Pharmaceuticals and Medical Devices Safety Information

No. 278 March 2011

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

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

Office of Safety I,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

Pharmaceuticals and Medical Devices Safety Information
No. 278 March 2011

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Revision of Package Insert of Inferior Vena Cava Filter**	*P*	The inferior vena cava (IVC) filter is a medical device to be placed in the IVC to prevent pulmonary embolism associated with deep venous thrombosis or other diseases. Filter migration and filter fracture associated with long-term use of IVC filters have been reported in Japan and overseas, and some of which led to filter embolization and/or IVC perforation. The MHLW requires marketing authorization holders (MAHs) of these devices to revise the "Warnings" section in the package insert. The details are described in this section.	5
2	**Promotion of Safety Measures Using the PMDA medi-navi**		"PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)" is an information distribution service which informs the important safety information regarding pharmaceuticals and medical devices when such information is issued. The use of PMDA medi-navi is encouraged to enhance safety measures. The details are described in this section.	7
3	**Isosorbide (and 1 other)**	*P* *C*	This section presents the 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 February 15, 2011.	10
4	**Gorinsan (and 17 others)**		Revision of Precautions (No. 224)	14
5	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of March 1, 2011.	21

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

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

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

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

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

Abbreviations

ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
ARDS	Acute respiratory distress syndrome
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
CRP	C-reactive protein
CT	Computed tomography
DIHS	Drug-induced hypersensitivity syndrome
DLST	Drug lymphocyte stimulation test
DSU	Drug safety update
EPPV	Early Post-marketing Phase Vigilance
FDA	Food and Drug Administration
HCO3	Bicarbonate
HCV RNA	Hepatitis C virus ribonucleic acid
HHV-6	Human herpesvirus 6
HJ	Hugh-Jones
HUS	Haemolytic uraemic syndrome
IVC	Inferior vena cava
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
$PaCO_2$	Arterial carbon dioxide partial pressure
PaO_2	Arterial oxygen partial pressure
pH	Hydrogen ion concentration
SP-D	Surfactant protein D
SpO_2	Oxygen saturation
TEN	Toxic epidermal necrolysis
US	United States
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Revision of Package Insert of Inferior Vena Cava Filter

1. Introduction

Inferior vena cava (IVC) filter is a cage-like device that is placed in the IVC to prevent pulmonary embolism associated with deep venous thrombosis or other diseases. There are three types of IVC filters: "temporary IVC filters (and catheters)" to be temporarily placed in the IVC, "permanent IVC filters" to be permanently placed, and "retrievable IVC filters" which can be retrieved with a dedicated device within a certain period following placement or can be left in the patient as a permanent device.

Filter migration and fracture associated with long-term use of IVC filters have been reported in Japan and overseas. Some of these cases led to filter embolization and/or IVC perforation. Based on the above, precautions for use of IVC filters are added to the "Precautions" section in the package insert. The details are described below.

2. Reporting on IVC filter malfunctions

(1) U.S.

The U.S. Food and Drug Administration (FDA) announced in August 2010 that 328 cases of filter migration, 56 cases of filter fracture, 146 cases of filter embolizations, and 70 cases of IVC perforation associated with long-term use of IVC filters have been reported since 2005. The FDA alerted healthcare professionals to carefully follow-up IVC filter recipients and consider removal of the filter from patients with retrievable IVC filters as soon as protection from pulmonary embolism is no longer needed.[1)]

(2) Japan

In Japan, 11 similar cases to those in the USA associated with long-term use of IVC filters have been reported between 2006 and October 2010. Specifically, 6 cases of filter fracture (leading to venous perforation in 1 case), 1 case of filter migration (filter tilt, leading to venous perforation), 2 cases of venous perforation (filter condition unknown), and 2 cases of duodenal perforation (filter condition unknown) were reported. The indwelling time before filter fracture or vinous perforation were observed varied from 1 year to approximately 12 years. After the adverse event occurred, 9 cases were followed up without any additional treatment, 1 case underwent surgical filter removal, and treatment was unknown in the remaining one patient.

3. Safety measures

In light of these circumstances, the MHLW issued a notification on December 3, 2010 and required the marketing authorization holders (MAHs) to include the following descriptions in the "Warnings" section in the package insert:[2)]

- There is a risk of filter fracture or other adverse events associated with long-term use of IVC filter
- Periodical monitoring of filter condition is needed during long-term use of IVC filter
- Consider filter removal from patients for whom IVC filters are no longer needed

Take the following precautions and follow-up patients carefully after IVC filter placement.

(1) Permanent inferior vena cava filter
Adverse events including filter fracture, filter migration, and filter embolization associated with long-term use have been reported. The filter condition should be monitored by periodical follow-up after placement. If filter fractures or other adverse events are observed, additional treatment should be considered as appropriate.

(2) Retrievable inferior vena cava filters (IVC filters which can be retrieved with a dedicated device within a certain period following placement or can be left in the patient as a permanent device)
In addition to (1), removal of this product is recommended, if continuous use of this product is not medically necessary and it can be removed safety, after considering the patient's risk.

<References> (including provisionally translated titles)

1) http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm221676.htm
2) Joint PFSB/SD Notification No. 1203-2 and PFSB/ELD/OMDE Notification No. 1203-1, by the Director of Safety Division, Pharmaceutical and Food Safety Bureau and by the Director of Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated December 3, 2010, "Revision of Package Insert of Inferior Vena Cava Filter"

2

Promotion of Safety Measures Using the PMDA medi-navi

The PMDA medi-navi is a free e-mail service which informs of releases of very important safety information regarding pharmaceuticals and medical devices as soon as it is available. Subscriptions to the PMDA medi-navi are encouraged to enhance pharmaceutical and medical device safety measures.

* PMDA medi-navi information is distributed only in Japanese.

1. Introduction

The PMDA medi-navi (official name, Pharmaceutical and Medical Device Information E-mail Alert Service) is a free e-mail service provided by the PMDA to help healthcare professionals to enhance pharmaceutical and medical device safety measures. It provides important safety information regarding pharmaceuticals and medical devices, such as Dear Healthcare Professional Letters, Revisions of Precautions, recall information, and regulatory approval information (e.g., review reports of new drugs) when such information is issued.

Pharmaceutical and medical device safety information can be obtained in a timely and reliable manner just by subscribing to the PMDA medi-navi.

Not only pharmaceutical and medical device safety management supervisors but also those who are collecting information required for safe use of drugs and medical devices are encouraged to use the PMDA medi-navi for faster information collection.

See “3. PMDA medi-navi subscription” for details.

2. Information provided by the PMDA medi-navi

The PMDA medi-navi provides the following information. The information will be distributed mostly on the same day of its announcement. The subscribers can select the type of information that they wish to receive.

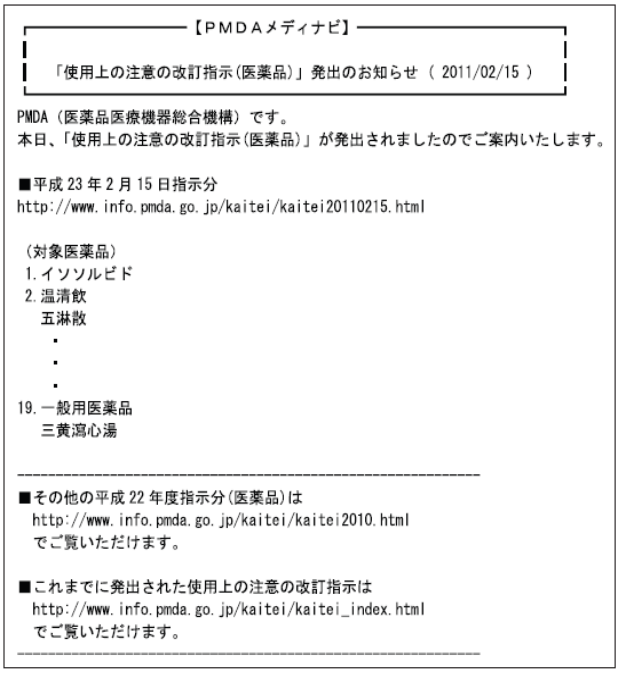
Other than the information listed below, important information such as MHLW’s press releases will also be provided.

- Dear Healthcare Professional Letters
  Important information prepared and issued by MAHs when urgent safety measures are required
- Revisions of Precautions
  Information about revisions of Precautions section required by MHLW to MAHs
- Pharmaceuticals and medical devices safety information
  Information provided by the MHLW, in principle monthly, which includes descriptions of safety measures recently taken and Revisions of Precautions
- Drug Safety Update (DSU)
  Information on all revisions of Precautions sections published by the pharmaceutical industry, which includes the MHLW-requested revisions and MAHs’ voluntary revisions
- Self-inspection information
  Information on self-inspections required by the MHLW to MAHs of medical devices

- Recall information (Class I)
  Information on Class I recall of pharmaceuticals and medical devices (refers to a situation in which use of the product may cause serious adverse health effects or deaths)
- PMDA Medical Safety Information
  Easy to understand, graphic-based information of frequently reported near-miss incidents and adverse events or malfunctions related to pharmaceuticals and medical devices to provide precautions to be taken by healthcare professionals for ensuring safety use of the product
- Regulatory approval information
  Information on review reports and summaries of product applications for pharmaceuticals and medical devices

An example of e-mail information is shown in **Figure 1**. When "Revision of Precautions (drugs)" are issued, the e-mail message containing the list of relevant drugs and links to the revision information will be sent.

Figure 1 Example of PMDA medi-navi information



【PMDAメディナビ】

「使用上の注意の改訂指示(医薬品)」発出のお知らせ（ 2011/02/15 ）

PMDA（医薬品医療機器総合機構）です。
本日、「使用上の注意の改訂指示(医薬品)」が発出されましたのでご案内いたします。

■平成 23 年 2 月 15 日指示分
http://www.info.pmda.go.jp/kaitei/kaitei20110215.html

（対象医薬品）
1.イソソルビド
2.温清飲
　五淋散
　・
　・
　・
19.一般用医薬品
　三黄瀉心湯

■その他の平成 22 年度指示分(医薬品)は
http://www.info.pmda.go.jp/kaitei/kaitei2010.html
でご覧いただけます。

■これまでに発出された使用上の注意の改訂指示は
http://www.info.pmda.go.jp/kaitei/kaitei_index.html
でご覧いただけます。

Note

PMDA medi-navi information is distributed only in Japanese.

3. How to subscribe to the PMDA medi-navi

To receive the PMDA medi-navi service, a subscription is necessary. Anyone can subscribe to this service, free of charge.

Please visit the PMDA medi-navi website (http://www.info.pmda.go.jp/info/idx-push.html) and fill out the on-line subscription form with the necessary information (e.g., affiliation, e-mail address).

The subscribers can select the information that they wish to receive.

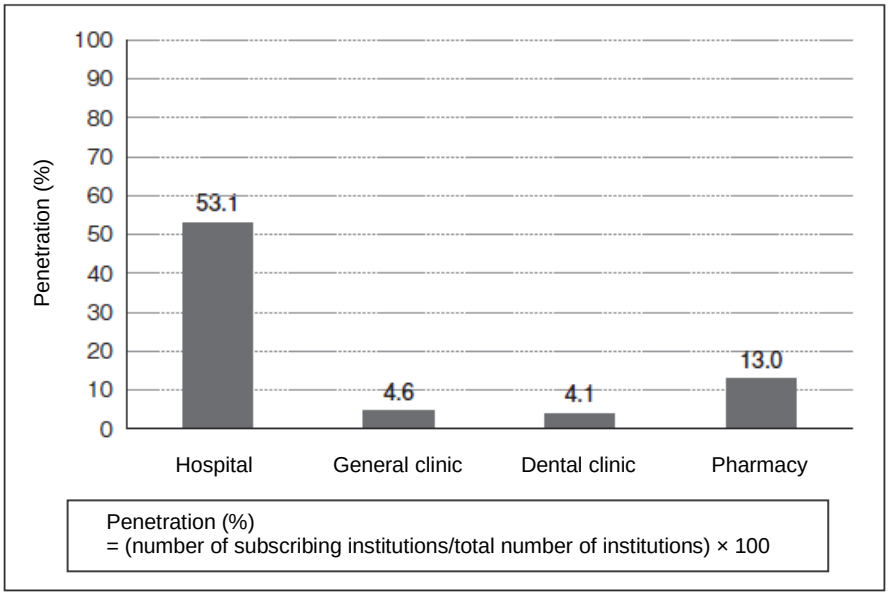
The PMDA medi-navi website has a link on the PMDA website and is also linked to the drug safety information page of the MHLW website.

4. Current status and invitation to use the PMDA medi-navi for enhancement of safety measures

At present, the number of hospitals, clinics and dispensing pharmacies in Japan is estimated to be approximately 230,000. However, only 31,467 subscribers (18,985 unique institutions excluding overlaps) use the PMDA medi-navi as of December 2010 (Figure 2). The MHLW has held a "meeting to exchange opinions to promote the Pharmaceutical and Medical Device Information E-mail Alert Service" in order to have PMDA medi-navi used by more healthcare providers. Based on the discussion at the meeting, the PMDA is making efforts to improve the PMDA medi-navi to provide more usable and easier to understand services.

We hope the PMDA medi-navi will be used by more healthcare professionals including, not only pharmaceutical and medical device safety management supervisors, but also physicians, pharmacists, nurses, and clinical engineers. The active use of the service is encouraged to enhance pharmaceutical and medical device safety measures.

Figure 2 Penetration (%) of the information distribution service based on the institution count



3

Important Safety Information

This section presents the 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 the package inserts of drugs that have been revised in accordance with the Notification dated February 15, 2011.

[Brand name]: Major product names are showed.

1 Isosorbide

Brand Name (name of company)	ISOBIDE (Kowa Company, Ltd.)
Therapeutic Category	Diuretics
Indications	Reduction of intracranial pressure in patients with brain tumor, reduction of intracranial pressure in patients with increased intracranial pressure due to head trauma, diuresis in patients with renal/ureteral calculus, reduction of intraocular pressure in patients with glaucoma, treatment for patients with Meniere's disease

≪PRECAUTIONS (underlined parts are revised)≫

[Contraindications]

Patients with a history of hypersensitivity to this drug or any ingredients of this drug

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored, and if abnormalities including rash, dyspnoea, decreased blood pressure, or palpitation are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

<Reference Information>

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

- Shock, anaphylactoid symptoms: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 21,000 (2010).
Launched into Japan: June 1968

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (discontinuation)		Clinical course and therapeutic measures
1	Female 30s	Cerebrovascular arteriovenous malformation (gastritis)	42 g 27 days	**Anaphylactic shock** Allergic history: Loxoprofen sodium hydrate (Anaphylactic shock) Day 1 of administration: The patient started receiving isosorbide 21 g × 2/day to reduce the intracranial pressure at the department of neurosurgery. Day 20 of administration: The dose of isosorbide was changed to 14 g × 3/day due to

				headache. On day 27 of administration (day of discontinuation) Palpitation and dyspnoea occurred at 60 minutes after taking isosorbide. The patient visited an outpatient department because of redness in both hands and facial pallor. The patient was diagnosed with anaphylaxis. (respiratory rate, 22; heart rate, 129; blood pressure, 149/82 mmHg; SpO_2, 99%; no disturbed consciousness) Administration of isosorbide was discontinued. The patient was admitted to the hospital. Drip infusion of concentrated glycerin/fructose was started. adrenaline, chlorpheniramine maleate, and glycyrrhizin/glycine/cysteine were administered for the treatment of anaphylactic shock. 1 day after discontinuation: The symptoms ameliorated, and the patient was discharged from the hospital.
	Concomitant medications: prednisolone, phenobarbital, magnesium oxide, famotidine			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (discontinuation)		Clinical course and therapeutic measures
2	Female 30s	Meniere's disease (none)	21 g for 1 day	**Anaphylactic shock** Day of administration: The patient visited the hospital for vertigo. Isosorbide 63 g, adenosine triphosphate disodium hydrate, and mecobalamin were prescribed for suspected Meniere's disease. Generalised urticaria and dyspnoea occurred after taking the medications. (blood pressure not measured) Hydroxyzine hydrochloride, hydrocortisone sodium succinate and maintenance fluid are administered at the emergency hospital. Betamethasone/d-chlorpheniramine maleate, and diphenhydramine ointment were prescribed at the department of internal medicine (changes in blood pressure and detailed course unknown). 11 days after discontinuation: The patient recovered. Only mecobalamin was prescribed. 13 days after discontinuation: The patient recovered.
	Concomitant medications: adenosine triphosphate disodium hydrate, mecobalamine			

2 Unseiin

Brand Name (name of company)	OHSUGI Unseiin Extract Granule (Ohsugi Pharmaceutical Co., Ltd.)
Therapeutic Category	Kampo medicines
Indications	Patients with a sallow complexion and hot flushes; menstrual irregularity, dysmenorrhea, chinomichi-shou (autonomic imbalance syndrome peculiar to women caused by blood stagnation）, climacteric disturbance; neurosis

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia: If pyrexia, cough, dyspnoea or abnormal chest sound are observed, administration of this drug should be discontinued, examinations including chest X-ray and chest CT scan should be performed immediately, and appropriate measures including administration of corticosteroids should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2008 to January 12, 2011)

- Interstitial pneumonia: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs: approximately 17,000 (for FY 2009)

Launched into Japan : October 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (discontinuation)		Clinical course and therapeutic measures
1	Male 60s	Skin eruption (hypertension)	7.5 g for 11 days	**Interstitial pneumonia** Day 1 of administration: The patient started receiving unseiin for treatment of skin eruption in the head. Day 11 of administration (last day of administration) Administration of unseiin was discontinuation. 8 days after discontinuation. Pyrexia occurred. 11 days after completion: The patient was admitted to the hospital. The chest CT showed ground-glass opacities in most of the left lung and part of the right lung. Steroid pulse therapy and administration of meropenem hydrate and minocycline hydrochloride were started based on the diagnosis of acute respiratory distress syndrome (ARDS) and severe pneumonia. 13 days after discontinuation: Based on chest x-ray, the ground-glass opacities mostly disappeared. 14 days after discontinuation: Steroid pulse therapy was discontinuation. 15 days after discontinuation: Administration of meropenem hydrate was discontinuation . 19 days after discontinuation: Administration of minocycline hydrochloride was discontinuation. 24 days after discontinuation: Symptoms ameliorated, and the patient was discharged from hospital. Bronchoscopy was recommended to identify the cause of pneumonia after the symptoms had improved, however, the patient refused.
	Concomitant medications: nifedipine			

Clinical symptoms

	11 days after discontinuation	24 days after discontinuation
Pyrexia	Severe	No

Sputum	No	No
Cough	Mild	No
Shortness of breath (HJ classification)	III	I

Laboratory examination

	11 days after discontinuation	12 days after discontinuation	15 days after discontinuation
WBC (/mm^3)	6300	4890	9410
LDH (U/L)	249	223	196
KL-6 (U/mL)	—	342	—
SP-D (ng/mL)	—	215.3	—
CRP (mg/dL)	7.1	8.4	0.7

Immune serum test

	11 days after discontinuation
Antinuclear antibody	Negative
Chlamydia	Negative

DLST

	35 days after discontinuation
Unseiin	Positive

Blood gas test

	11 days after discontinuation	12 days after discontinuation:
pH	7.46	7.451
PaO_2 (torr)	47.7	80.6
$PaCO_2$ (torr)	37	38.8
HCO_3 (mEq/L)	25.9	26.6

4

Revision of Precautions (No. 224)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated February 15, 2011 (excluding those presented in "3. Important Safety Information" of this Bulletin).
[Brand names]: Major product names are showed.

1 <Kampo medicines>

Gorinsan

[Brand Name]	TSUMURA Gorinsan Extract Granules for Ethical Use (Tsumura & Co.)
[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia**: If pyrexia, cough, dyspnoea, or abnormal chest sound are observed, administration of this drug should be discontinued, examinations including chest X-ray and chest CT scan should be performed immediately, and appropriate measures including administration of corticosteroids should be taken.

2 <Kampo medicines>

San'oshashinto

[Brand Name]	TSUMURA San'oshashinto Extract Granules for Ethical Use (Tsumura & Co.)
[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia**: If pyrexia, cough, dyspnoea or abnormal chest sound are observed, administration of this drug should be discontinued, examinations including chest X-ray and chest CT scan should be performed immediately, and appropriate measures including administration of corticosteroids should be taken. **Hepatic dysfunction, jaundice**: Hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), Al-P and γ-GTP or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

3 <Digestive organ agents-Miscellaneous>

Mesalazine (Tablet 250 mg, 500mg, Granule, Enema)

[Brand Name]	PENTASA Tablets 250 mg, 500 mg, PENTASA Enema 1 g (Kyorin Pharmaceutical Co., Ltd.), MESALAZINE GRANULES 50% "AKP" (Kobayashi Kako Co., Ltd.)
[Important Precautions]	Hepatitis, hepatic dysfunction, or jaundice have been reported. Patients should be carefully monitored through monitoring of hepatic function including AST (GOT) and ALT (GPT) during the treatment. If any abnormalities are observed, appropriate measures such as reducing the dose or discontinuing administration should be taken.
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatitis, hepatic dysfunction, jaundice**: Hepatitis, hepatic dysfunction with elevated AST (GOT), ALT (GPT), and γ-GTP or jaundice may occur. Patients should be carefully monitored by checking hepatic function test levels. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

4 <Digestive organ agents-Miscellaneous>

Mesalazine (Tablet 400 mg)

[Brand Name] ASACOL tablets 400 mg (Zeria Pharmaceutical Co., Ltd.)

[Important Precautions] Hepatitis, hepatic dysfunction, or jaundice have been reported. Patients should be carefully monitored through monitoring of hepatic function including AST (GOT) and ALT (GPT) during the treatment. If any abnormalities are observed, appropriate measures such as reducing the dose or discontinuing administration should be taken.

[Adverse Reactions (clinically significant adverse reactions)] **Myocarditis, pericarditis, pleurisy**: Myocarditis, pericarditis, or pleurisy may occur. Patients should be carefully monitored. If chest pain, abnormal electrocardiogram, or pleural effusion is observed, appropriate measures such as discontinuing administration should be taken.
Hepatitis, hepatic dysfunction, jaundice: Hepatitis, hepatic dysfunction with elevated AST (GOT), ALT (GPT), and γ-GTP or jaundice may occur. Patients should be carefully monitored by checking hepatic function tests levels. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

5 <Thyroid and parathyroid hormone preparations>

Dried thyroid
Liothyronine Sodium

[Brand Name] THYRADIN POWDER (Aska Pharmaceutical Co., Ltd.)
5 mcg THYRONAMIN TABLETS, 25 mcg THYRONAMIN TABLETS
(Takeda Pharmaceutical Company Limited)

[Adverse Reactions (clinically significant adverse reactions)] **Adrenal crisis**: Adrenal crisis may occur in patients with adrenal cortical insufficiency or pituitary insufficiency. This drug should be administered after adrenal cortical insufficiency is thoroughly improved by replacement of corticosteroid. If symptoms including general malaise, decreased blood pressure, decreased urine output, and dyspnoea occur, appropriate measures should be taken.

6 <Thyroid and parathyroid hormone preparations>

Levothyroxine Sodium Hydrate

[Brand Name] THYRADIN-S TABLETS 25, 50, 100, THYRADIN-S POWDER 0.01%
(Aska Pharmaceutical Co., Ltd.)

[Careful Administration] Low birth weight baby, premature baby

[Adverse Reactions (clinically significant adverse reactions)] **Adrenal crisis**: Adrenal crisis may occur in patients with adrenal cortical insufficiency or pituitary insufficiency. This drug should be administered after adrenal cortical insufficiency is thoroughly improved by replacement of corticosteroid. If symptoms including general malaise, decreased blood pressure, decreased urine output, and dyspnoea occur, appropriate measures should be taken.
Late-onset circulatory collapse: Late-onset circulatory collapse may occur in low birth weight babies and premature babies. Late-onset circulatory collapse is likely to occur especially in very low birth weight babies and extremely premature babies and also at an early stage of administration of this drug. Patients should be carefully monitored, and if decreased blood pressure, decreased urine output, or decreased serum sodium are observed, appropriate measures should be taken.

[Pediatric use]	Late circulatory failure is likely to occur especially in very low birth weight babies and extremely premature babies and also at an early stage of administration of this drug. This drug should be carefully administrated with monitoring of the baby's condition (e.g., blood pressure, urine output, and serum sodium).

7 <Hormones-Miscellaneous>

Goserelin Acetate

[Brand Name]	Zoladex 1.8 mg depot, Zoladex 3.6 mg depot, Zoladex LA 10.8 mg depot (AstraZeneca K.K.)
[Important Precautions]	Some cases of haemorrhage around the injection site leading to haemorrhagic shock have been reported. The attention should be paid to the following points. 1) Select an injection site where vascular injuries are unlikely to occur. 2) Use of this drug should be carefully determined in patients with bleeding tendency (e.g., patients receiving anticoagulants)
[Precautions concerning Use]	Delete the sentence, "This drug should be administered subcutaneously in the anterior abdomen." Carefully select an injection site where vascular injuries are unlikely to occur.

8 <Urogenital and anal organ agents-Miscellaneous>

Oxybutynin Hydrochloride

[Brand Name]	Pollakisu 1 mg Tablets, Pollakisu 2 mg Tablets, Pollakisu 3 mg Tablets (Sanofi-Aventis K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Urinary retention**: Urinary retention may occur. Patients should be carefully monitored. If any symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

9 <Miscellaneous metabolism agents-Miscellaneous>

Pirfenidone

[Brand Name]	Pirespa Tablets 200 mg (Shionogi & Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Agranulocytosis, leucopenia, neutropenia**: Agranulocytosis, leucopenia, or neutropenia may occur. Patients should be carefully monitored through periodical blood tests etc. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

10 <Antineoplastics-Antibiotics>

Actinomycin D

[Brand Name]	COSMEGEN IV Injection 0.5mg (MSD K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

11 <Antineoplastics-Miscellaneous>

Cisplatin (Excluding intra-arterial injection)

[Brand Name] BRIPLATIN INJECTION 10 mg, 25 mg, 50 mg (Bristol Myers K.K.), Randa Inj. 10 mg/20 mL, 25 mg/50 mL, 50 mg/100 mL (Nippon Kayaku Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Leukoencephalopathy (including reversible posterior leukoencephalopathy syndrome)**: Leukoencephalopathy (including reversible posterior leukoencephalopathy syndrome) may occur. If symptoms including staggering gait, lisp, convulsion, headache, confusion, or visual disturbance are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

12 <Antineoplastics-Miscellaneous>

Tamoxifen Citrate

[Brand Name] nolvadex tablets 10 mg, 20 mg (AstraZeneca K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Fulminant hepatitis, hepatitis, cholestasis, hepatic failure**: Serious hepatic disorders including fulminant hepatitis, hepatitis, or cholestasis may occur and some of the cases may result in hepatic failure. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

13 <Acting mainly on gram-positive and gram-negative bacteria, rickettsia and chlamydia>

Minocycline Hydrochloride (oral dosage form, injectable dosage form)

[Brand Name] MINOMYCIN CAPSULES 50 mg, 100 mg, MINOMYCIN TABLETS 50 mg, 100 mg, MINOMYCIN GRANULES 2%, MINOMYCIN INTRAVENOUS 100 mg (FOR DRIP USE) (Pfizer Japan Inc.)

[Adverse Reactions (clinically significant adverse reactions)] **Drug-induced hypersensitivity syndrome (DIHS)**: Rash and pyrexia may occur as the initial symptoms followed by serious late-onset hypersensitivity symptoms with swollen lymph nodes, organ damage such as hepatic dysfunction, leukocytosis, eosinophilia, and atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. The reactivation of viruses including HHV-6 has been found to be frequently associated with DIHS. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised.

14 <Synthetic antibacterials>

Prulifloxacin

[Brand Name] SWORD TABLETS 100 (Meiji Seika Pharma Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), or erythema multiforme** may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Interstitial pneumonia may occur. If pyrexia, cough, dyspnoea or abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

15 <Antivirals>

Ribavirin (Capsules)

[Brand Name]

REBETOL Capsules 200 mg (MSD K.K.)

[Precautions of Dosage and Administration]

The usual treatment duration in patients with serogroup 1 (genotype I (1a) or II (1b)) and high blood HCV RNA is 48 weeks.
According to clinical studies, if the patient receiving concomitant therapy with this drug and interferon alfa-2b (genetical recombination) or peginterferon alfa-2b (genetical recombination) discontinues the treatment, the efficacy of this therapy is compromised. The therapy should therefore be continued for 48 weeks to the extent possible, even with dose reduction or drug suspension. If the patient fails to respond after continuing the treatment for 24 weeks or longer, discontinuation of administration should be considered.

[Important Precautions]

Monotherapy of this drug is ineffective for chronic hepatitis C. This drug should be used concomitantly with interferon alfa-2b (genetical recombination), peginterferon alfa-2b (genetical recombination) or interferon beta. Nevertheless, the safety and efficacy of this drug used for over 48 weeks have not been established.

[Adverse Reactions (clinically significant adverse reactions)]

<Administration of this drug in combination with interferon beta>
Delirium, hallucination: Patients should be carefully monitored. If any abnormalities are observed, discontinuation of therapy should be considered. If the symptoms are severe or do not disappear after dose reduction, administration should be discontinued, and appropriate measures should be taken.
Interstitial pneumonia: If respiratory symptoms including pyrexia, cough, and dyspnoea, or chest X-ray abnormalities are observed, administration should be discontinued and appropriate measures such as administration of corticosteroids should be taken. Patients should be instructed to contact a physician immediately if cough or dyspnoea, etc. occurs.
Cardiac failure: Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
Haemolytic uraemic syndrome (HUS): Haemolytic uraemic syndrome (HUS) characterized by thrombocytopenia, anaemia, and renal failure may occur. Patients should be carefully monitored by performing periodic blood tests (platelet count, red blood cell count, haemogram, etc.) and renal function analyses. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
Nephrotic syndrome: Serious proteinuria with decreased serum total protein and decreased serum albumin may occur. Patients should be carefully monitored by performing periodic urine tests (urine protein). If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

16

<Biological preparations-Miscellaneous>

Interferon Beta (for administration in combination with ribavirin)

[Brand Name]

FERON for Injection (1×10^6IU), (3×10^6IU), (6×10^6IU) (Toray Industries Inc.)

[Precautions of Dosage and Administration]

The duration of treatment with this drug and ribavirin should be carefully determined based on the clinical efficacy (e.g., HCV-RNA, ALT) and the severity of adverse reactions. Changes in white blood cell count, neutrophil count, platelet count, and haemoglobin level should be carefully monitored, and if any abnormalities are observed, dose change or discontinuation of administration should be considered. The usual treatment duration in patients with serogroup 1 and high blood HCV RNA is 48 weeks. Otherwise the treatment duration should be 24 weeks.

[Important Precautions]

When this drug is administered long-term, the clinical efficacy and the severity of adverse reactions should be considered. If the patient fails to respond, administration should be discontinued. The treatment duration of concomitant therapy with this drug and ribavirin for improvement of viraemia in patients with chronic hepatitis C and in patients with compensated cirrhosis type C is 48 weeks (total dose, 936 million IU) and 34 to 36 weeks (total dose, 399 million IU), respectively. The safety and efficacy have not been established in cases where the treatment duration exceeds the above period.

[Adverse Reactions (clinically significant adverse reactions)]

<**Administration of this drug in combination with ribavirin**>

Delirium, hallucination: Patients should be carefully monitored. If any abnormalities are observed, discontinuation of therapy should be considered. If the symptoms are severe or do not disappear after dose reduction, administration of this drug should be discontinued, and appropriate measures should be taken.

Interstitial pneumonia: If respiratory symptoms including pyrexia, cough, and dyspnoea, or chest X-ray abnormalities are observed, administration should be discontinued, and appropriate measures such as administration of corticosteroids should be taken. Patients should be instructed to contact a physician immediately if cough or dyspnoea, etc. occurs. In addition, interstitial pneumonia associated with the concomitant use of a similar drug (interferon alfa preparations) and Shosaikoto has been reported. Concomitant use with Shosaikoto should therefore be avoided.

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

Haemolytic uraemic syndrome (HUS): Haemolytic uraemic syndrome (HUS) characterized by decreased platelets, anaemia, and renal failure may occur. Patients should be carefully monitored by performing periodic blood tests (platelet count, red blood cell count, haemogram, etc.) and renal function analyses. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

Nephrotic syndrome: Serious proteinuria with decreased serum total protein and decreased serum albumin may occur. Patients should be carefully monitored by performing periodic urine tests (urine protein), and if any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

17 <Over-the-counter drugs>

Unseiin Gorinsan

[Brand Name] JPS Unseiin Extract Tablet N, JPS Kampo Unseiin Granule 80
(JPS Pharmaceutical Co., Ltd.)

[Consultation] If you experience any of the following symptoms after taking the product, immediately discontinue the use of the product, and show this document to your physician or pharmacist for consultation.
If the following symptoms are observed after taking this drug:
The following serious symptoms occur in rare cases. In such cases, immediately seek medical aid.

Interstitial pneumonia: Shortness of breath, dyspnoea, and pyrexia etc. may occur together with cough.

18 <Over-the-counter drugs>

San'oshashinto

[Brand Name] JPS San'oshashinto Extract Tablet N, JPS Kampo Granule 18
(JPS Pharmaceutical Co., Ltd.)

[Consultation] If you experience any of the following symptoms after taking the product, immediately discontinue the use of the product, and show this document to your physician or pharmacist for consultation.
If the following symptoms are observed after taking this drug:
The following serious symptoms occur in rare cases. In such cases, immediately seek medical aid.

Interstitial pneumonia: Shortness of breath, dyspnoea, and pyrexia etc. may occur together with cough.

Hepatic dysfunction: General malaise, jaundice (skin and white of the eyes become yellow) etc. may occur.

5

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of March 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg	Pfizer Japan Inc.	June 22, 2010*1 October 27, 2010*2
Ambrisentan Volibris Tablets 2.5 mg	GlaxoSmithKline K.K.	September 17, 2010
Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg	Nippon Shinyaku Co., Ltd.	September 17, 2010
Levetiracetam E Keppra Tablets 250 mg, 500 mg	UCB Japan Co., Ltd.	September 17, 2010
Abatacept (Genetical Recombination) ORENCIA FOR I.V. INFUSION 250 mg	Bristol-Myers K.K.	September 21, 2010
Temsirolimus TORISEL Injection 25 mg	Pfizer Japan Inc.	September 22, 2010
Paclitaxel Abraxane I.V. Infusion 100 mg	Taiho Pharmaceutical Co., Ltd.	September 24, 2010
Teriparatide (Genetical Recombination) FORTEO s.c. injection kit 600 μg	Eli Lilly Japan K.K.	October 1, 2010
Telmisartan/Amlodipine Besilate Micamlo Combination Tablets AP	Nippon Boehringer Ingelheim Co., Ltd.	October 7, 2010
Bazedoxifene Acetate Viviant Tablets 20 mg	Pfizer Japan Inc.	October 13, 2010
Laninamivir Octanoate Hydrate INAVIR DRY POWDER INHALER 20 mg	Daiichi Sankyo Company, Limited	October 19, 2010
Botulinum Toxin Type A BOTOX for injection 50 Unit, 100 Unit*3	GlaxoSmithKline K.K.	October 27, 2010
Adalimumab (Genetical Recombination) HUMIRA Subcutaneous Injection 40 mg Syringe 0.8 mL*4	Abbott Japan Co., Ltd.	October 27, 2010
Olanzapine Zyprexa Tablet 2.5 mg, 5 mg, 10 mg, Zyprexa Fine Granule 1 %, Zyprexa Zydis Tablet 5 mg, 10 mg*5	Eli Lilly Japan K.K.	October 27, 2010

Peramivir Hydrate RAPIACTA Bag for Intravenous Drip Infusion 300 mg, RAPIACTA Vial for Intravenous Drip Infusion 150 mg*[6]	Shionogi & Co., Ltd.	October 27, 2010
Polyethylene Glycol Treated Human Normal Immunoglobulin Venoglobulin IH 5% I.V. 0.5 g/10 mL, 1 g/20 mL, 2.5 g/50 mL, 5 g/100 mL*[7]	Benesis Corporation	October 27, 2010
Drospirenone/Ethinylestradiol YAZ Combination Tablet	Bayer Yakuhin, Ltd.	November 16, 2010
Eltrombopag Olamine REVOLADE Tablets 12.5 mg, 25 mg	GlaxoSmithKline K.K.	December 10, 2010
Nepafenac Nevanac Ophthalmic Suspension 0.1%	Alcon Japan Ltd.	December 10, 2010
Bendamustine Hydrochloride TREAKISYM Injection 100 mg	SymBio Pharmaceuticals Limited	December 10, 2010
Levocetirizine Hydrochloride Xyzal Tablets 5 mg	GlaxoSmithKline K.K.	December 10, 2010
Diquafosol Sodium DIQUAS ophthalmic solution 3%	Santen Pharmaceutical Co., Ltd.	December 13, 2010
Tolvaptan Samsca tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	December 14, 2010
Sodium Hyaluronate Crosslinked Polymer/Sodium Hyaluronate Crosslinked Polymer Crosslinked with Vinylsulfone SYNVISC 2 mL (intra-articular injection)	Genzyme Japan K.K.	December 14, 2010
Exenatide Byetta Subcutaneous Injection 5 µg Pen 300, 10 µg Pen 300	Eli Lilly Japan K.K.	December 17, 2010
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg	Wakamoto Co., Ltd.	December 24, 2010
l-Menthol MINCLEA catapasm for internal use 0.8%	Nippon Pharmaceutical Co., Ltd.	January 11, 2011
Levofloxacin Hydrate CRAVIT INTRAVENOUS DRIP INFUSION BAG 500 mg/100 mL, CRAVIT INTRAVENOUS DRIP INFUSION 500 mg/20 mL	Daiichi Sankyo Company, Limited	January 11, 2011
Paliperidone Invega Tablets 3 mg, 6 mg, 9 mg	Janssen Pharmaceutical K.K.	January 17, 2011
Ciclesonide Alvesco 50 µg Inhaler 112 puffs, Alvesco 100 µg Inhaler 112 puffs, Alvesco 200 µg Inhaler 56 puffs*[6]	Teijin Pharma Limited.	January 21, 2011
Roxatidine Acetate Hydrochloride ALTAT CAPSULES 37.5, 75*[6]	ASKA Pharmaceutical Co., Ltd.	January 21, 2011
Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg	Janssen Pharmaceutical K.K.	February 4, 2011

*1 The originally approved indication for “post herpetic neuralgia”

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

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

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

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

*6 An additional administration for “pediatrics”

*7 An additional indication for “improvement of muscular weakness associated with polymyositis or dermatomyositis (limited to patients who are not adequately responsive to steroids)”