Pharmaceuticals and Medical Devices Safety Information

No. 219 November 2005

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

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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 issue (Pharmaceuticals and Medical Devices Safety Information No. 217).

1 Barium Sulfate (excepting preparation for CT)

Brand Name (name of company)	E-Z-HD (Toho Chemical Laboratory Co., Ltd.) Umbrasol-A, Enemastar Enema Powder (FUSHIMI Pharmaceutical Co., Ltd.) Neo Darm Sol (Kyosei Pharmaceutical Co., Ltd.) Neobalgin HD, Neo Balgin-S, Neobalgin UHD, Neo Balgin Kyosei (Kyosei Pharmaceutical Co., Ltd.) Bamster G75, Bamster S100, S130, and S200 (Kyosei Pharmaceutical Co., Ltd.) Bari-Enema, Bari-Enema 300, Bari-Enema LC, Bari-Enema HD75% (Teikoku Medix Co., Ltd.) Baricate R (Otsuka Pharmaceutical Factory, Inc.) Bariconc F (Sakai Chemical Industry Co., Ltd.) Baricon Meal (Horii Pharmaceutical Ind., Ltd.) Barytester A240 Powder (FUSHIMI Pharmaceutical Co., Ltd) Barytgen, Barytgen-Deluxe, Barytgen HD, Barytgen SHD, Barytgen Sol, Barytgen Sol 120 and 145 (Fushimi Pharmaceutical Co., Ltd.) Baritop 100 and 120, Baritop-HD, Baritop P, Baritop Sol 150 (Sakai Chemical Industry Co., Ltd.) Baribright P, Baribright R, Baribrightsol 180 (Sakai Chemical Industry Co., Ltd.) Balgin-S No.2, Balgin-S Sol No.3 (Kyosei Pharmaceutical Co., Ltd.) Barojectsol 100 (Horii Pharmaceutical Ind., Ltd.) Barosperse W (Horii Pharmaceutical Ind., Ltd.) Barosperse Enemaset (Horii Pharmaceutical Ind., Ltd.)
Therapeutic Category	X-ray contrast media
Indications	(E-Z-HD, Neobalgin UHD, Baricon Meal, Barytester A240 Powder, Barytgen SHD, Baritop-HD) Esophagus/stomach/duodenum double contrast radiography (Enemastar Enema Powder, Neo Darm Sol, Bari-Enema, Bari-Enema 300, Bari-Enema LC, Bari-Enema HD75%, Barojectsol 100, Barosperse Enemaset) Digestive tract (large intestine) imaging (others) Digestive tract imaging

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

[Contraindications]	Patients with digestive tract atresia or suspected of the disease Patients with a history of hypersensitivity to barium sulfate drugs
[Careful Administration]	Patients with intestinal diverticulum.
[Important Precautions]	Medical history should be obtained prior to administration and carefully monitor patients as shock and anaphylactoid symptoms may occur in patients with a history of hypersensitivity to other pharmaceuticals and in patients who are susceptible to hypersensitivity such as asthma and atopic dermatitis. It has been reported that gastrointestinal perforation, intestinal obstruction, and barium appendicitis, etc due to retained barium sulfate within digestive tract occurred on rare occasions. Caution should be exercised to the following points since severer outcome may be seen especially in elderly patients.

1) Administer a laxative in accordance with the patients' daily defecation pattern.
2) Patients should be instructed to take sufficient amount of fluid as barium sulfate needs to be defaecated expeditiously.
3) Patients should be instructed to check defecation conditions and to immediately visit a medical institution if gastrointestinal symptoms such as persisting dyschezia and abdominal pain occur.
4) If gastrointestinal symptoms such as abdominal pain etc. are observed, abdominal examination and imaging test (simple X-ray, ultrasound, CT, etc.) should be conducted and appropriate measures should be taken.

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock, anaphylactoid symptoms may occur. Patients should be carefully monitored, and if pallor facial, cold extremities, blood pressure decreased, cyanosis, loss of consciousness, flushing, urticaria, face oedema, laryngeal oedema, and dyspnoea etc. are observed, appropriate measures should be taken.

Gastrointestinal perforation, intestinal obstruction, and peritonitis: Gastrointestinal perforation, intestinal obstruction, and peritonitis may occur. Patients should be carefully monitored. If abnormalities such as abdominal pain after the test, abdominal examination and imaging test (simple X-ray, ultrasound, CT, etc.) should be conducted and appropriate measures should be taken.

[Use in the Elderly]

As gastrointestinal motility is often impaired in the elderly, gastrointestinal perforation due to retained barium sulfate is more likely to occur. Extreme caution should be exercised for defecation of barium sulfate after the test as the outcome may be severer when this symptom occurs.

<Reference Information>

Company report
The number of related adverse reaction reports since the initial marketing (approximately 51 years)
(exclusive of "causality could be denied" and inclusive of "causality is unknown")
• Shock: 18 cases (no fatal case)
• Gastrointestinal perforation, etc.: 27 cases (of which 4 had fatal cases)
The number of patients treated with Barium for a year estimated by MAH (Marketing Authorisation Holder): approximately 17.5 million (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	X-ray with contrast upper gastrointestinal tract (none)	289 g 1 day	**Anaphylactic shock** Medical history: postoperative cholelithiasis On day 1 of administration: This drug and concomitant medications were administered for stomach fluoroscopy screening. 30 minutes after administration: Redness generalized, sweaty, and nausea occurred. 1 hour after administration: The patient visited hospital. Systolic blood pressure was 64 mmHg. The patient was diagnosed with shock state. Symptoms indicated improvement tendency with drip infusion (fluid replacement 500 mL, betamethasone sodium phosphate 4 mg, and dL-chlorpheniramine maleate 10 mg). Oral administration of betametahzone 1.5 mg and Olopatadine hydrochloride 5 mg was implemented. Symptoms gradually improved.	Company report

				3 hours after administration: The patient walked back home independently. 1 day after administration: The patient made a follow-up visit. Redness, abnormality in sweaty was not observed. 13 days after administration: The patient made a follow-up visit. Subjective symptoms disappeared.	
	Concomitant medications: sodium bicarbonate/tartaric acid, sennoside				

Clinical Laboratory Values

	On day 1 of administration	1 day after administration	3 days after administration	7 days after administration
Systolic blood pressure (mmHg)	64	136	144	112
Diastolic blood pressure (mmHg)	--	72	84	74
WBC (/mm^3)	--	13000	--	--

WBC: White Blood Cell

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 30s	X-ray with contrast upper gastrointestinal tract (none)	400 g 1 day	**Anaphylactic shock** The patient was allergic to shellfish (shrimp/crab) On day 1 of administration: This drug, sodium bicarbonate/tartaric acid, and dimeticone were administered for complete medical checkup at workplace. Stomach X-ray examination was conducted (first stomach fluoroscopy screening ever). Sennoside at 24 mg was administered to expedite excretion of this drug after the test. 1 hour after administration: Cervical red exanthema was noted. The patient experienced several times of diarrhoea. Although the patient returned to work, red wheals on the trunk and extremities were confirmed. 3 hours after administration: The patient developed respiratory discomfort and hypotension paroxysm and visited our hospital. 3 hours and 10 minutes after administration: The patient was hospitalized being collapsed with a diagnosis of acute allergic symptoms. Blood pressure and pulse were impalpable at the time of hospitalization. Generalized wheals were observed. While the patient remained conscious, she complained of respiratory discomfort. D.I.V. entry was accomplished and 500 mg of hydrocortisone sodium succinate and 20 mL of glycyrrhizin/glycine/cysteine were administered as drip infusion. 3 hours and 15 minutes after administration: Blood pressure was elevated to 70 mgHg and higher. Pulse became palpable. 6 hours after administration: Wheals tended to disappear. The patient had a clear consciousness. Respiratory discomfort disappeared.	Company report

				1 day after administration: The patient had a breakfast and oral administration of betamethasone/d-chlorpheniramine maleate was initiated. The patient was discharged from the hospital with stabilized and improved conditions. The patient recovered afterwards.	
	Concomitant medications: sodium bicarbonate/tartaric acid, dimeticone, sennoside				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 70s	X-ray with contrast upper gastrointestinal tract (decreased appetite)	394.4 g 1 day	**Peritonitis** Before administration: Appetite impaired was noted. On day 1 of administration: The patient received upper gastrointestinal fluoroscopy screening at the medical institution A. In the test, the patient received administration of suspending solution prepared with added water to 400 mg of this product to make 180-200 w/v%. After coming home, as abdominal pain and vomiting of this drug occurred, the patient was hospitalized at the medical institution A. 1 day after administration: Oliguria and blood pressure decreased were observed. The patient was transported to medical institution B and emergency laparotomy was performed. Extensive gastrectomy (reconstruction of B-2), Braun anastomosis, and partial jejunectomy were performed. Blood pressure was gradually improved and urination was achieved due to endotoxin adsorption therapy after the operation. 33 days after administration: The patient was discharged.	Company report
	Concomitant medications: sodium bicarbonate/tartaric acid, dimeticone				

Clinical Laboratory Values

	1 day after administration
WBC (/mm^3)	4700
BUN (mg/dL)	40.3
Cr (mg/dL)	2.14
CRP (mg/dL)	20.54
PT (%)	48.4
APPT (sec.)	33.8
Fibrinogen (mg/dL)	483

WBC: White Blood Cell
BUN: Blood Urea Nitrogen
Cr: Creatinine
CRP: C-Reactive Protein
PT (%): Prothrombin Activity (%)
APPT: Activated Partial Thromboplastin Time

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Female 70s	X-ray with contrast upper gastrointestinal tract (none)	280 g 1 day	**Intestinal perforation, peritonitis** The patient was previously healthy. On day 1 of administration: This drug was administered at the health checkup. Although the patient received oral administration of lapactic (senna extract) after the test, there was no defaecation. 1 day after administration: Left lower abdominal pain occurred after night meal. The patient was transported to the hospital by ambulance since vomiting was also confirmed. No peritoneal irritation sign was observed at the time of consultation. Residue of barium stool was confirmed by abdominal X-ray. The patient was diagnosed with intestinal obstruction due to barium stool. No reaction of the bowels was obtained in spite of two glycerin enemas. Later, another enema was performed with lukewarm water, there was no reaction. The patient was hospitalized for follow-up. 2 days after administration: As abdominal pain was increased in the early morning, X-ray was conducted, and barium trapped inside pelvis was confirmed. The patient was diagnosed with rectal perforation. Emergency operation was performed. In the middle (Ra) portion of anterior rectal wall, approximately 2.5 cm of perforated site was found. Colostomy was conducted for obstruction of intestinal perforation site and transverse colon. 2 days after administration onward: While septic shock was developed after the operation, the patient improved with conservative medical management, and she was discharged. 66 days after administration: The patient recovered.	Company report
	Concomitant medications: sodium bicarbonate/tartaric acid, dimeticone, senna extract				

Clinical Laboratory Values

	On day 1 of administration	2 days after administration (pre operation)	2 day after administration (post operation)	3 days after administration	6 days after administration
RBC ($\times 10^4/mm^3$)	427	398	414	360	357
Haemoglobin (g/dL)	13.0	12.1	12.7	11.2	10.9
Haematocrit (%)	41.5	37.2	39.2	33.8	32.7
WBC ($/mm^3$)	4200	7000	1600	11100	6700
CRP (mg/dL)	0.05	0.0	--	30.6	9.4

RBC: Red Blood Cell
WBC: White Blood Cell
CRP: C-Reactive Protein

2 Fludarabine Phosphate

Brand Name (name of company)	Fludara for iv Inj. 50 mg (Nihon Schering K.K.)
Therapeutic Category	Antimetabolites
Indications	Chronic lymphocytic leukaemia accompanied with anaemia or thrombocytopenia

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

[Adverse Reactions (clinically significant adverse reactions)]

Autoimmune thrombocytopenia: Autoimmune thrombocytopenia may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.
Aplasia pure red cell: Aplasia pure red cell may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

<Reference Information>

Company report
The number of related adverse reaction reports since the initial marketing (approximately 5 years)
(exclusive of "causality could be denied" and inclusive of "causality is unknown")
- Autoimmune thrombocytopenia: 4 cases (no fatal case.)
- Aplasia pure red cell: 5 cases (no fatal case.)

The number of patients treated with Fludarabine for a year estimated by MAH: approximately 1000 (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 60s	Chronic lymphocytic leukaemia (none)	20 mg/m^2 5 days × 6 courses	**Idiopathic thrombocytopenic purpura** 3 months before administration: Swollen lymph nodes of neck, mediastinum, axilla, abdomen, and inguina were observed. As atypical lymphocyte of 86.8% was confirmed by aspiration bone marrow, the patient was diagnosed with chronic lymphocytic leukaemia (B-CLL: Binet stage B). On day 1 of administration: WBC and atypical lymphocyte were 51900/mm^3 and 91.5%, respectively. Administration of this drug was started on a 5-day cycle of IV administration with a 23-day cessation. On day 156 of administration (day of completion of administration): Administration of the 6th course was completed. 27 days after completion: While the laboratory values of WBC 5000/mm^3 and atypical lymphocyte 24.0% confirmed the effectiveness, platelet decreased to $3.2 \times 10^4/mm^3$. Aspiration bone marrow confirmed atypical lymphocyte of 67.5%. The patient was diagnosed to have a complication of idiopathic thrombocytopenic purpura (ITP) from high values of nuclear cell count $27.7 \times 10^4/mm^3$, blood megakaryocyte 38/mm^3, and PA-IgG (platelet associated IgG) 212 ng/10^7cells. 4 months after completion: The patient had diplopia. Head MRI confirmed no abnormalities. The patient was diagnosed with myasthenia gravis (MG) from anti-acetylcholine receptor antibody 79 nmol/L (normal range: ≤0.2 nmol/L).	Company report

				5 months after completion: Administration of prednisolone at 20 mg was started for ITP and MG. 7 months after completion: Diplopia disappeared. Platelet count was 5.4 × 10^4/mm^3. 8 months after completion: Relapse of generalized MG occurred. Symptoms were improved with administration of methylprednisolone and plasma exchange. 12 months after completion: Symptoms were improved.	
	Concomitant medications: none				

Clinical Laboratory Values

	73 days before administration	27days after completion	125 days after completion	374 days after completion
RBC (×10^4/mm^3)	442	367	417	420
PLT (×10^4/mm^3)	25.3	3.2	1.7	10.9
WBC (/mm^3)	30200	5000	9400	7300

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 70s	Chronic lymphocytic leukaemia (diabetes mellitus)	12.6 mg/m^2 5 days × 4 courses	**Aplasia pure red cell** 5 years before administration: The patient was diagnosed with chronic lymphocytic leukaemia (Rai stage III, Binet stage C). Treatment had not been conducted since then. On day 1 of administration: Administration of this drug was started on a 5-day cycle of IV administration with an approximately 23-day cessation. On day 108 of administration (day of completion of administration): Administration of the 4th course was completed. Anaemia was aggravated. Although blood transfusions were repeated, no improvement was observed. 27 days after completion: Bone marrow examination was conducted. The patient was diagnosed with aplasia pure red cell for markedly depleted erythroblast count of 0.1%. 49 days after completion: After administration of ciclosporin at 200 mg/day was started, intervals of blood transfusion were gradually prolonged. 80 days after completion: Blood transfusion was conducted. Blood transfusion was no longer necessary after this time. 87 days after completion: The patient recovered. 122 days after completion: Bone marrow examination revealed that erythroblast count increased to 12.2% and haemoglobin varied between 10-20 g/dL range afterwards.	Company report
	Concomitant medications: glimepiride, nizatidine				

Clinical Laboratory Values

	6 days before administration	On day 1 of the 4th cycle	10 days after completion	14 days after completion	42 days after completion
RBC ($\times 10^4/mm^3$)	300	250	187	149	206
PLT ($\times 10^4/mm^3$)	13.1	14.8	11.1	12.1	11.2
Haemoglobin (g/dL)	9.4	8.5	6.6	5.4	6.8
WBC ($/mm^3$)	90300	34400	25900	25800	24000
Lymphocytes ($\times 10^3/mm^3$)	89.4	29.8	22.4	21.8	20.7

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female 70s	Chronic lymphocytic leukaemia (type II diabetes mellitus)	25 mg/m^2 3 days × 3 courses	**Aplasia pure red cell** 34 months before administration: The patient was diagnosed with chronic lymphocytic leukaemia (B-CLL: Rai stage I). Afterward, the patient was followed up without any treatment. On day 1 of administration: As lymphocytosis, progressive platelets decreased, and multiple lymphadenopathy occurred, the patient was diagnosed with exacerbation of the disease. Administration of this drug was started on a 3-day cycle (25 mg/m^2 of this drug + 250 mg/m^2 of cyclophosphamide) with a 25-day cessation. A total of 3 courses were to be implemented. On day 60 of administration (day of completion of administration): Administration of the 3rd course was completed. 20 days after completion: Exacerbation of anaemia was confirmed. 27 days after completion: Since Haemoglobin and reticulocyte count were decreased to 7.7 g/dL and 2‰, respectively. The patient was diagnosed with aplasia pure red cell by bone marrow aspiration. 41 days after completion: The patient was hospitalized for progressive anaemia. Blood transfusion of concentrated human red blood cell was conducted. 48 days after completion: Administration of ciclosporin at 250 mg was started. 153 days after completion: The patient recovered.	Company report
	Concomitant medications: cyclophosphamide, sodium bicarbonate, allopurinol, magnesium oxide, gliclazide, teprenone				

Clinical Laboratory Values

	6 days before administration	6 days after completion	40 days after completion	153 days after completion
RBC ($\times 10^4/mm^3$)	457	409	224	430
Haemoglobin (g/dL)	14.1	12.8	6.5	13
PLT ($\times 10^4/mm^3$)	11.4	9.6	28.2	19.9
WBC ($/mm^3$)	129400	3500	9800	10600

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

2

Revision of PRECAUTIONS

(No. 170)

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

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1 <Antiarrhythmic agents> Bepridil Hydrochloride

[Brand Name] Bepricor Tablets 50 and 100 (Nippon Organon K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **QT prolongation, ventricular tachycardia (including Torsades de pointes), ventricular fibrillation:** QT prolongation, ventricular tachycardia (including Torsades de pointes), ventricular fibrillation, and Adams-Stokes syndrome may occur. Electrocardiography should be conducted periodically and on an as needed basis. If any abnormal changes or symptoms are observed, discontinue administration and take appropriate measures such as intravenous administration of lidocaine and magnesium sulfate, defibrillation and pacing etc.

<Reference Information> Company report

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2 <Antimetabolites> Cytarabine (preparation for high dose therapy)

[Brand Name] Cylocide N Injection (Nippon Shinyaku Co., Ltd.)

[Warning]

WARNING

Since high dose cytarabine therapy (hereinafter called this therapy) involves high risks, patients should be monitored under supervision by a physician in hospital environment during and after administration for a certain period of time.
This therapy should only be conducted at medical institutions that can capably provide emergency medical care, by physicians sufficiently educated and experienced in cancer chemotherapy, and only be applied to cases determined to be suitable for this therapy. In case of concomitant use with other antitumor medicine, caution should be exercised by referring to the package inserts for each concomitant medication in choosing patients indicated for this treatment.

[Precautions of Dosage and Administration] In case of concomitant therapy with other antitumor medicine for acute lymphocytic leukaemia and malignant lymphoma, refer to the package inserts for each concomitant medication.

<Reference Information> Company report

<Adrenal hormone preparations>

3 Dexamethasone (oral dosage form) (without the indication for gastrointestinal symptoms associated with use of antitumor agent)
Dexamethasone Acetate
Dexamethasone Sodium Phosphate (injectable dosage form) (without the indication for malignant lymphoma)

[Brand Name] Decadron Elixir (Banyu Pharmaceutical Co., Ltd.), Dexa-Mamallet (Showa Yakuhin Kako Co., Ltd.), Dexamethasone Tablets (ASAHI KASEI) (Asahi Kasei Pharma Corporation), Dexamethasone E (Towa Pharmaceutical Co., Ltd.), Dexamethasone Elixir "Nissin" (Nisshin Pharmaceutical Co., Ltd.), Mitasone (Toyo Pharmar Co., Ltd.)
Dexamethasone Acetate Injection (Aqueous Suspension) (Fuji Pharma Co., Ltd.)
Solcort Injection (Fuji Pharma Co., Ltd.), Deron S Injection (Towa Pharmaceutical Co., Ltd.)

[Relative Contraindications]

Patients with uncontrolled diabetes mellitus

[Adverse Reactions (clinically significant adverse reactions)] Peptic ulcer, gastrointestinal perforation, pancreatitis
Osteoporosis, aseptic necrosis of femoral and humeral heads, myopathy, spinal compression fracture, long bone pathological fracture, thromboembolism

<Reference Information> Company report

<Adrenal hormone preparations>

4 Dexamethasone Palmitate

[Brand Name] Limethason (Mitsubishi Pharma Corporation)

[Relative Contraindications]

Patients with uncontrolled diabetes mellitus

<Reference Information> Company report

<Adrenal hormone preparations>

5 Sodium Prasterone Sulfate (injectable dosage form)

[Brand Name] Mylis Injection (Nippon Organon K.K.) and others

[Warning]

WARNING

This drug may cause bradycardia foetal or foetal distress and cases of death have been reported.
Maternal and fetal conditions should be carefully monitored through tocodynamometer etc. when administering this product. Furthermore, conditions should also be carefully monitored after administration. If any abnormalities are observed, take appropriate measures.
The package insert should be thoroughly read in advance.

[Contraindications]

Patients with a history of hypersensitivity to any components of this drug

[Important Precautions] It has been reported that estrogen, a metabolite of this drug, may enhance oxytocin sensitivity of the myometrium although to a minor extent. Maternal and fetal conditions should be carefully monitored through tocodynamometer etc. when administering this product. Furthermore, conditions should also be carefully monitored after administration. If any abnormalities are observed, take appropriate measures.

[Adverse Reactions (clinically significant adverse reactions)] **Bradycardia foetal, foetal distress:** Foetal death may occur due to bradycardia foetal or foetal distress. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

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6 <Adrenal hormone preparations> Sodium Prasterone Sulfate (vaginal suppository)

[Brand Name] Mylis Vaginal Suppositories (Nippon Organon K.K.)

[Warning]

WARNING

This drug may cause bradycardia foetal or foetal distress and cases of death have been reported.
Maternal and fetal conditions should be carefully monitored through tocodynamometer etc. when administering this product. Furthermore, conditions should also be carefully monitored after administration. If any abnormalities are observed, take appropriate measures.
The package insert should be thoroughly read in advance.

[Contraindications] Patients with a history of hypersensitivity to any components of this drug

[Important Precautions] It has been reported that estrogen, a metabolite of this drug, may enhance oxytocin sensitivity of myometrium although to a minor extent. Maternal and fetal conditions should be carefully monitored through tocodynamometer etc. when administering this product. Furthermore, conditions should also be carefully monitored after administration. If any abnormalities are observed, take appropriate measures.

[Adverse Reactions (clinically significant adverse reactions)] **Bradycardia foetal, foetal distress:** Foetal death may occur due to bradycardia foetal or foetal distress. Patients should be carefully monitored and if abnormalities are observed, take appropriate measures including vaginal douche.

<Reference Information> Company report

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7 <Adrenal hormone preparations> Dexamethasone Metasulfobenzoate Sodium (injectable dosage form)

[Brand Name] Selftison Inj. (Showa Yakuhin Kako Co., Ltd.), Mesadoron Injection 2 mg and 3 mg (Kobayashi Kako Co., Ltd)

[Warning]

WARNING

Cancer chemotherapies including this drug should be conducted in medical institution that can provide emergency medical care under supervision of a physician with sufficient knowledge and experience in the chemotherapy, and only be indicated if it is appropriate to conduct this therapy. Caution should be exercised by referring to the package inserts for each concomitant medication in choosing patients indicated for this therapy. Patients or their family members should be fully advised of the efficacy and risks of this drug, and informed consent should be obtained from them before starting treatment.

[Relative Contraindications] Patients with uncontrolled diabetes mellitus

[Precautions of Dosage and Administration] In case of concomitant therapy with other antitumor medicine for malignant lymphoma, refer to the package inserts for each concomitant medication.

[Adverse Reactions (clinically significant adverse reactions)]	Peptic ulcer, gastrointestinal perforation, pancreatitis Osteoporosis, aseptic necrosis of femoral and humeral heads, myopathy, spinal compression fracture, long bone pathological fracture, thromboembolism
<Reference Information>	Company report

<Adrenal hormone preparations>

8 Dexamethasone Sodium Phosphate (injectable dosage form) (with the indication for malignant lymphoma)

[Brand Name]	Orgadrone Injection (Nippon Organon K.K.), Decadron Phosphate Injection (Banyu Pharmaceutical Co., Ltd.), Dexart Injection (Fuji Pharma Co., Ltd.)
[Precautions of Dosage and Administration]	In case of concomitant therapy with other antitumor medicine for malignant lymphoma, refer to the package inserts for each concomitant medication.
<Reference Information>	Company report

<Urogenital and anal organ agents-Miscellaneous>

9 Ritodrine Hydrochloride (oral dosage form)

[Brand Name]	Utemerin Tab. 5 mg (Kissei Pharmaceutical Co., Ltd.) and others
[Careful Administration]	Patients with diabetes mellitus, with a family history of diabetes mellitus, and with risk factors for diabetes mellitus such as hyperglycaemia or obesity
[Important Precautions]	Diabetic ketoacidosis due to rapid elevation of blood glucose level or aggravation of diabetes mellitus may occur during administration of this drug. Diabetic ketoacidosis may be life-threatening to maternal and fetal life. Patients should be carefully monitored for symptoms of diabetes mellitus such as thirst, excessive drinking, polyuria, and pollakiuria, as well as blood glucose level, urinary glucose, and ketones in urine etc. prior to administration. If any abnormalities are observed after initiation of administration, immediately discontinue administration and take appropriate measures.
[Adverse Reactions (clinically significant adverse reactions)]	**Hyperglycaemia, diabetic ketoacidosis:** Diabetic ketoacidosis due to rapid elevation of blood glucose level or aggravation of diabetes mellitus may occur. Diabetic ketoacidosis may be life-threatening to maternal and fetal life. Patients should be carefully monitored. If any abnormalities are observed, immediately discontinue administration and take appropriate measures.
[Clinically Significant Adverse Reactions (similar drugs)]	Pulmonary oedema, cardiac failure, agranulocytosis, leucopenia, platelets decreased, shock, arrhythmia, hepatic function disorder, jaundice, oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), pleural effusion, maternal intestinal obstruction, neonatal hypertrophic interventricular septum, and hypoglycaemia neonatal have been reported with injectable form of this drug. Patients should be carefully monitored. If any abnormalities are observed, take appropriate measures such as discontinuation of administration.
<Reference Information>	Company report

10 <Urogenital and anal organ agents-Miscellaneous>
Ritodrine Hydrochloride (injectable dosage form)

[Brand Name] Utemerin Injection 50 mg (Kissei Pharmaceutical Co., Ltd.) and others

[Careful Administration] Patients with diabetes mellitus, with a family history of diabetes mellitus, and with risk factors for diabetes mellitus such as hyperglycaemia or obesity

[Important Precautions] Diabetic ketoacidosis due to rapid elevation of blood glucose level or aggravation of diabetes mellitus may occur during administration of this drug. Diabetic ketoacidosis may be life-threatening to maternal and fetal life. Patients should be carefully monitored for diabetes mellitus symptoms such as thirst, excessive drinking, polyuria, and pollakiuria, as well as blood glucose level, urinary glucose, and ketones in urine etc. prior to administration. If any abnormalities are observed after initiation of administration, immediately discontinue administration and take appropriate measures.

[Adverse Reactions (clinically significant adverse reactions)]

Pancytopenia, agranulocytosis, white blood cell decreased, platelets decreased: Pancytopenia, agranulocytosis, white blood cell decreased, and platelets decreased may occur. Patients should be carefully monitored. If any abnormalities are observed, discontinue administration and take appropriate measures.

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome): Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored and if symptoms such as pyrexia, erythema, pruritis, ocular hyperaemia, or stomatitis etc. are observed, take appropriate measures.

Hyperglycaemia, diabetic ketoacidosis: Diabetic ketoacidosis due to rapid elevation of blood glucose level or aggravation of diabetes mellitus may occur. Diabetic ketoacidosis may be life-threatening to maternal and fetal life. Patients should be carefully monitored. If any abnormalities are observed, immediately discontinue administration and take appropriate measures.

Hypoglycaemia neonatal: Hypoglycaemia neonatal may occur. Patients should be carefully monitored. If any abnormalities are observed, take appropriate measures.

<Reference Information> Company report

11 <Protein and amino acid preparations>
Elental, Elental P, Enterued, Twinline

[Brand Name]
Elental (Ajinomoto Co., Inc.)
Elental P (Ajinomoto Co., Inc.)
Enterued (Terumo Corporation)
Twinline (EN Otsuka Pharmaceutical Co., Ltd.)

[Important Precautions] Dumping syndrome-like hypoglycemia may occur after administration if dosing concentration is too high or dosing rate is too fast in patients administered with this drug through a tube. Caution should be exercised to dosing concentration and dosing rate.

[Adverse Reactions (clinically significant adverse reactions)]

Hypoglycemia: Dumping syndrome-like hypoglycemia (malaise, sweaty, cold sweat, pallor facial, convulsion, and depressed level of consciousness etc.) may occur after completion of administration. If these symptoms are confirmed, appropriate measures should be taken.

<Reference Information> Company report

12 <Vaccines> Pneumococcal Vaccine

[Brand Name]	Pneumovax (Banyu Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Cellulitis/cellulitis-like reaction:** Transient cellulitis /cellulitis-like reactions (redness, swelling, pain, and pyrexia, etc.) may occur primarily on injection site after vaccination. If these symptoms are observed, appropriate measures should be taken.
<Reference Information>	Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of November 1, 2005)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Bosentan Hydrate / Tracleer Tablets 62.5 mg	Actelion Pharmaceuticals Japan Ltd.	June 10, 2005
Tamibarotene / Amnolake Tablets 2 mg	Toko Pharmaceutical Industrial Co., Ltd.	June 13, 2005
Tocilizumab (Genetical recombination) / Actemra for Intravenous Infusion 200	Chugai Pharmaceutical Co., Ltd.	June 13, 2005
Adenosine / Adenoscan Injection 60 mg	Daiichi Suntory Pharma Co., Ltd.	June 21, 2005
Voriconazole / Vfend Tablets 50 mg and 200 mg, Vfend 200 mg for Intravenous Use	Pfizer Japan Inc.	June 27, 2005
Luliconazole / Lulicon Cream 1%, Lulicon Solution 1%	Pola Chemical Industries, Inc.	July 20, 2005
Fludeoxyglucose / FDGscan Injectable	Nihon Medi-Physics Co., Ltd.	August 1, 2005
Fludeoxyglucose / FDGscan-MP Injectable	The Medical and Pharmacological Research Center Foundation	August 1, 2005
Monteplase (Genetical recombination) / Cleactor Injection 400000, 800000, and 1600000[*1]	Eisai Co., Ltd.	August 5 2005
Follitropin Beta (Genetical recombination) / Follistim Inj. 75 and 150	Nippon Organon K.K.	August 11, 2005
Doripenem Hydrate / Finibax 0.25 g IV Solution	Shionogi & Co., Ltd.	September 16, 2005
Dehydrated Ethanol / Anhydrous Ethanol Injection “Fuso”	Fuso Pharmaceutical Industries, Ltd.	September 16, 2005
Dehydrated Ethanol / Dehydrated Ethanol Inj. “Merck”	Merck Pharma Ltd.	September 20, 2005
Pilocarpine Hydrochloride / Salagen Tab. 5 mg	Kissei Pharmaceutical Co., Ltd.	September 22, 2005
Gemtuzumab Ozogamicin (Genetical recombination) / Mylotarg Injection 5 mg	Wyeth K.K.	September 22, 2005
Alteplase (Genetical recombination) / Activacin for Injection 6000000, 12000000, and 24000000[*2]	Kyowa Hakko Kogyo Co., Ltd.	October 11, 2005
Alteplase (Genetical recombination) / Grtpa Inj. 6000000, 12000000, and 24000000[*2]	Mitsubishi Pharma Corporation	October 11, 2005

Candesartan Cilexetil Blopress Tablets 2, 4, and 8[*3]	Takeda Pharmaceutical Company Limited	October 11, 2005

Note) Subject to additional indications etc.

*1: An additional indication for "lysis of pulmonary thrombosis of acute pulmonary embolism accompanied with unstable homodynamic"

*2: An additional indication for "the improvement of dysfunction in the acute stage of ischemic cerebrovascular disease (within 3 hours of onset)"

*3: An additional indication for "the treatment of patients in the condition of chromic cardiac failure (mild to moderate) for which administration of angiotensin converting enzyme (ACE) inhibitors is not appropriate"

Reference Material

Future Perspective of pharmacogenomics

"Pharmacogenomics (genome pharmacology)" is defined as "conducting explanatory and verifiable analysis and evaluation of efficacy and safety of the investigational drugs through procedures such as stratification of subjects etc. using pharmacokinetic genome testing in clinical pharmacology studies and other clinical studies" [1] according to PFSB/ELD Notification No. 0318001 issued by the Director of the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau (PFSB) within Ministry of Health, Labour and Welfare (MHLW) on March 18, 2005. Also, according to the guidance[2] published by the U.S. FDA in March 2005, it is stated as "The promise of pharmacogenomics lies in its potential to help identify sources of inter-individual variability in drug response; this information will make it possible to individualize therapy with the intent of maximizing effectiveness and minimizing risk.".

Pharmacogenomics is expected to play an important role in understanding genetic factors in each patient regarding potential risks for adverse reactions and difference in drug efficacy in each field of research, and active research has been conducted.

Individual difference in drug response is associated with physique, age, and sex etc. as well as other genetic factors such as genetic polymorphism of drug-metabolizing enzyme, drug transporter and receptor etc[3].

As an example of usage of pharmacogenomics, attempts have been made to identify subpopulation of increased risks of adverse reactions and less responsive to drug efficacy within population by research on genetic polymorphism that may affect pharmacokinetics.

Following 2 types of genetic mechanism have been reported as examples of cases where genetic polymorphism influences pharmacotherapy.

1. Cases of which drug concentration in the body changes due to increased or decreased metabolic rate by genetic polymorphism of drug-metabolizing enzyme (cytochrome P450: CYP2C9, CYP2D6, CYP2C19, N-acetyl transfer enzyme: NAT2, UDP-glucuronyl transferase: UGT1A1 etc.)
2. Cases of which genetic polymorphism of drug transporter etc. affects drug response or incidence of adverse reactions (example: multidrug resistance gene (MDR1), β_2 receptor (β_2AR)).

Especially regarding anticancer drug, irinotecan hydrochloride, among aforementioned item 1, the following has been reported; ① SN-38, which is an active metabolite of irinotecan hydrochloride, is detoxified by glucuronosyltransferase (UGT). ② Genetic polymorphism of UGT1A1, which is a single molecular species of UGT, has been recognized, and increased risks for serious adverse reactions (especially neutropenia, etc.) are caused by decreased activity of glucuronic acid conjugate with *UGT1A1*28* (TA direct repeat of promoter is 7 times (wild-type is 6 times)). ③ Distribution of genetic polymorphism of UGT1A1 differs interracially. ④ It has been reported that there is a high possibility of the occurrence of serious adverse reactions when there is a combination of *UGT1A1*28* with either *UGT1A1*27* or *UGT1A1*6* in Japanese population[4, 5].

Revision to the package insert of irinotecan hydrochloride was made to additionally state that dosage reduction in the initial dose should be considered for patients with *UGT1A1*28* as homozygote for its increased risk of neutrophilopenia by the US FDA in June, 2005. The test agent for UGT1A1 of genetic polymorphism is now available only for the purpose of research in Japan. MHLW requested MAH to promote its development and practical use.

Findings regarding genetic polymorphism and drug response are currently being accumulated and further development in the usage of pharmacogenomics is expected as one of the measures for implementation of more effective and safer pharmacotherapy. In particular, if the identification of patients with risk factors of adverse reactions is available in advance, it will contribute to prediction/prevention base safety measures.

(Reference)

Table 1 Examples of genetic polymorphism of drug-metabolizing enzyme and drug response[3)]

Gene	Prevalence of genetic polymorphism	Drug	Drug response related to genetic polymorphism
CYP2C9	0.2-1%: homozygote 14-28%: heterozygote	Warfarin[6)] (anticoagulants)	Haemorrhage
CYP2D6	5-10% (slow metabolizer)	β blocker (metoprolol, timolol etc.)[7)]	Increased β-antagonist activity
CYP2C19	3-6% (Caucasian) 8-23% (Asian)	Omeprazole[8)] (proton pump inhibitor)	Higher eradication rate of helicobacter pylori by using the drug in a triple-drug combination with clarithromycin and amoxicillin
NAT2	$T^{341}C$ allele 35% (African) 45% (Caucasian)	Isoniazid[3)] (antituberculosis drug)	Peripheral neuropathy/optic neuritis
UGT1A1	12%: homozygote, 48%: heterozygote (Caucasian)[9)] 3-6%: homozygote, 15-21%: heterozygote (Japanese)[10), 11)]	Irinotecan hydrochloride[12)] (DNA topoisomerase I inhibitor)	Leucopenia (neutropenia), diarrhoea

Table 2 Examples of genetic polymorphism in drug transporter and receptor and drug response[3)]

Gene	Proportion of high-risk patient	Drug	Drug response related to genetic polymorphism
Multidrug resistance gene (MDR 1)	24%	Digoxin[13)]	Elevated plasma concentration
β_2 receptor (β_2AR)	37%	Albuterol[14)]	Impaired responsiveness to β_2 agonist

<References>

1) "Information service etc. for related administrative agencies for the preparation of guidelines for pharmacogenomics in clinical studies of medicinal products" (PFSB/ELD Notification No. 0318001 issued by the Director of the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau (PFSB) within Ministry of Health, Labour and Welfare (MHLW) on March 18, 2005) (In Japanese)
2) U. S. FDA: Guidance for Industry Pharmacogenomic Data Submissions (2005)
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4) Yuichi Ando: Personalized therapy by irinotecan hydrochloride based on genetic polymorphism of glucuronyl transferase UGT1A1, 9: Saishin Igaku 74-82 (2005) (In Japanese)
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