resulting from bone marrow depression or diarrhoea have been confirmed. This drug should be prescribed in facilities equipped with adequate supportive medical resources in case of emergency and by physicians who have sufficient knowledge and experience with cancer chemotherapy, only to patients for which administration of this drug is judged as being appropriate. Selection of applicable patients should be made carefully, such as by not administering this drug to the following patients.

	(1) Patients with bone marrow depression (2) Patients with a concomitant infectious disease (3) Patients with diarrhoea (stools watery) (4) Patients with paralysis intestinal and intestinal obstruction (5) Patients with interstitial pneumonia or pulmonary fibrosis (6) Patients with a large amount of ascites and pleural effusion (7) Patients with jaundice (8) Patients receiving atazanavir sulfate (9) Patients who have a history of hypersensitivity to ingredients of this drug
[Contraindications]	Patients receiving atazanavir sulfate
[Interactions (contraindications for concomitant use)]	Atazanavir sulfate
<Reference Information>	Company report

13 <Allergic agents-Miscellaneous> Loratadine

[Brand Name]	Claritin Tablets 10 mg (Schering-Plough K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice**: Hepatic function disorder with significant elevations of AST (GOT), ALT (GPT), γ-GTP, Al-P, LDH, and bilirubin etc., and jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

14 <Kampo medicines> Bofutsushosan

[Brand Name]	TSUMURA Bofutsushosan Extract Granules for Ethical Use (Tsumura & Co.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia**: If fever, cough, dyspnea, abnormal pulmonary sound (fine crackle), etc. are observed, administration of this product should be discontinued, and examinations such as chest X-ray should be performed immediately and appropriate measures such as administration of adrenocortical hormones should be taken. Besides, the patient should be advised to discontinue this product immediately and to make contact with the physician in the event of fever, cough, dyspnea, etc.
<Reference Information>	Company report

15 <Acting mainly on acid-fast bacteria> Rifampicin

[Brand Name]	Rifadin Capsules (Daiichi Pharmaceutical Co., Ltd.), Rimactane Capsules (Nihon Ciba-Geigy K.K.), and others
[Contraindications]	Patients receiving anti-HIV drug (indinavir, saquinavir, nelfinavir, amprenavir, atazanavir sulfate, delavirdine) or praziquantel
[Interactions (contraindications for concomitant use)]	Anti-HIV drug (indinavir, saquinavir, nelfinavir, amprenavir, atazanavir sulfate, delavirdine) Praziquantel

[Adverse Reactions (clinically significant adverse reactions)]	Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), lichen planus eruption, pemphigus-like and pemphigoid eruption, and erythroderma (dermatitis exfoliative)
<Reference Information>	Company report Ridtitid, W., et al.: Clin. Pharmacol. Ther., 72: 505 (2002)

16 <Synthetic antibacterials> Linezolid

[Brand Name]	Zyvox Tablets 600 mg, Zyvox Injection 600 mg (Pfizer Japan Inc.)
[Adverse Reactions (clinically significant adverse reactions)]	**Optic neuropathy**: Optic neuropathy may occur. If abnormalities are observed, appropriate measures, such as discontinuation of administration, should be taken.
<Reference Information>	Company report

17 <Anthelmintics> Ivermectin

[Brand Name]	Stromectol Tablets 3 mg (Banyu Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Toxic epidermal necrolysis (Lyell syndrome)**: Toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

18 <Anthelmintics> Praziquantel

[Brand Name]	Biltricide Tablets (Bayer Yakuhin, Ltd.)
[Contraindications]	Patients receiving rifampicin
[Interactions (contraindications for concomitant use)]	Rifampicin
<Reference Information>	Ridtitid, W., et al.: Clin. Pharmacol. Ther., 72: 505 (2002)

19 Over the counter drugs Bofutsushosan

[Brand Name]	TSUMURA Kampo Bofutsushosan Extract Granules (Tsumura & Co.), and others
[Consultation]	In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation. If the following symptoms are observed after taking this drug In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case. **Interstitial pneumonia:** Shortness of breath, dyspnoea, pyrexia, etc. accompanying cough may occur.
<Reference Information>	Company report