Pharmaceuticals and Medical Devices Safety Information

No. 266 February 2010

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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).

Published by
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

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Pharmaceuticals and Medical Devices Safety Information

No. 266 February 2010

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—

The 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 for 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, it is mandatory for such providers 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

Proper procedures for soft contact lens care

1. Introduction

Proper procedures for soft contact lens care are essential to prevent eye disorders such as corneal infection.Disinfectant solutions for soft contact lens care (quasi-drugs); merely immersing the lenses in the disinfectant solution is not sufficient to eradicate Acanthamoeba, one of the causes of corneal infection, completely. Cleaning procedure by rubbing the lenses in the proper way prior to disinfection procedure is important to ensure that the disinfectant solutions produce the intended effect.

The National Consumer Affairs Center of Japan has published a report entitled "Effectiveness of disinfectant solutions for soft contact lenses against Acanthamoeba—a report based on a survey on contact lens care —" dated December 16, 2009 (http://www.kokusen.go.jp/news/data/n-20091216_1.html) [1)]. It indicates follows:

(1) The disinfectant solutions for soft contact lenses do not have sufficient disinfecting effect by themselves to eradicate Acanthamoeba completely.

(2) Soft contact lenses of users who had been practicing proper procedures (hand washing with soap, cleaning lenses by rubbing, and periodical replacement of lens cases) showed lower Acanthamoeba contamination and lower detection rates of bacteria.

Learning the proper care procedures and practicing the recommended care procedure are important for users to avoid contracting corneal infection and other eye disorders while wearing soft contact lenses.

On the same day when the above report was released, the Ministry of Health, Labour, and Welfare issued a request to the parties concerned that they intensify their efforts to provide the public with relevant information about the proper use of disinfectant solutions for soft contact lenses.

In the present issue, we would like to inform about our efforts to disseminate information for proper procedures of soft contact lens care using disinfectant solutions as well as the proper use of contact lenses.

2. Acanthamoeba corneal infection associated with contact lens wear

Acanthamoeba corneal infection is an intractable disease of the cornea, which cause symptoms including hyperemia, visual impairment, and severe eye pain, and may lead to blindness. Acanthamoeba is a protoctista widely found in a variety of natural habitats including soil, fresh water and seawater; it is also found in house dust, groundwater, and around washbasins. When Acanthamoeba can invade the cornea from the corneal injury incurred by a mechanical stimulation during wearing contact lenses, it causes infection[1)]. To prevent such infection, proper procedures of contact lens care and eradication of Acanthamoeba are essential in proper use.

3. Proper procedures of soft contact lens care

There are three major types of disinfectant solutions for soft contact lens care: povidone iodine-based solutions, hydrogen peroxide-based solutions and multi-purpose solutions (MPS: these are all-in-one disinfectant solutions for cleaning, rinsing, disinfection and storage).

<Disinfectant solutions for soft contact lenses>

Solution type	Ease of use	Safety	Disinfecting effect during storage
MPS	Very easy	Allergic reactions due to ingredients of the solution may occur.	Yes
Hydrogen peroxide-based solutions	Comparatively troublesome (requires neutralization)	Cause no allergic reaction. Corneal disorders may occur when the lenses are worn without completing the neutralization step.	No
Povidone iodine-based solutions	No rubbing is required. Neutralization is required.	Contraindicated for people allergic to iodine	No

(Source: Guidelines for Contact Lenses, Journal of Japanese Ophthalmological Society. 109 (10): 638-665, 2005)

Though disinfectant solutions differ in their disinfecting properties and ease of use by their types, all of them have only a limited effect by themselves to eradicate Acanthamoeba.

Soft contact lens users should be instructed to read thoroughly the package inserts of soft contact lenses and disinfectant solutions and to follow the instructions for proper lens care procedures. The following is a list of points to which special attention should be paid for the prevention of eye infections.

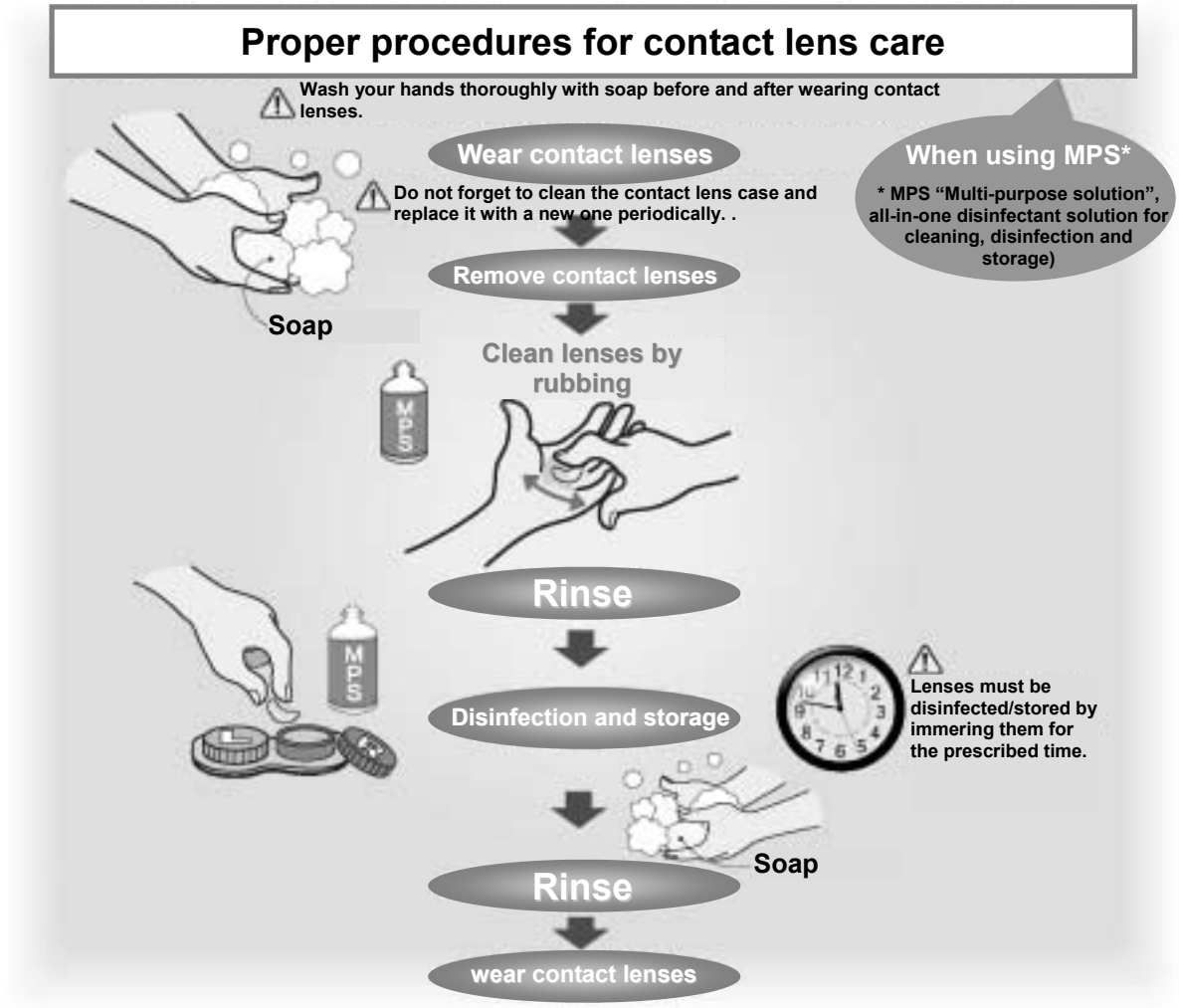
<Disinfectant solutions for soft contact lenses>

1) Wash your hands thoroughly with soap before wearing and removing contact lenses
2) Rub the lens thoroughly with your fingers (approximately 20 to 30 rubs on each side).
3) Lens cases have to be kept clean. Wash and dry the lens case every day, and replace the old case with a new one periodically.
4) Always, use a new solution for cleaning and storage of the lenses and must not use tap water and well water instead of the solution.

<Soft contact lenses>

1) If you feel any abnormality in your eyes (pain, blurred vision, etc.), consult an ophthalmologist as soon as possible.
2) Even if you do not feel any abnormality in your eyes, you should get periodic eye check-ups.
3) Follow the prescribed period of use of products that are worn for a prescribed time, such as single-use lenses and 2 week disposable lenses.

<Reference information> Proper care of contact lenses



4. Dissemination of information related to proper use of contact lenses

The Japan Contact Lens Association, a trade organization of manufacturers and vendors of contact lenses and disinfectant solutions for soft contact lenses, has created posters and leaflets and distributed them to ophthalmology institutions, drug stores, etc. The association has also set up a website for promoting proper use[2]. The Ministry of Health, Labour and Welfare has also issued a notification on December 16, 2009, requesting the Japan Contact Lens Association and others to place information on proper use, which is clearly visible and comprehensive, in the instructions for use and on the package , and to intensify their efforts to provide the public with relevant information. [3]

The Japan Contact Lens Society also provides information about proper use of contact lenses on its website[4].

The Pharmaceuticals and Medical Devices Agency (PMDA) has also taken various measures to raise public awareness on the proper use of soft contact lenses and the disinfectant solutions. The PMDA posts a Q&A page regarding contact lenses on its web site for the public, and a consultation service[6] that could provide advice is available(Phone No. 03-3506-9436, from 9:00 to 17:00, Monday through Friday [except for public holidays, year-end and New Year holidays]).

5. Request to healthcare providers

The cooperation of healthcare providers such as doctors who prescribe contact lenses is essential for the proper use of soft contact lenses and disinfectant solutions. We ask for the understanding and cooperation of healthcare providers concerned in providing users with relevant information by giving instructions when prescribing the lenses and at routine eye check-ups.

6. Closing comments

This information is also available on the website of the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/topics/2009/12/tp1216-1.html).

For further information, you may also visit the following websites:

<References>

1) Report by the National Consumer Affairs Center of Japan
   "Effectiveness of disinfectant solutions for soft contact lenses against Acanthamoeba—a report based on a survey on contact lens care—"
   http://www.kokusen.go.jp/pdf/n-20091216_1.pdf
   Website of the National Consumer Affairs Center of Japan
   http://www.kokusen.go.jp/
2) Website of the Japan Contact Lens Association
   Contact lens and lens care
   http://www.jcla.gr.jp/info/info.html
   Campaign for prevention of eye disorders caused by improper care of contact lenses.
   http://www.jcla.gr.jp/trouble/trouble.html
   Prevention of eye disorders caused by improper care of contact lenses
   http://www.jcla.gr.jp/trouble/trouble_d.html
3) Pharmaceuticals and Medical Devices Information website, Notifications related to medical devices
   http://www.info.pmda.go.jp/mdevices/md-others.html
4) Website of the Japan Contact Lens Society, Proper care of contact lenses
   http://www.clgakkai.jp/general/study.html
5) Pharmaceuticals and Medical Devices Information website, Medical Devices Q&A
   http://www.info.pmda.go.jp/mdevicesqa/mdevicesqa.html
6) Pharmaceuticals and Medical Devices Agency, Consultation service for medical device users
   http://www.info.pmda.go.jp/kusuri/kusurijyoho.html

2

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 January 12, 2010.

1 Bicalutamide

Brand name (name of company)	Casodex Tablets 80 mg (AstraZeneca K.K.) BICALUTAMIDE Tablets 80 mg "DK" (Daiko Pharmaceutical Co., Ltd.) BICALUTAMIDE Tablets 80 mg "F" (Fuji Pharma Co., Ltd.) BICALUTAMIDE Tablets 80 mg "JG" (Nihon Generic Co., Ltd.) BICALUTAMIDE Tablets 80 mg "KN" (Kobayashi Kako Co, Ltd.) BICALUTAMIDE Tablets 80 mg "NK" (Nippon Kayaku Co., Ltd.) BICALUTAMIDE Tablets 80 mg "NP" (Nipro Pharma Corporation) BICALUTAMIDE Tablets 80 mg "SN" (Shiono Chemical Co., Ltd.) BICALUTAMIDE Tablets 80 mg "TCK" (Tatsumi Kagaku Co., Ltd.) BICALUTAMIDE Tablets 80 mg "Aska" (ASKA Pharmaceutical. Co., Ltd.) BICALUTAMIDE Tablets 80 mg "Amel" (Kyowa Pharmaceutical Industry Co., Ltd.) BICALUTAMIDE Tablets 80 mg "Ohara" (OHARA Pharmaceutical Co., Ltd.) BICALUTAMIDE Tablets 80 mg "Sawai" (Sawai Pharmaceutical Co., Ltd.) BICALUTAMIDE Tablets 80 mg "Sandoz" (Sandoz K.K.) BICALUTAMIDE Tablets 80 mg "Taiyo" (Taiyo Yakuhin Co., Ltd.) BICALUTAMIDE Tablets 80 mg "Nichi-Iko" (Nichi-Iko Pharmaceutical Co., Ltd.) BICALUTAMIDE Tablets 80 mg "Mylan" (Mylan Seiyaku Ltd.) BICALUTAMIDE Tablets 80 mg "Meiji" (Meiji Seika Kaisha Ltd.)
Therapeutic Category	Antineoplastics - Miscellaneous
Indications	Prostate cancer

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis fulminant, hepatic function disorder, jaundice: Hepatitis fulminant, hepatic function disorder with elevations of AST (GOT), ALT (GPT), ALP, γ-GTP, and/or LDH, or jaundice may occur. Patients should be carefully monitored in the light of performing regular hepatic function tests. If any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) in about the last 3 years (April 1, 2006 to November 30, 2009):
- Hepatitis fulminant: 1 case (fatality)

The number of patients treated with Bicalutamide for a year estimated by MAH: approximately 111,000 (January to December 2009).
Marketed in Japan in: May 1999

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Prostate cancer (none)	80 mg for 150 days	**Hepatitis fulminant** History of prior treatment: orchiectomy Day 1 of administration: Oral administration of bicalutamide was started at 80 mgfor the treatment of prostate cancer. Day 8 of administration: AST (GOT): 25 IU/L, ALT (GPT): 16 IU/L Day 120 of administration: Hepatic function disorder occurred with AST (GOT) of 293 IU/L, ALT (GPT) of 409 IU/L. Asthenia and anorexia developed. Approximately 4 months after administration: Malaise gradually worsened. Day 151 of administration (day of discontinuation): Administration of this drug was discontinued. Total bilirubin: 8.9 mg/dL, AST (GOT): 2020 IU/L, ALT (GPT): 2096 IU/L, prothrombin time: 38.1%, blood ammonia: 97 μg/dL. No hepatic encephalopathy. No hepatic atrophy on CT scan. Drug-induced hepatitis was suspected and administration of prednisolone was started at 60 mg. Glycyrrhizin/glycine/cysteine 100 mL was administered. The patient was kept at rest and observed. 1 day after discontinuation: AST (GOT): 1388 IU/L, ALT (GPT): 1745 IU/L, total bilirubin: 9.8 mg/dL, prothrombin time: 33.9%, blood ammonia: 89 μg/dL. No hepatic encephalopathy. 3 days after discontinuation: Prothrombin time improved to 34.6%, AST (GOT) to 584 IU/L, and ALT (GPT) to 1186 IU/L. 8 days after discontinuation: No further improvement of hepatic function. 10 days after discontinuation: Hepatic function showed assign of deterioration. It was decided that plasmapheresis is required in case of any further deterioration of hepatic function. 11 days after discontinuation: Prothrombin time: 26.3%. The CT scan revealed a diffuse and inhomogeneous low-density area in the hepatic parenchyma. Transfusion of 6 units of fresh frozen human plasma.12 days after discontinuation: First session of plasmapheresis was performed. 14 days after discontinuation: Second session of plasmapheresis was performed. The level of consciousness was decreased and the patient exhibited flapping tremor. 15 days after discontinuation: Prothrombin time: 19.2%. The patient was almost in a coma. 16 days after discontinuation: According to family members, the treatment was abandoned. 20 days after discontinuation: Death was confirmed. (Autopsy findings: none, cause of death: hepatitis fulminant)
	Concomitant medications: None			

Clinical Laboratory Values

	Day 8 of administration	Day 120 of administration	Day 151 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	10 days after discontinuation	11 days after discontinuation	15 days after discontinuation
Total protein (g/dL)	—	—	—	—	6.0	5.5	5.5	5.9
Albumin (g/dL)	—	—	—	—	3.4	3.0	3.1	3.6
Total bilirubin (mg/dL)	1.2	0.8	8.9	9.8	13.2	17.5	18.8	19.2
Direct bilirubin (mg/dL)	0.3	—	—	6.5	8.9	12.3	12.4	10.3
AST (GOT) (IU/L)	25	293	2020	1388	584	488	493	437
ALT (GPT) (IU/L)	16	409	2096	1745	1186	817	829	431
LDH (IU/L)	147	342	688	364	291	368	356	401
ALP (IU/L)	208	202	537	483	503	527	489	280
γ-GTP (IU/L)	16	—	—	313	293	210	196	45
Cholinesterase (IU/L)	—	—	—	—	203	173	169	276
BUN (mg/dL)	12	15	13	12	12	13	12	11
Serum creatinine (mg/dL)	0.66	0.66	0.63	0.63	0.65	0.65	0.60	0.60
CRP (mg/dL)	—	—	—	—	0.28	0.27	0.33	0.55
WBC (/mm^3)	8800	5500	6300	5200	11400	10100	11000	5600
PLT ($\times 10^4/mm^3$)	20.3	18.4	15.4	15.1	16.3	11.8	12.2	7.1
Prothrombin time (%)	—	—	38.1	33.9	34.6	31.0	26.3	19.2
PT-INR (INR)	—	—	—	2.16	2.11	2.37	2.81	3.39
APTT (sec)	—	—	—	—	39.7	52.7	52.8	41.6
Fibrinogen (mg/dL)	—	—	—	—	172	111	126	133
Blood ammonia (μg/dL)	—	—	97	89	66	—	—	121
HBs antigen	—	—	(–) 0.2	—	—	—	—	—
IgM HA antibody	—	—	<0.1	—	—	—	—	—

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)
ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)
LDH: Lactate dehydrogenase
ALP: Alkaline phosphatase
γ-GTP: gamma-glutamyl transpeptidase
BUN: Blood urea nitrogen
CRP: C-reactive protein
WBC: White blood cell count
PLT: Platelet
PT-INR: Prothrombin time-international normalized ratio
APTT: Activated partial thromboplastin time

2 Fludarabine phosphate

Brand name (name of company)	Fludara Tablets 10mg, Fludara I.V. Injection 50 mg (Bayer Yakuhin Ltd.)
Therapeutic Category	Antimetabolites
Indications	• Chronic lymphocytic leukaemia with anaemia or thrombocytopenia • Following recurrent or refractorydiseases: Low-grade B-cell non-Hodgkin's lymphoma Mantle cell lymphoma • Prior treatment to allogenic hematopoietic stem cell transplantation for the treatment of the following diseases (this indication applies only to Fludara I.V. Injection 50 mg): Acute myeloid leukaemia, myelodysplastic syndrome, chronic myeloid leukaemia, chronic lymphocytic leukaemia, malignant lymphoma, multiple myeloma.

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

[Adverse Reactions (clinically significant adverse reactions)]

Cerebral haemorrhage, pulmonary haemorrhage, gastrointestinal haemorrhage: Cerebral haemorrhage, pulmonary haemorrhage, or gastrointestinal haemorrhage may occur. Patients should be carefully monitored, and if abnormalities are observed, administration should be discontinued immediately and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) in about the last 3 years (April 1, 2006 to November 15, 2009):
- Cerebral haemorrhage, pulmonary haemorrhage: 1 case (no fatality)

The number of patients treated with Fludarabine phosphate for a year estimated by MAH: approximately 2,700 (from October 2008 to September 2009)
Marketed in Japan in:
April 2000 (Injectable dosage form)
July 2007 (Oral dosage form)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 40s	Prior treatment to bone marrow transplantation for the treatment of acute myeloid leukaemia (abnormal hepatic function, disseminated intravascular coagulation, esophagitis, gastritis, febrile neutropenia)	41 mg for 5 days	**Pulmonary haemorrhage** Day 1 of administration: Administration of fludarabine phosphate was started at 41 mg for prior treatment to bone marrow transplantation. Day 5 of administration: Completion of administration of this drug. (Day of discontinutation) 2 days after completion: Allogenic cord blood transplantation was performed (two HLA incompatibilities, unrelated). 3 days after completion: Sepsis, superficial esophagitis and gastritis accompanied bygastrointestinal haemorrhage occurred. Upper endoscopic thrombin spraying was performed for the treatment of superficial esophagitis and gastritis accompanied by gastrointestinal haemorrhage. The patient was fasted and given

				parenteral nutrition. 4 days after completion: Diffuse pulmonary alveolar haemorrhage occurred. The patient was treated with methylprednisolone pulse therapy and respiratory management by mechanical ventilation using endotracheal intubation. 11 days after completion: Superficial esophagitis and gastritis accompanied by gastrointestinal haemorrhage were in remission. 17 days after completion: Sepsis and diffuse pulmonary alveolar haemorrhage werein remission. The patient recovered from diffuse pulmonary alveolar haemorrhage and could be extubated.
	Concomitant medications: Melphalan, thiotepa, tacrolimus hydrate, voriconazole, biapenem, concentrated human red blood cells, concentrated human platelets			

3

Revision of PRECAUTIONS

(No. 213)

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 January 12, 2010 (excluding those presented in "2. Important Safety Information" of this Bulletin).

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1 <Psychotropics>

Amoxapine

[Brand Name]	Amoxan Fine Granules 10%, Amoxan Capsules 10 mg, 25 mg, and 50 mg (Wyeth K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder with significant elevations of AST (GOT), ALT (GPT) and/or γ-GTP levels, or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

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2 <Digestive organ agents - Miscellaneous>

Infliximab (Genetical recombination)

[Brand Name]	Remicade for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corp.)
[Careful administration]	Infliximab should be administered with care to patients with a present or past history of serious blood dyscrasia (pancytopenia, aplastic anaemia, etc.).
[Adverse reactions (clinically significant adverse reactions)]	**Serious blood disorder:** Pancytopenia, thrombocytopenia, leucopenia, or granulocytopenia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

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3 <Hemorrhoidal preparations>

Aluminum potassium sulfate hydrate/tannic acid

[Brand Name]	Zione Injection with Physiological Saline, Zione Injection/Lidocaine (Mitsubishi Tanabe Pharma Corp.)
[Precautions of Dosage and Administration]	Administer the preparation with caution because administration of the preparation below the dentate line or leaking of the preparation below the dentate line may cause incarcerated hemorrhoid or anal pain.
[Important Precautions]	The preparation should be administered with great caution because incarcerated hemorrhoid or anal pain may occur in association with administration of the preparation. (These events may occur if the preparation is administered below the dentate line or leaks below the dentate line. In such cases, appropriate measures should be taken such as taking sitz bath or administration of anti-inflammatory agents. In case the incarcerated hemorrhoid fails to disappear, appropriate measures such as surgical treatment should be taken.)

4 <Analgesics, anti-itchings, astringents, anti-inflammatory agents>

Flurbiprofen (External dosage form)

[Brand Name] Adofeed Pap 40 mg and 80 mg (Lead Chemical Co., Ltd.), Stayban Pap 40 mg (Tokuhon Corporation), and others

[Adverse reactions (clinically significant adverse reactions)]

Anaphylactic shock, anaphylactoid symptoms: Aaphylactic shock or anaphylactoid symptoms may occur. Patients should be carefully monitored and if any abnormalities including distressed feeling of chest, chills, cold sweat, dyspnoea, numbness in extremities, blood pressure decreased, angioedema, or urticaria occur, administration should be discontinued and appropriate measures should be taken.

5 <Miscellaneous metabolism agents - Miscellaneous>

Cinacalcet hydrochloride

[Brand Name] Regpara Tablets 25 mg and 75 mg (Kyowa Hakko Kirin Co., Ltd.)

[Adverse reactions (clinically significant adverse reactions)]

Gastrointestinal haemorrhages, gastrointestinal ulcers: Gastrointestinal haemorrhages or gastrointestinal ulcers may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

6 <Antineoplastics - Miscellaneous>

Letrozole

[Brand Name] Femara Tablets 2.5 mg (Novartis Pharma K.K.)

[Adverse reactions (clinically significant adverse reactions)]

Cardiac failure, angina pectoris: Cardiac failure or angina pectoris may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing treatment, should be taken.

Hepatic function disorder, jaundice: Hepatic function disorder with significant elevations of AST (GOT) and/or ALT (GPT) levels, or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Toxic epidermal necrosis (TEN), erythema multiforme: Toxic epidermal necrosis (TEN) or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing treatment, should be taken.

7 <Antivirals>

Ribavirin (Tablets)

[Brand Name] Copegus Tablets 200 mg (Chugai Pharmaceutical Co., Ltd.)

[Important Precautions]

Depressive symptoms or suicide attempt may occur. Also, manic state or aggressive behaviour may occur and the patient may exhibit harmful behaviour to others. The patient's mental state should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability are observed, whether to continue therapy or not should be carefully discussed and appropriate measures such as discontinuing treatment should be considered. Patients who have shown such symptoms were recommended to be followed up after completion of the treatment.

Patients and their families should be well informed and understand that depressive symptoms or suicide attempt may occur and other psychoneurotic symptoms including manic state, aggressive behaviour, insomnia, anxiety, irritation, excitement, aggression, and irritability may also occur. They should be instructed to consult a doctor immediately if such symptoms are observed.

[Adverse reactions (clinically significant adverse reactions)]	**<Administration of this drug in combination with peginterferon alpha-2a (genetical recombination)>** **Depression, suicidal ideation, suicide attempt, manic state, aggressive behaviour:** Patients should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability occur, appropriate measures, such as discontinuing treatment, should be taken.

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8 **<Antivirals>**

Ribavirin (Capsules)

[Brand Name]	Rebetol Capsules 200 mg (Schering-Plough K.K.)
[Important Precautions]	Depressive symptoms or suicide attempt may occur. Also, manic state or aggressive behaviour may occur and the patient may exhibit harmful behaviour to others. The patient's mental state should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability are observed, whether to continue therapy or not should be carefully discussed and appropriate measures such as discontinuing treatment should be considered. Patients who have shown such symptoms were recommended to be followed up after completion of the treatment. Patients and their families should be well informed and understand that depressive symptoms or suicide attempt may occur and other psychoneurotic symptoms including manic state, aggressive behaviour, insomnia, anxiety, irritation, excitement, aggression, and irritability may also occur. They should be instructed to consult a doctor immediately if such symptoms are observed.
[Adverse reactions (clinically significant adverse reactions)]	**<Administration of this drug in combination with interferon alpha-2b (genetical recombination) or with peginterferon alpha-2b (genetical recombination) >** **Depressive symptoms, suicide attempt, manic state, aggressive behaviour:** Patients should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability occur, appropriate measures, such as discontinuing treatment, should be taken. **<Administration of this drug in combination with interferon beta>** **Serious depressed state, suicide attempt, manic state, aggressive behaviour:** Patients should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability occur, appropriate measures, such as discontinuing treatment, should be taken.

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9 **<Vaccines>**

Freeze-dried BCG Vaccine

[Brand Name]	Freeze-dried BCG Vaccine (for transdermal vaccination, for one person) (Japan BCG Laboratory)
[Contraindication to this vaccine]	The vaccine is contraindicated in patients with a known history of anaphylaxis due to any of the ingredients of the vaccine.
[Adverse reactions (clinically significant adverse reactions)]	**Anaphylactic shock, anaphylactoid symptoms:** Anaphylactic shock or anaphylactoid symptoms may occur. Patients should be carefully monitored after vaccination, and appropriate measures should be taken if any abnormalities are observed.

<Biological preparations - Miscellaneous>

10 Interferon Alfa (BALL-1)
Interferon Alfa (NAMALWA)
Interferon Alfa-2b (Genetical recombination)
Interferon Alfacon-1 (Genetical recombination)
Interferon Beta (Not for administration in combination with ribavirin)
Interferon Beta-1a (Genetical recombination)
Interferon Beta-1b (Genetical recombination)
Peginterferon Alpha-2a (Genetical recombination)
Peginterferon Alpha-2b (Genetical recombination)

[Brand Name]

OIF 2,500,000 IU for Injection, 5,000,000 IU for Injection, and 10,000,000 IU for Injection (Otsuka Pharmaceutical Co., Ltd.)
Sumiferon 300, 600, Sumiferon DS300, DS600 (Dainippon Sumitomo Pharma Co., Ltd.)
Intron A Sterile Powder for Injection 300, 600, and 1,000 (Schering-Plough K.K.)
Advaferon Subcutaneous Injection 900, 1200, and 1800 (Astellas Pharma Inc.)
IFNβ MOCHIDA 1,000,000 units for Injection, 3,000,000 units for Injection, and 6,000,000 units for Injection. (Mochida Pharmaceutical Co., Ltd.)
AVONEX IM Injection Syringe 30 μg (Biogen Idec Japan Ltd.)
BETAFERON SC Injection, BETAFERON SC Injection 960 (Bayer Yakuhin Ltd.)
PEGASYS SC Injection 90 μg, and 180 μg (Chugai Pharmaceutical Co., Ltd.)
PegIntron Sterile Powder for SC Injection 50 μg/0.5 mL, 100 μg/0.5 mL, and 150 μg/0.5 mL (Schering-Plough K.K.)

[Important Precautions]

Depressive symptoms or suicide attempt may occur. Also, manic state or aggressive behaviour may occur and the patient may exhibit harmful behaviour to others. The patient's mental state should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability are observed, whether to continue therapy or not should be carefully discussed and appropriate measures such as discontinuing treatment should be considered. Patients who have shown such symptoms were recommended to be followed up after completion of the treatment.
Patients and their families should be well informed and understand that depressive symptoms or suicide attempt may occur and other psychoneurotic symptoms including manic state, aggressive behaviour, insomnia, anxiety, irritation, excitement, aggression, and irritability may also occur. They should be instructed to consult a doctor immediately if such symptoms are observed.

[Adverse Reactions (clinically significant adverse reactions)]

Depressive symptoms, suicide attempt, manic state, aggressive behaviour: Patients should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability occur, appropriate measures, such as discontinuing treatment, should be taken.

<Biological preparations - Miscellaneous>

11 Interferon Beta (For administration in combination with ribavirin)

[Brand Name]

FERON for Injection 1,000,000 units, 3,000,000 units, and 6,000,000 units (Toray Industries Inc.)

[Important Precautions]

Depressive symptoms or suicide attempt may occur. Also, manic state or aggressive behaviour may occur and the patient may exhibit harmful behaviour to others. The patient's mental state should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability are observed, whether to continue therapy or not should be carefully discussed and appropriate measures such as discontinuing treatment should be considered. Patients who have shown such symptoms were recommended to be followed up after completion of the treatment.
Patients and their families should be well informed and understand that depressive symptoms or suicide attempt may occur and other psychoneurotic symptoms including manic state, aggressive behaviour, insomnia, anxiety, irritation, excitement, aggression, and irritability may also occur. They should be instructed to consult a doctor

	immediately if such symptoms are observed.
[Adverse Reactions (clinically significant adverse reactions)]	**<Monotherapy of this product>** **Serious depressed state, suicide attempt, manic state, aggressive behaviour:** Patients should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability occur, appropriate measures, such as discontinuing treatment, should be taken. **<Administration of this drug in combination with ribavirin>** **Serious depressed state, suicide attempt, manic state, aggressive behaviour:** Patients should be carefully monitored, and if symptoms such as insomnia, anxiety, irritation, excitement, aggression, or irritability occur, appropriate measures, such as discontinuing treatment, should be taken.

12 **<Biological preparations - Miscellaneous>**

Interferon Gamma-1a (Genetical recombination)
Interferon Gamma-n1

[Brand Name]	Imunomax-γ for Injection 50, 100, and 300 (Shionogi & Co., Ltd.) OGAMMA 100 (Otsuka Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Serious depressed state:** Serious depressed state may occur. The patient's mental state should be carefully monitored, and if symptoms such as insomnia, anxiety, or irritation are observed, whether to continue the therapy or not should be carefully discussed and appropriate measures such as discontinuing treatment should be considered. Patients and their families should be well informed and understand that these psychoneurotic symptoms may occur and they should be instructed to consult a doctor immediately if insomnia, anxiety or other symptoms are observed. Suicide attempt, manic state, and aggressive behaviour have been reported with similar drugs (interferon alpha and interferon beta preparations).

4

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 collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of February 1, 2010)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Tebipenem Pivoxil ORAPENEM FINE GRANULES 10% FOR PEDIATRIC	Meiji Seika Kaisha, LTD.	August 26, 2009
Dutasteride Avolve Capsules 0.5 mg	GlaxoSmithKline K.K.	September 4, 2009
Mirtazapine REFLEX TABLETS 15 mg	Meiji Seika Kaisha, LTD.	September 7, 2009
Mirtazapine REMERON Tablets 15 mg	Schering-Plough K.K.	September 7, 2009
Mometasone Furoate Asmanex Twisthaler 100 μg 60 doses	Schering-Plough K.K.	September 14, 2009
Aliskiren Fumarate Rasilez Tablets 150 mg	Novartis Pharma K.K.	October 1, 2009
Bimatoprost LUMIGAN OPHTHALMIC SOLUTION 0.03%	Senju Pharmaceutical Co., Ltd.	October 5, 2009
Paroxetine Hydrochloride Hydrate PAXIL Tablets 10 mg, 20 mg[*1]	GlaxoSmithKline K.K.	October 16, 2009
Interferon Beta FERON Injections 1×10^6 IU, 3×10^6 IU, 6×10^6 IU[*2]	Toray Industries, Inc.	October 16, 2009
Ribavirin REBETOL Capsules 200 mg[*3]	Schering-Plough K.K.	October 16, 2009
Voglibose BASEN Tablets 0.2, BASEN OD Tablets 0.2[*4]	Takeda Pharmaceutical Company Limited	October 19, 2009
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL, 400 mg/16 mL Intravenous Infusion[*5]	Chugai Pharmaceutical Co., Ltd.	November 6, 2009
Amlodipine Besilate/ Atorvastatin Calcium Hydrate Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban	Pfizer Japan Inc.	December 2, 2009

Aprepitant EMEND Capsules 80 mg, 125 mg, EMEND Capsule Set	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate GLACTIV Tablets 25 mg, 50 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate JANUVIA Tablets 25mg, 50 mg, 100 mg	Banyu Pharmaceutical Co., Ltd.	December 11, 2009
Tadalafil Adcirca Tablets 20 mg	Eli Lilly Japan K.K.	December 11, 2009
Dexamethasone Cipecilate Erizas Capsule for Nasal Spray 400 μg	Nippon Shinyaku Co., Ltd.	December 11, 2009
Mesalazine ASACOL Tablets 400 mg	Zeria Pharmaceutical Co., Ltd.	December 16, 2009
Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cells) Cervarix	GlaxoSmithKline K.K.	December 22, 2009
Vancomycin Hydrochloride Vancomycin Ophthalmic Ointment 1%	Toa Pharmaceutical Co., Ltd.	December 28, 2009
Nitric Oxide INOflo for Inhalation 800ppm	Air Water Inc.	January 1, 2010
Tosufloxacin Tosilate Hydrate OZEX fine granules 15% for pediatric	Toyama Chemical Co., Ltd.	January 12, 2010
Budesonide / Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses	AstraZeneca K.K.	January 13, 2010
Adalimumab (Genetical Recombination) HUMIRA SC Injection 40 mg Syringe 0.8 mL*6	Abbott Japan Co., Ltd.	January 20, 2010
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion 100*7	Mitsubishi Tanabe Pharma Corp.	January 20, 2010
Nonacog Alfa (Genetical Recombination) BeneFIX Intravenous 500, 1000, 2000	Wyeth K.K.	January 20, 2010
Fentanyl Durotep MT Patch 2.1 mg, 4.2 mg, 8.4 mg, 12.6 mg, 16.8 mg*8	Janssen Pharmaceutical K.K.	January 20, 2010
Pramipexole Hydrochloride Hydrate BI•Sifrol Tablets 0.125 mg, 0.5 mg*9	Nippon Boehringer Ingelheim Co., Ltd.	January 20, 2010
Miriplatin Hydrate MIRIPLA for Intra-arterial Injection 70 mg	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Meropenem Hydrate Meropen Vial for IV Drip Infusion 0.25 g, 0.5g, Meropen Kit for Intravenous Drip Infusion 0.5 g*10	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Peramivir Hydrate RAPIACTA Vial for IV Drip Infusion 150 mg, RAPIACTA Bag for IV Drip Infusion 300 mg	Shionogi & Co., Ltd.	January 27, 2010

*1: An additional indication for "treatment of patients with social anxiety disorder"

*2: An additional indication for "improvement of viremia associated with chronic hepatitis C in combination therapy with ribavirin in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy"

*3: An additional indication for "improvement of viremia associated with chronic hepatitis C in combination therapy with interferon beta in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy"

*4: An additional indication for "inhibition of the development of type II diabetes mellitus in patients with abnormal glucose tolerance (only when diet and exercise therapies failed to improve the condition)"

*5: An additional indication for “treatment of patients with advanced or recurrent, inoperable non-squamous non-small cell lung cancer except for squamous cell carcinoma”
*6: An additional indication for “treatment of patients with psoriasis vulgaris or psoriasis arthropathica, which is not adequately responsive to conventional therapies”
*7: An additional indication for “treatment of patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis, which is not adequately responsive to conventional therapies”
*8: An additional indication for “analgesia of moderate to severe chronic pain cannot be managed by treatments with non-opioid analgesics and weak opioid analgesics (only in patients who switch from an opioid analgesic.)”
*9: An additional indication for “treatment of patients with moderate to severe idiopathic restless leg syndrome”
*10: An additional indication for “treatment of patients with febrile neutropenia”