Pharmaceuticals and Medical Devices Safety Information

No. 254 January 2009

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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).

Pharmaceuticals and Medical Devices Safety Information

No. 254 January 2009

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

[Outline of Information]

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

To Pharmaceuticals and Medical Devices Safety Management Supervisor
—Please use our e-mail alert service—

Pharmaceuticals and Medical Devices Agency is providing a "Pharmaceuticals and Medical Devices Information E-mail Alert Service" (http://www.info.pmda.go.jp/info/idx-push.html, Japanese only), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of PRECAUTIONS is issued. You are encouraged to register to and use the service.

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

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

1

Pharmaceuticals and Medical Devices Information E-mail Alert Service

Please subscribe to the Pharmaceuticals and Medical Devices Information E-mail Alert Service

(Faster than any other services, we ensure to provide information necessary for duties with safety management supervisors for drug and medical devices for free.)

1. Introduction

As stipulated by the Medical Care Law and the Pharmaceutical Affairs Law, safety management supervisors for drug and medical devices in medical institutions should implement improvement measures including collecting and managing information necessary for safe use of pharmaceuticals and medical devices, and make sure to promptly keep persons handling drugs and medical devices informed of necessary information.

In order to enable prompt collection of safety information and effective implementation of such duties, PMDA is offering a free e-mail alert service, "Pharmaceuticals and Medical Devices Information E-mail Alert Service", which provides particularly important safety information regarding pharmaceuticals, etc.,when such information is issued. You can subscribe to this service at the following URL. You are encouraged to register and make active use of the service.

"Pharmaceuticals and Medical Devices Information E-mail Alert Service" by PMDA
http://www.info.pmda.go.jp/info/idx-push.html (Japanese only)

In "Enhancement and thorough implementation of measures for prevention of medication error due to similarity of brand names of pharmaceuticals (precautions)", a Notification of Secretary-General of Health Policy Bureau and Pharmaceutical and Food Safety Bureau, MHLW, dated December 4, 2008, safety management supervisors for drug and medical devices are encouraged to use this service proactively.

2. Scheme of the Pharmaceuticals and Medical Devices Information E-mail Alert Service

This is a free e-mail service that informs you of important information, such as "Revision of PRECAUTIONS" and "Pharmaceuticals and Medical Devices Safety Information" issued by MHLW and "Dear Healthcare Professional Letters" and "Recall Information (Class I)" issued by marketing authorization holders (MAH), along with the links to access such information, by e-mail sent to the pre-registered addresses, when such information is issued.

By subscribing to this service, healthcare professionals working in medical institutions can obtain important safety information regarding pharmaceuticals, etc. in a timely manner and make use of such information for safety measures.

3. Types of Information communicated by the Pharmaceuticals and Medical Devices Information E-mail Alert Service

Information disseminated through the service is as follows (as of January 2009):

- Dear Healthcare Professional Letters

  "Dear Healthcare Professional Letters" are issued by MAHs when safety measures are urgently required.

- Pharmaceuticals and Medical Devices Safety Information

  "Pharmaceuticals and Medical Devices Safety Information" is issued based on adverse reaction information collected by MHLW. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. It is issued monthly.

- Revision of PRECAUTIONS

  "Revision of PRECAUTIONS" provides information about the request for revision of PRECAUTIONS made by MHLW to the MAHs.

- Drug Safety Update (DSU)

  "Drug Safety Update (DSU)", issued by the pharmaceutical industry, compiles new precautions for use of drugs.

- Notification of self-inspection

  "Notification of Self-Inspection" is a notification about self-inspection of medical devices issued by MHLW.

- Recall Information (Class I)

  "Recall Information (Class I)" provides information about Class I (refers to a situation in which use of the product may cause serious adverse health effects or death) recall of pharmaceuticals and medical devices.

Among the information listed above, you can choose and receive by e-mail the contents you need. For example, if you choose to receive information about "Pharmaceuticals and Medical Devices Safety Information", you will be informed of the release of "Pharmaceuticals and Medical Devices Safety Information" and the link to access the information by e-mail as follows, when it is issued.

> PMDA informs you that "Pharmaceuticals and Medical Devices Safety Information" (No. ○, dated on ○, ○○, 20○○) has been newly issued.
> The Pharmaceuticals and Medical Devices Safety Information is available at PMDA's website (http://www.pmda.go.jp/english/service/precautions.html).

4. How to subscribe to the Pharmaceuticals and Medical Devices Information E-mail Alert Service

You need to subscribe to receive this service. The service is intended to those who belong to hospitals and other medical facilities, pharmacies, MAHs, or medical education institutions.

Please access to http://www.info.pmda.go.jp/info/idx-push.html (Japanese only) and enter information required for subscription (affiliation, name, e-mail address, etc.). By subscribing the types of information you want to receive, you will receive only the information you need by e-mail. This service is free.

At present, the number of hospitals, clinics, and dispensing pharmacies in Japan is estimated to be approximately 230 thousand. As of the end of December 2008, however, only 17924 subscribers use this service. We encourage more subscribers, including safety management supervisors for drug and medical devices and other healthcare providers, and your active use of the service for safety measures for drugs, etc.

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Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated November 28, 2008.

1 Enteral nutrition (Elental, Elental P, Ensure·H, Ensure Liquid, Enterued, Twinline, Harmonic-F, Harmonic-M, Racol)

❶ Elental, Elental P, Ensure·H, Ensure Liquid, Twinline, Harmonic-F, Harmonic-M, Racol

Brand Name (name of company)	Elental (Ajinomoto Co., Inc.) Elental P (Ajinomoto Co., Inc.) Ensure·H (Meiji Dairies Corporation) Ensure Liquid (Meiji Dairies Corporation) Twinline (EN Otsuka Pharmaceutical Co., Ltd.) Harmonic-F (SSP Co., Ltd.) Harmonic-M (SSP Co., Ltd.) Racol (EN Otsuka Pharmaceutical Co., Ltd.)
Therapeutic Category	Protein and amino acid preparations
Indications	**Elental** This drug is a very low residual, easily absorbable high-calorie enteral nutrient called elemental diet or elemental nutrition, which consists of ingredients requiring minimum digestion. In general, the drug is used preoperatively or postoperatively when nutritional management is difficult with tube feeding nutrition containing undigested proteins. Particularly, the drug is used in the following situations: 1. Postoperative nutritional management when tube feeding nutrition containing undigested proteins is difficult 2. Nutritional management in patients with a disease that requires colonic irrigation 3. Nutritional management immediately after surgical procedure 4. Nutritional management in patients with abnormal gastrointestinal conditions (e.g., ruptured suture, short-bowel syndrome, and various gastrointestinal fistulae) 5. Nutritional management in patients with special gastrointestinal diseases (e.g., Crohn's disease, colitis ulcerative, ischochymia syndrome, pancreopathy, and protein-losing gastroenteropathy) 6. Nutritional management when high-calorie transfusion is difficult (e.g., extensive burns) **Elental P** This drug is used for nutritional management in neonates and infants with the following conditions. Basically, the drug should be used in patients under 2 years of age. 1. Digestion and absorption disorders due to surgical procedures, such as small bowel resection and ileostomy 2. Malignant tumors 3. After the surgical procedure for cardiac disorders 4. Intractable diarrhea 5. When preoperative colonic preparation is required

	6. When nutritional management with nutrition containing undigested proteins is difficult after a gastrointestinal procedure 7. When nutritional management with nutrition containing undigested proteins is difficult due to conditions such as conservative treatment for Hirschsprung's disease (short segment), biliary atresia, and malnutrition **Ensure·H** In general, this drug may be used for postoperative nutrition support. Particularly, the drug is used for tube feeding in patients with the following conditions who have difficulties in oral food intake and require enteral nutrient high in calorie per unit volume (1.5 kcal/mL) over the long term. 1. Patients who require restriction of fluid intake (e.g., patients complicated by cardiac failure or renal failure) 2. Patients with increased resting energy consumption (e.g., patients with thermal burn or complicated infection) 3. Patients in need of dose reduction of enteral nutrition (e.g., patients who complain of dose-dependent abdominal distension) 4. When administration of enteral nutrition in a shorter time is desired (e.g., after oral or otorhinolaryngologic surgeries) **Ensure Liquid, Racol** In general, these drugs may be used for postoperative nutrition support. Particularly, they are used for tube feeding in patients who have difficulties in oral food intake over the long term. **Twinline** In general, this drug may be used for postoperative nutrition support. Particularly, it is used for tube feeding in patients who have difficulties in oral food intake over the long term. **Harmonic-F, Harmonic-M** In general, these drugs may be used for postoperative nutrition support. Particularly, they are used for tube feeding in patients who have difficulties in oral food intake over the long term.

《**PRECAUTIONS** (underlined parts are additions)》

[Contraindications]	Patients with a history of hypersensitivity to ingredients of this drug
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms**: Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored. If blood pressure decreased, consciousness disturbed, dyspnoea, cyanosis, nausea, chest distressed feeling flushed face, itching, and sweaty, etc. occur, administration should be immediately discontinued and appropriate measures should be taken.

❷ Enterued

Brand Name (name of company)	Enterued (Terumo Corporation)
Therapeutic Category	Protein and amino acid preparations
Indications	In general, this preparation may be used for postoperative nutrition support. Particularly, it is used for tube feeding in patients who have difficulties in oral food intake over the long term.

《**PRECAUTIONS** (underlined parts are additions)》

[Contraindications]

Patients with a history of hypersensitivity to ingredients of this drug

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored. If blood pressure decreased, consciousness disturbed, dyspnoea, cyanosis, nausea, chest distressed feeling flushed face, itching, and sweaty, etc. occur, administration should be immediately discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2005 to October 2, 2008) (events for which a causality to the drug could not be denied)

- Shock, anaphylactoid symptoms: 8 cases (of which one had a fatal case)

The number of patients treated with Enteral nutrition for a year estimated by MAH: approximately 1.96 million (FY 2007)

Marketed in Japan in:
September 1981 (Elental)
May 1987 (Elental P)
June 1988 (Ensure Liquid)
July 1989 (Enterued)
July 1993 (Twinline)
October 1995 (Ensure·H)
December 1999 (Racol)
October 2001 (Harmonic-F, Harmonic-M)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male Under age of 10	Unknown (asthma bronchial, dermatitis atopic, hypoxic encephalopathy, hypersensitivity)	Unknown 1 day	**Anaphylactic reaction** Medical history: marked allergy (IgE 3000–8000 IU/mL) The patient was born in a normal delivery. He had dermatitis atopic and repeated diarrhoea since his infancy. He was given breast milk for 1 month and then formula. He was given Bonlact formula from the age 1 year and 6 months. He completely avoided bovine milk and eggs. Asthma bronchial developed at age 2 years and 10 months. At age 2 years and 10 months, the patient had pyrexia (39.5ºC) and, after meal, convulsion and respiratory arrest. He was immediately admitted to the hospital. Hypoxic encephalopathy developed despite resuscitation. He received tube feeding (gastric). Day of administration: The patient was switched to this preparation (Ensure Liquid) from other enteral nutrition. A few minutes after the administration, generalised urticaria, wheezing, dyspnoea, and mild cyanosis (+) developed. The patient was immediately treated with adrenaline subcutaneous injection, hydrocortisone sodium succinate intravenous injection, chlorpheniramine maleate intravenous injection, aminophylline hydrate intravenous injection, and oxygen. Approximately after 30 minutes, the symptoms were improved.
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Nutritional support (brain contusion, asthma)	1000 mL Approx. 3 years and 5 months	**Anaphylactic reaction** Medical history: no history of allergy Approx. 1 year before administration: The patient was hospitalized for the treatment of brain contusion and was receiving tube feeding. On day 1 of administration: Administration of this drug (Ensure Liquid) was initiated. In year 3 and month 4 of administration: Skin red was reported after the administration of this drug. On year 3, month 4, day 5 of administration: Skin red, respiratory distress, wheezing, pulse increased was confirmed after administration of this drug. This drug was continued. The patient was treated with chlorpheniramine maleate and hospitalized. On year 3, month 4, day 12 of administration: She was discharged from the hospital without particular symptoms. On year 3, month 4, day 13 of administration: The patient experienced similar symptoms after discharge from the hospital. On year 3, month 4, day 14 of administration (day of discontinuation): This drug and all other drugs were discontinued. 6 days after discontinuation: The patient was recovered.
	Concomitant medications: pranlukast hydrate, sodium valproate, theophylline			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female Under age of 10	Nutritional support (cerebral palsy, asthma bronchial)	8 mL One day	**Anaphylactic shock** The patient had received nutritional support with other enteral nutrition (nutrition for neonates and infants) via a nasointestinal tube and she was switched to this drug. Before administration: The patient received nutritional support with the elemental diet for neonates and infants without any problems (for approximately 1 year). Day of administration: This drug (Racol) was discontinued approximately 15 minutes after the initiation of administration due to development of percutaneous oxygen saturation decreased, tachycardia, diarrhoea, and pallor facial, blood pressure decreased (blood pressure unmeasurable). Approximately 1 hour after administration, the patient was treated with water-soluble hydrocortisone intravenous injection for flushed face and expanded erythema of the body. The symptoms gradually improved over several hours and the patient recovered on the same day. Allergy test was performed (nonspecific IgE 349 IU/mL; specific IgE for bovine milk and casein, class 4; α-lactalbumin, class 3; β-lactoglobulin, class 2; soy, class 1; egg white, class 6, wheat, class 3, and banana, class 3).

				After discontinuation: After the preparation was discontinued and the elemental diet for neonates and infants was resumed, similar symptoms have not developed (for approximately 2 years).
	Concomitant medications: phenobarbital, tizanidine hydrochloride, sodium cromoglicate, carbocisteine, ambroxol hydrochloride, clarithromycin, sucralfate hydrate			

2 Lornoxicam

Brand Name (name of company)	Lorcam tab. 2 mg and 4 mg (Taisho Pharmaceutical Co., Ltd.)
Therapeutic Category	Antipyretics and analgesics, anti-inflammatory agents
Indications	○ Relief of pain and inflammation associated with: Rheumatoid arthritis, arthrosis deformans, lumbago, periarthritis scapulohumeralis, or neck, shoulder and arm syndrome. ○ Treatment of pain and inflammation following: Surgery, trauma, or tooth extraction.

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis fulminant, hepatic function disorder, and jaundice: Serious hepatitis such as hepatitis fulminant, hepatic function disorder with a increase in AST (GOT), ALT (GPT), γ-GTP, or Al-P levels, or jaundice may occur. Patients should be closely monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2005 to October 27, 2008) (events for which a causality to the drug could not be denied)

- Hepatitis fulminant: 1 case (a fatal case)

The number of patients treated with Lornoxicam for a year estimated by MAH: approximately 2.7 million (October 2007 to September 2008)

Marketed in Japan in: February 2001

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Fractured nose (uterine myoma, insomnia)	12 mg 82 days	**Hepatitis fulminant** On day 1 of administration: This drug (4 mg TID) was initiated at Hospital A for fractured nose. Approximately on day 75 of administration: The patient noted malaise. Abdominal pain upper developed. On day 82 of administration (day of discontinuation): The patient visited Hospital B. Blood test showed acute liver disorder. The patient was hospitalized on the same day. Administration of the drug was discontinued. 4 days after discontinuation: Coagulability worsened. Severe hepatitis was noted. 8 days after discontinuation: The patient was transferred to Hospital C. Methylprednisolone sodium succinate drip infusion (1 g, once) was initiated. Tests for hepatitis viruses, cytomegalovirus, EB virus: negative. 12 days after discontinuation: Grade 2 hepatic encephalopathy was noted. Hepatitis fulminant was diagnosed. The patient was transferred to ICU and treated with artificial liver support. Haemodialysis filtration (HDF) was initiated (performed for 4 consecutive days). 13 days after discontinuation: Plasma exchange (PE) was initiated (performed for 3 consecutive days at first and every other day for 8 days). 23 days after discontinuation: Total bilirubin 20.9 mg/dL, direct bilirubin 8.3 mg/dL (D/T ratio 0.397). DLST (this drug): false positive. Because marked hepatic atrophy was noted on imaging, AFP did not increase and remained at 5.8 ng/mL, living-donor liver transplantation was scheduled and the patient was transferred to the department of surgery of Hospital D. Approx. 1 month after discontinuation: Living-donor liver transplant was performed. Approx. 15.5 months after discontinuation: Finally, the patient died of sepsis and bleeding tendency.
	Concomitant medications: brotizolam, sofalcone, keishibukuryogan, chlordiazepoxide			

Clinical Laboratory Values

	On day 82 of admin. (day of discontinu-ation)	4 days after discontinu-ation	8 days after discontinu-ation	12 days after discontinu-ation	13 days after discontinu-ation	16 days after discontinu-ation	17 days after discontinu-ation	20 days after discontinu-ation	22 days after discontinu-ation	23 days after discontinu-ation
TP (g/dL)	6.7	6.0	5.1	5.8	5.7	5.5	5.7	5.4	5.7	6.0
Alb (g/dL)	3.6	3.3	—	—	3.3	3.6	3.8	3.6	3.8	3.8
Al-P (IU/L)	527	581	475	296	307	241	248	344	300	288
AST (GOT) (IU/L)	2100	601	425	76	77	62	63	77	79	81
ALT (GPT) (IU/L)	1947	962	505	127	130	71	66	75	68	63
LDH (IU/L)	804	357	329	339	362	304	331	444	405	375
γ-GTP (IU/L)	222	208	143	—	95	32	40	33	28	22
T-BIL (mg/dL)	5.1	11.3	18.2	17.4	18.2	11.9	14.5	20.6	21.3	20.9
D-BIL (mg/dL)	—	—	11.5	8.1	8.8	4.6	5.3	9.1	8.8	8.3
Ammonia (μg/dL)	—	157	—	145	128	106	102	146	151	157
Pt (seconds)	—	22.6	30.9	—	26.2	19.1	19.0	24.3	22.7	20.3
Pt (%)	—	35.0	14.3	—	19.0	32.7	33.0	21.6	24.3	30.1

TP: Total Protein
Alb: Albumin
Al-P: Alkaline Phosphatase
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
T-BIL: Total bilirubin
D-BIL: Direct bilirubin
Pt: Prothrombin Time

3

Revision of PRECAUTIONS

(No. 203)

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 dated November 28, 2008 (excluding those presented in "2. Important Safety Information" of this Bulletin).

<Antipyretics and analgesics, anti-inflammatory agents, Vasoconstrictors>

1 Ergotamine Tartrate·Anhydrous Caffeine
Ergotamine Tartrate·Anhydrous Caffeine·Isopropylantipyrine
Dihydroergotamine Mesilate

[Brand Name]

Cafergot Tablets (Novartis Pharma K.K.)
CLEAMINE A and S Tab. (Nichi-Iko Pharmaceutical Co., Ltd.)
Dihydergot Tablets 1 mg (Novartis Pharma K.K.), and others

[Contraindications]

Patients with cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis etc. confirmed by echocardiogram, and patients with a history of such diseases.

<Diuretics>

2 Acetazolamide
Acetazolamide Sodium

[Brand Name]

DIAMOX POWDER, DIAMOX TABLETS 250 mg (Sanwa Kagaku Kenkyusho Co.,Ltd.)
DIAMOX Inj.500 mg (Sanwa Kagaku Kenkyusho Co.,Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder and jaundice: Hepatic function disorder with elevations of AST (GOT), ALT (GPT), or Al-P, etc. and jaundice may occur. Patients should be closely monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Vasodilators>

3 Diltiazem Hydrochloride (oral dosage form)

[Brand Name]

HERBESSER Tablets 30 and 60, HERBESSER R Capsules 100 mg and 200 mg (Mitsubishi Tanabe Pharma Corporation), and others

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythroderma (exfoliative dermatitis), acute generalised exanthematous pustulosis may occur. If erythema, blister, pustule, pruritus, fever, enanthema, etc. occur, administration should be discontinued, and appropriate therapeutic measures should be taken.

4 <Antituberculosis> Ethambutol Hydrochloride

[Brand Name] Esanbutol Tablets 125 mg and 250 mg (Sandoz K.K.), EBUTOL 125 mg and 250 mg Tablets (Kaken Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

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

Platelets decreased: Platelets decreased may occur. Patients should be carefully monitored through periodic blood testing, etc. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

5 <Human blood preparations> Octocog Alfa (Genetical recombination)

[Brand Name] Kogenate-FS BIO-SET 250, 500, and 1000 IU for injection (Bayer Yakuhin, Ltd.)

[Important Precautions] Inhibitors to blood coagulation factor VIII may develop in patients. Especially after initiation of the substitution therapy with factor VIII preparations, it is known that the risk of inhibitor formation is increased especially during the stage where the numbers of administration are few (relatively shortly after the initiation of substitution therapy) or where the short intensive substitution therapy is given. If the expected haemostatic effect is not obtained after the administration, this drug should be suspected. Patients should be carefully managed through examinations of recovery rate and inhibitor, and appropriate measures should be taken for possible inhibitor formation.

[Adverse Reactions (clinically significant adverse reactions)]

Anaphylactoid symptoms: Anaphylactoid symptoms may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

6 <Human blood preparations> Freeze-dried Human Blood Coagulation Factor VIII Concentrate Rurioctocog Alfa (Genetical recombination)

[Brand Name] CROSS EIGHT M 250, 500, and 1000 (Japanese Red Cross Society), Conco-eight-HT (Benesis Corporation), Confact F (The Chemo-Sero-Therapeutic Research Institute)
ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method 250, 500, and 1000, Recombinate 250, 500, and 1000 (Baxter Limited)

[Important Precautions] Inhibitors to blood coagulation factor VIII may develop in patients. Especially after initiation of the substitution therapy with factor VIII preparations, it is known that the risk of inhibitor formation is increased especially during the stage where the numbers of administration are few (relatively shortly after the initiation of substitution therapy) or where the short intensive substitution therapy is given. If the expected haemostatic effect is not obtained after the administration, this drug should be suspected. Patients should be carefully managed through examinations of recovery rate and inhibitor, and appropriate measures should be taken for possible inhibitor formation.

7 <Human blood preparations>

Freeze-dried Concentrated Human Blood Coagulation Factor IX
Freeze-dried Human Blood Coagulation Factor IX Complex

[Brand Name]

Christmassin M i.v. 400 and 1000 units (Benesis Corporation), Novact M (The Chemo-Sero-Therapeutic Research Institute)
PPSB-HT "NICHIYAKU" (Nihon Pharmaceutical Co., Ltd.)

[Important Precautions]

Inhibitors to blood coagulation factor IX may develop in patients. If the expected haemostatic effect is not obtained after the administration, this drug should be suspected. Patients should be carefully managed through examinations of recovery rate and inhibitor, and appropriate measures should be taken for possible inhibitor formation.

4

List of products subject to Early Post-marketing Phase Vigilance

(As of January 1, 2009)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Raltegravir Potassium / Isentress Tablets 400 mg	Banyu Pharmaceutical Co., Ltd.	July 7, 2008
Norethisterone/Ethinylestradiol / Lunabell Tablets	Nobelpharma Co., Ltd.	July 8, 2008
Argatroban Hydrate / Slonnon HI Injection 10 mg/2 mL[*1]	Daiichi Sankyo Co., Ltd.	July 16, 2008
Argatroban Hydrate / Novastan HI inj. 10 mg/2 mL[*1]	Mitsubishi Tanabe Pharma Corporation	July 16, 2008
Sapropterin Hydrochloride / Biopten Granules 2.5%[*2]	Asubio Pharma Co., Ltd.	July 16, 2008
Sodium Risedronate Hydrate / Actonel Tab. 17.5 mg[*3]	Ajinomoto Co., Inc.	July 16, 2008
Sodium Risedronate Hydrate / Benet Tablets 17.5 mg[*3]	Takeda Pharmaceutical Company Limited	July 16, 2008
Diazoxide / Aroglycem Capsules 25 mg	Schering-Plough K.K.	July 22, 2008
Yttrium (^{90}Y) Ibritumomab Tiuxetan (Genetical recombination) / Zevalin yttrium (^{90}Y) injection	Bayer Yakuhin, Ltd.	August 4, 2008
Indium (^{111}In) Ibritumomab Tiuxetan (Genetical recombination) / Zevalin indium (^{111}In) injection	Bayer Yakuhin, Ltd.	August 4, 2008
Levobupivacaine Hydrochloride / POPSCAINE 0.75% inj. 75 mg/10 mL, POPSCAINE 0.75% inj. 150 mg/20 mL, POPSCAINE 0.25% inj. 25 mg/10 mL, POPSCAINE 0.25% inj. bag 250 mg/100 mL, POPSCAINE 0.75% inj. syringe 75 mg/10 mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL	Maruishi Pharmaceutical Co., Ltd.	August 5, 2008
Estradiol / Julina Tablets 0.5 mg	Bayer Yakuhin, Ltd.	September 16, 2008
Mometasone Furoate Hydrate / Nasonex Nasal Solution 50 μg 56 metered spray	Schering-Plough K.K.	September 16, 2008
Cetuximab (Genetical recombination) / Erbitux Injection 100 mg	Merck Serono Co., Ltd.	September 19, 2008
Tazobactam·Piperacillin Hydrate / ZOSYN	Taiho Pharmaceutical Co., Ltd.	October 1, 2008
Neostigmine Methylsulfate·Atropine Sulfate Hydrate / Atvago Reverse Intravenous Injection Syringe 3 mL and 6 mL	Terumo Corporation	October 1, 2008

Ramosetron Hydrochloride Irribow Tablets 2.5 μg and 5 μg	Astellas Pharma Inc.	October 7, 2008
Rifabutin MYCOBUTIN Capsules 150 mg	Pfizer Japan Inc.	October 7, 2008
Pegaptanib Sodium MACUGEN IVT Inj. KIT 0.3 mg	Pfizer Japan Inc.	October 14, 2008
Interferon Alfa (NAMALWA) Sumiferon 300 and 600, Sumiferon DS 300 and 600*4	Dainippon Sumitomo Pharma Co., Ltd.	October 16, 2008
Estradiol Julina Tablets 0.5 mg*5	Bayer Yakuhin, Ltd.	October 16, 2008
Freeze-dried Polyethylene Glycol Treated Human Normal Immunoglobulin kenketu glovenin-I-NICHIYAKU*6	Nihon Pharmaceutical Co., Ltd.	October 16, 2008
Ciclosporin Neoral Oral Solution, Neoral Capsules 10 mg, 25 mg, and 50 mg*7	Novartis Pharma K.K.	October 16, 2008
Somatropin (Genetical Recombination) Genotropin 5.3 mg, Genotropin MiniQuick s.c. inj. 0.6 mg, 1.0 mg, 1.4 mg, Genotropin Inj. 12 mg*8	Pfizer Japan Inc.	October 16, 2008
Bepridil Hydrochloride Hydrate Bepricor Tablets 50 mg and 100 mg*9	Schering-Plough K.K.	October 16, 2008
Adapalene Differin Gel 0.1%	Galderma Pharma S.A.	October 21, 2008
Tacrolimus Hydrate Graceptor Capsules 0.5 mg, 1 mg, and 5 mg	Astellas Pharma Inc.	October 28, 2008
Anti-human Thymocyte Immunoglobulin, Rabbit Thymoglobuline for Intravenous Infusion 25 mg	Genzyme Japan K.K.	November 28, 2008
Pirfenidone Pirespa Tablets 200 mg	Shionogi & Co., Ltd.	December 12, 2008
Lamotrigine Lamictal Tablets 2 mg, 5 mg, 25 mg, and 100 mg	GlaxoSmithKline K.K.	December 12, 2008
Tafluprost TAPROS ophthalmic solution 0.0015%	Santen Pharmaceutical Co., Ltd.	December 16, 2008
Phenobarbital Sodium NOBELBAR 250 mg for Injection	Nobelpharma Co., Ltd.	December 16, 2008
Haemophilus influenzae type b conjugate vaccine ActHIB	Sanofi Pasteur-Daiichi Sankyo Vaccine Co., Ltd.	December 19, 2008

*1: An additional indication for "prophylaxis of thrombosis in patients with heparin-induced thrombocytopenia (HIT) type II"

*2: An additional indication for "reducing blood phenylalanine levels in patients with hyperphenylalaninemia (tetrahydrobiopterin-responsive hyperphenylalaninemia) due to tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency"

*3: An additional indication for "Paget disease of bone"

*4: An additional indication for "the improvement of viremia in compensated cirrhosis type C (except in the patients with HCV serogroup 1 and high blood HCV-RNA level)"

*5: An additional indication for "osteoporosis postmenopausal"

*6: An additional indication for "pemphigus (only for cases not adequately responsive to corticosteroids)"

*7: An additional indication for "dermatitis atopic (patients who are not adequately responsive to conventional therapies)"

*8: An additional indication for "SGA (Small-for-Gestational Age) dwarfism without epiphyseal closure"

*9: An additional indication for "sustained arterial fibrillation when other antiarrhythmic agents cannot be used or are ineffective"