

Pharmaceuticals and Medical Devices Safety Information

No. 259 July 2009

Table of Contents

1. Important Safety Information	3
1 Monobasic Sodium Phosphate Monohydrate and Anhydrous Dibasic Sodium Phosphate.....	3
2. Revision of PRECAUTIONS (No. 207) Blonanserin (and 4 others)	9
3. List of products subject to Early Post-marketing Phase Vigilance	11
Reference 1. About Oseltamivir Phosphate (Tamiflu) < The brief summary of the review results of the investigation by the Subcommittee on Drug Safety (held on June 16, 2009)>.....	14

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

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

Translated by
Pharmaceuticals and Medical Devices Agency



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

*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. 259 July 2009

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	Monobasic Sodium Phosphate Monohydrate and Anhydrous Dibasic Sodium Phosphate	<i>P</i> <i>C</i>	Presents contents of revisions and a summary of cases 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 May 29, 2009.	3
2	Blonanserin (and 4 others)		Revision of PRECAUTIONS (No. 207)	9
3	Products subject to Early Post-marketing Phase Vigilance		Lists products subject to Early Post-marketing Phase Vigilance as of July 1, 2009.	11

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.

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 May 29, 2009.

1 Monobasic Sodium Phosphate Monohydrate and Anhydrous Dibasic Sodium Phosphate

Brand Name (name of company)	Visiclear tablets (ZERIA Pharmaceutical Co., Ltd.)
Therapeutic Category	Non-main therapeutic purpose agents – Miscellaneous
Indications	Elimination of intestinal contents as pretreatment prior to colonoscopy

«PRECAUTIONS (underlined parts are additions) »

[Warning]

WARNING

Acute renal failure or acute phosphate nephropathy (nephrocalcinosis) may occur as serious adverse events associated with this drug. Such events often result in persistent renal impairment, which may require dialysis for a prolonged period. Therefore, before administration, patients should be carefully interviewed about medical history, and monitored. Additionally, this drug should be administered carefully to the following high risk patients:

- Elderly patients
- Patients with decreased circulating blood volume, renal disease, or active colitis
- Patients being treated with drugs (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, NSAIDs, etc.) that influence renal blood flow or renal function

Severe arrhythmia or convulsions may occur as adverse events associated with administration of this drug. Before administration, sufficient steps should be taken to confirm that (See sections “Contraindications,” “Careful Administration” and “Important Precautions”):

- There have been no findings that suggest that the patient may have cardiovascular disease, renal disease or an electrolyte abnormality (dehydration, secondary electrolyte abnormality associated with diuretic use, etc.)
- The patient is not taking any medicine that may influence their electrolyte concentrations
- The patient is not taking any medicine that may cause prolongation of the QT interval
- The patient has normal serum electrolyte concentrations

[Contraindications]

Patients with disease complications associated with ascites (excessive Sodium phosphate absorption may occur.)
Patients with gastrointestinal obstruction or with suspected gastrointestinal obstruction (Intestinal perforation may occur. Further, excessive sodium phosphate absorption may occur.)
Patients with serious renal impairment or acute phosphate nephropathy (Renal impairment or acute phosphate nephropathy may be exacerbated..)

[Careful Administration]

Patients with renal impairment (the rate of elimination of phosphoric acid or sodium may be slowed, and occur adverse reactions.)
Elderly patients (See “Use in the Elderly” section)

[Important Precautions]

Attention should be paid to drinking of water.

• Drinking of water during administration

Excessive volume of water intake than that indicated for this drug may cause hyponatraemia, resulting in potential hyponatraemia-related convulsions or loss of consciousness.

Further, insufficient water intake may, as with other effective cathartics, cause decreased circulating blood volume due to excessive fluid loss.

Insufficient water intake, vomiting, or use of diuretics may exacerbate dehydration.

• Drinking of water from a day before colonoscopy to just before administration of the drug, and following administration:

Pretreatment for colonoscopy may cause dehydration. Patients should drink an appropriate volume of water from the day before colonoscopy until administration of the drug, and also following administration.

Acute renal failure, acute phosphate nephropathy

Serious acute renal failure and acute phosphate nephropathy (nephrocalcinosis) have been reported in patients treated with this drug.

Patients should be instructed to consult a doctor immediately if any findings (edema, decreased fluid output, persistent general malaise, etc.) that suggest reduced renal function develop following colonoscopy.

[Adverse reactions (clinically significant adverse reactions)]

Acute renal failure, acute phosphate nephropathy: Serious adverse events may occur when using this drug, such as acute renal failure or acute phosphate nephropathy (nephrocalcinosis). Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

[Use in the Elderly]

Since elderly individuals generally have deteriorated physiological function, this drug should be administered with care and with adequate monitoring. A clinical trial showed that the incidence of “abnormal electrocardiograms and cardiac disorders” is higher in the elderly compared with the non-elderly [21.1% (15/71) vs 11.2% (53/474)]. In particular, since sodium phosphate is mostly excreted via the kidneys, patients with decreased renal function treated with this drug are more likely to experience adverse reactions. As elderly patients often have impaired renal function, and are likely to have electrolyte abnormalities, it is advisable to examine renal function and serum electrolytes prior to administration of this drug to them. If abnormalities such as dizziness, light-headedness and decreased blood pressure are observed, administration should be discontinued and appropriate measures should be taken. Since elderly individuals may experience rare but serious renal conditions, such as acute renal failure, they should be carefully monitored and if any abnormalities are observed, appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 2 years (June 2007 to April 14, 2009) (events for which a causality to the drug could not be denied):

- Serious renal impairment including acute renal failure: 13 cases (no fatal cases)
- The number of patients treated with this drug for a year estimated by MAH (Marketing Authorization Holder): approximately 54,000 (April 2008 to March 2009)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Pretreatment for colonoscopy (Crohn's disease, osteoporosis, chronic gastritis, reflux esophagitis, adhesive ileus, allergic rhinitis)	50 tablets 1 day	<p>Acute tubular necrosis</p> <p>Medical history: appendicitis, colitis, asthma, Crohn's disease, Sweet's syndrome, ileus</p> <p>4 days before administration: The patient was admitted to a hospital for gastrointestinal and systemic examinations for Crohn's disease. Blood test revealed no abnormalities.</p> <p>1 day before administration: The patient took 5 mg of sodium picosulfate hydrate as a pretreatment for colonoscopy.</p> <p>Day of administration: Administration of this drug was initiated as a pretreatment for colonoscopy.</p> <p>2 hours and 30 minutes after administration: Administration was completed.</p> <p>4 hours after administration: Colonoscopy was started. No active lesions of Crohn's disease were identified. No extra intestinal complications of the skin, joints, or eyes were noted. A feeling of discomfort, chills, and cyanosis developed in the evening. These symptoms improved after rest but general malaise persisted.</p> <p>3 days after administration: The feeling of discomfort, chills, cyanosis and general malaise remitted, although pyrexia (38.2°C) developed and blood tests showed increases in WBC (9270/mm³), CRP (0.61 mg/dL), creatinine (2.87 mg/dL) and BUN (45 mg/dL). Administration of a common cold drug and 300 mg of cefcapene pivoxil hydrochloride hydrate for cold-like symptoms, and 60 mg of loxoprofen sodium hydrate for pyrexia was initiated.</p> <p>4 days after administration: Levels of β_2-MG and urine NAG in the patient's urine increased to 1060 μg/L and 15.2 U/L, respectively, suggesting acute renal failure due to drug-induced tubular necrosis.</p> <p>6 days after administration: The patient was referred to the nephrology and rheumatism department and diagnosed with acute renal failure due to drug-induced renal tubular necrosis. The common cold drugs, cefcapene pivoxil hydrochloride hydrate, and loxoprofen sodium hydrate were discontinued and oral administration of 20 mg of prednisolone was initiated.</p> <p>14 days after administration: Symptoms were confirmed to be improving, and the prednisolone dose was reduced to 10 mg.</p> <p>15 days after administration: The patient was discharged from the hospital with an appointment for a follow-up visit after 4 weeks.</p> <p>41 days after administration: Blood test and DLST were performed. The results were negative. As the symptoms were considered to be further improving, the prednisolone dose was reduced to 7.5 mg.</p> <p>69 days after administration: BUN 25 mg/dL, creatinine 1.12 mg/dL. The prednisolone dose</p>

				<p>was reduced to 5 mg.</p> <p>97 days after administration: BUN 32 mg/dL, creatinine 1.11 mg/dL. The prednisolone dose was reduced to 4 mg.</p> <p>125 days after administration: BUN 23 mg/dL, creatinine 1.18 mg/dL. Prednisolone was discontinued.</p> <p>181 days after administration: No specific treatment, BUN 24 mg/dL, creatinine 1.14 mg/dL. As the clinical progression following the discontinuation of prednisolone was doing well, the patient was considered to have recovered.</p>
--	--	--	--	--

Clinical Laboratory Values

	4 days before administration	3 days after administration	4 days after administration	6 days after administration	10 days after administration	13 days after administration	41 days after administration	69 days after administration	97 days after administration	125 days after administration	181 days after administration
RBC ($\times 10^4/\text{mm}^3$)	488	485	—	488	507	487	455	434	425	428	440
Hemoglobin (g/dL)	13.4	13.2	—	13.1	14.1	13.5	12.4	11.8	12.0	12.0	12.1
Hematocrit (%)	42.4	41.3	—	41.3	42.8	41.0	38.7	37.2	37.4	37.9	39.2
WBC ($/\text{mm}^3$)	6450	9270	—	10220	10220	7930	7960	6670	7910	6200	6460
PLT ($\times 10^4/\text{mm}^3$)	31.4	31.7	—	35.2	41.9	—	—	—	—	—	—
UA (mg/dL)	5.5	8.7	—	7.7	5.9	6.5	6.4	6.8	6.2	6.2	6.2
BUN (mg/dL)	16	45	—	39	36	31	30	25	32	23	24
Creatinine (mg/dL)	0.73	2.87	—	2.54	1.85	1.49	1.25	1.12	1.11	1.18	1.14
Urine protein	(±)	(±)	(+)	(±)	(±)	(-)	(+)	(-)	(±)	(-)	(-)
Urine sugar	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Urine urobilinogen	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Urine β_2 -MG ($\mu\text{g/L}$)	—	—	1060	—	862	812	4400	516	68	308	240
Urine NAG (U/L)	—	—	15.2	—	—	—	—	—	—	—	—
Na (mEq/L)	141	140	—	139	142	140	139	140	140	140	143
K (mEq/L)	3.5	3.4	—	3.6	3.9	3.9	4.0	3.7	3.9	4.3	4.5
Cl (mEq/L)	106	106	—	106	109	108	106	109	104	105	106
P (mg/dL)	4.1	4.0	—	2.8	3.4	3.0	3.8	3.6	4.0	4.6	4.2
Ca (mg/dL)	9.2	8.8	—	8.9	8.7	8.2	8.9	8.5	9.0	9.4	9.2
CRP (mg/dL)	0.04	0.61	—	3.18	0.30	0.08	0.03	0.04	0.05	0.03	0.04
Body temperature ($^{\circ}\text{C}$)	37.0	38.2	38.2	37.2	36.8	36.8	—	—	—	—	—

RBC: Red Blood Cell

WBC: White Blood Cell

PLT: Platelet

UA: Uric Acid

BUN: Blood Urea Nitrogen

CRP: C-Reactive Protein

Concomitant medications: colchicine, salazosulfapyridine, cyclosporine, ranitidine hydrochloride, irsogladine maleate, dai-kenchu-to (da jian zhong tang) [Kampo Medicine], antibiotics-resistant lactic acid bacteria, alendronate sodium hydrate, fexofenadine hydrochloride, dimethicone, sodium picosulfate hydrate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 80s	Pretreatment for colonoscopy (colon diverticulum, hypertension, gastric ulcer)	50 tablets 1 day	<p>Acute renal failure</p> <p>Medical history: acute hepatitis, cataract, colon diverticulum, hypertension, gastric ulcer</p> <p>Approx. 6 years before administration: Treatment for gastric ulcers and hypertension with cimetidine and amlodipine besylate was initiated.</p> <p>Before administration: Colonoscopy was scheduled to follow up colonic polyps. No abnormalities were found before administration. Body weight 68.1 kg.</p> <p>Day of administration: Administration of the drug was initiated as a pretreatment for colonoscopy.</p> <p>5 hours after administration: Colonoscopy was performed. The frequency and volume of defecation decreased from the day following colonoscopy.</p> <p>5 days after administration: The patient noticed edema of the face and lower legs.</p> <p>9 days after administration: The patient visited the hospital with complaining mainly of edema. Examination revealed an elevated creatinine of 6.3 mg/dL. No urinary sediment abnormalities were found. Body weight was found to have increased to 73 kg. On the same day, the patient was admitted to the nephrology department. Abdominal echo showed a slight enlargement of both kidneys and 5-mm calcification (or perhaps calculi) at two sites in the left kidney. The patient was diagnosed with acute renal failure. On admission, the patient's condition was complicated with anasarca and metabolic acidosis. Oral administration of 3g of sodium bicarbonate (for 6 days) was initiated to treat the metabolic acidosis. The antihypertensive treatment was switched from amlodipine besylate tablets to OD tablets of the same drug.</p> <p>10 days after administration: Administration of 40 mg of furosemide was initiated as a diuretic to treat anasarca.</p> <p>11 days after administration: Polyuria occurred and furosemide was discontinued.</p> <p>13 days after administration: The patient's body weight returned to 68 kg, and 500 mL of "replacement fluid" was infused.</p> <p>14 days after administration: 1000 mL of replacement fluid was infused. Sodium bicarbonate was discontinued.</p> <p>15 days after administration: 1000 mL of replacement fluid was infused to replace lost fluid. No fluid replacement or other treatment was carried out afterward.</p> <p>22 days after administration: Blood tests showed a creatinine level of 2.6 mg/dL.</p> <p>23 days after administration: Creatinine values improved and the patient was discharged from the hospital. Following this, he was then followed up as an outpatient.</p> <p>91 days after administration: Blood tests showed creatinine level of 2.5 mg/dL.</p>

Clinical Laboratory Values

	762 days before administration	9 days after administration	11 days after administration	13 days after administration	15 days after administration	19 days after administration	22 days after administration	28 days after administration	56 days after administration	91 days after administration
BUN (mg/dL)	17	66	69	72	60	50	44	43	40	38
Creatinine (mg/dL)	0.7	6.3	6.2	5.2	3.9	3.0	2.6	2.3	2.2	2.5
UA (mg/dL)	7.6	9.0	9.5	10.2	9.2	9.1	9.0	9.5	9.4	10.0
Na (mEq/L)	143	140	138	138	135	130	130	137	139	142
K (mEq/L)	4.4	4.0	4.1	4.1	4.0	3.8	4.1	4.7	4.3	4.1
Cl (mEq/L)	107	109	103	100	97	93	93	101	104	105
Ca (mg/dL)	—	9.0	9.5	9.7	9.6	9.6	9.6	10.1	9.5	9.7
P (mg/dL)	—	6.2	5.9	5.3	4.6	3.8	4.0	3.9	3.7	3.2
Mg (mg/dL)	—	—	2.1	2.1	1.9	—	—	—	—	—
Urine β_2 -MG (μ g/L)	—	4343.9	—	—	2283.6	—	123.5	1024.5	2870.2	4914.6
Urine β_2 -MG/Cre (mg/g•CR)	—	12.9	—	—	5.0	—	0.4	3.8	10.0	28.7
Urine NAG (U/L)	—	5.5	—	—	6.6	—	4.4	3.1	3.2	3.2
Urine NAG/Cre (U/g•CR)	—	16.1	—	—	14.6	—	14.3	11.4	11.1	18.7
Ccr (mL/min)	—	—	12	—	—	—	—	—	—	—
Urine output (mL/day)	—	—	1900	2500	3500	2600	3600	—	—	—

BUN: Blood Urea Nitrogen

UA: Uric Acid

Ccr: Creatinine Clearance

Concomitant medications: cimetidine, amlodipine besylate

Revision of PRECAUTIONS

(No. 207)

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 May 29, 2009 (excluding those presented in “1. Important Safety Information” of this Bulletin).

1 <Psychotropics> Blonanserin

[Brand Name]	LONASEN Powder 2%, LONASEN Tablets 2 mg and 4 mg (Dainippon Sumitomo Pharma Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	<u>Agranulocytosis, platelets decreased</u> : Agranulocytosis or platelets decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration of the drug should be taken.

2 < Miscellaneous metabolism agents > Etanercept (genetical recombination)

[Brand Name]	ENBREL 25 mg for S.C. Injection, ENBREL 25 mg Syringe 0.5 mL for S.C. Injection (Wyeth K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	<u>Heart failure</u> : Heart failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration of the drug should be taken.

3 <Antineoplastics-Antibiotics> Amrubicin Hydrochloride

[Brand Name]	Calsed for injection 20 mg and 50 mg (Dainippon Sumitomo Pharma Co., Ltd.)
---------------------	--

[Warning]

WARNING

Patients or their family members should be fully advised of the benefit and harm of this drug, and informed consent should be obtained from them before starting treatment. As cases of interstitial pneumonia leading to death have been reported in patients treated with this drug, if any abnormalities are observed, the administration should be discontinued and appropriate measures should be taken.

There have been fatal cases reported associated with serious infectious disease (sepsis, pneumonia, etc.) resulting from serious myelosuppression, in which causality to the drug could not be denied. Patients should be carefully monitored, with particular attention paid to any signs of infection, and if any abnormality are observed, administration should be discontinued and appropriate measures should be taken.

This drug should only be administered to patients who are considered to be suitable for it, at a medical institution capable of appropriately handling emergencies, and under the supervision of a physician with substantial experience in chemotherapy.

[Careful Administration]

Patients with interstitial pneumonia or pulmonary fibrosis

[Important Precautions]	Due attention should be paid to the occurrence or exacerbation of infectious disease or bleeding tendency. <u>Before administration, a chest X-ray should be taken and a CT exam should be carried out, to check for the presence of interstitial pneumonia, etc., and the use of this drug should be a carefully considered decision, taking the results of these tests into account. After administration, patients should be carefully monitored for clinical symptoms (respiratory status, coughs, pyrexia, etc.) and chest X-ray tests should be periodically performed to check for the development of interstitial pneumonia.</u>
[Use in the Elderly]	Since the major elimination routes for this drug in animals are biliary excretion and metabolism, and as the rate of its urinary excretion in humans is also low, the liver appears to be a major contributor to the elimination of the drug. In elderly individuals, who often have deteriorated physiological function, the rate of drug elimination may be slow, thus causing the drug concentration in blood to remain high. <u>This drug should be administered cautiously with close monitoring of the patient's condition.</u> Particular attention should also be paid to adverse reactions such as myelosuppression, <u>and</u> if any abnormalities are observed, administering the drug with a prolonged infusion intervals, at a reduced dose, or only resuming drug administration after the patient recovers should be considered.

4 < Antineoplastics-Miscellaneous > Erlotinib Hydrochloride

[Brand Name]	Tarceva Tablets 25 mg, 100 mg, and 150 mg (Chugai Pharmaceutical Co., Ltd.)
[Careful Administration]	<u>Patients with gastrointestinal ulceration and intestinal diverticulum or patients with a history of such disease.</u>
[Important Precautions]	Adverse reactions such as interstitial pneumonia, rash, diarrhoea, <u>corneal perforation and corneal ulcer</u> may occur due to the administration of this drug. Patients should be instructed to immediately visit a medical institution if the onset or aggravation of the symptom is suspected.
[Adverse Reactions (clinically Significant adverse reactions)]	<u>Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythema multiforme: Serious Bullous / exfoliative skin disorders such as oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), and erythema multiforme may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing administration of the drug should be taken</u> <u>Gastrointestinal perforation: Gastrointestinal tract perforation may occur. Patients should be encouraged to perform abdominal X-ray or CT examinations for early symptom of gastrointestinal tract perforation such as abdominal pain if any abnormalities are found, appropriate measures such as discontinuing administration of the drug should be taken</u> <u>Corneal perforation, corneal ulcer: Corneal perforation, corneal ulcer may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration of the drug should be taken</u>

5 < Biological preparations-Miscellaneous > Peginterferon Alfa-2a (Genetical recombination)

[Brand Name]	Pegasys s.c. 90µg and 180µg (Chugai Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	Pancytopenia, agranulocytosis, leukopenia (below 2000/µL), thrombocytopenia (below 50000/µL), anaemia: Conditions of the patient should be carefully monitored through periodic blood test, etc. When reducing the dosage or discontinuing administration of this drug, refer to the section "Precautions of Dosage and Administration".

3

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 July 1, 2009)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Thyrotropin Human Alfa (genetical recombination) ----- THYROGEN IM Injection 0.9 mg	Sato Pharmaceutical Co., Ltd.	January 13, 2009
Etravirine ----- INTELENCE Tablets 100 mg	Janssen Pharmaceutical K.K.	January 19, 2009
Salmeterol Xinafoate/Fluticasone Propionate ----- Adoair 100 Diskus * ¹	GlaxoSmithKline K.K.	January 21, 2009
Salmeterol Xinafoate/Fluticasone Propionate ----- Adoair 250 Diskus * ²	GlaxoSmithKline K.K.	January 21, 2009
Ganirelix Acetate ----- Ganirest Subcutaneous 0.25mg Syringe	Schering-Plough K.K.	January 22, 2009
Maraviroc ----- CELSENTRI Tablets 150 mg	Pfizer Japan Inc.	January 22, 2009
Dasatinib Hydrate ----- SPRYCEL Tablets 20 mg and 50 mg	Bristol Myers K.K.	February 2, 2009
Estradiol·Norethisterone Acetate ----- MENOVID COMBIPATCH	ASKA Pharmaceutical Co., Ltd.	February 5, 2009
Thalidomide ----- THALID capsule 100	Fujimoto Pharmaceutical Corporation	February 6, 2009
Nilotinib Hydrochloride Hydrate ----- TASIGNA Capsules 200 mg	Novartis Pharma K.K.	February 16, 2009
Estradiol·Levonorgestrel ----- Wellnara	Bayer Yakuhin, Ltd.	February 17, 2009
Botulinum toxin type A ----- BOTOX Vista Injection 50 Units	GlaxoSmithKline K.K.	February 23, 2009
Enoxaparin Sodium ----- Clexane for Subcutaneous Injection Kit 2000 IU * ³	Sanofi-Aventis K.K.	February 23, 2009
Lanthanum Carbonate Hydrate ----- Fosrenol Chewable Tablets 250mg and 500mg	Bayer Yakuhin, Ltd.	March 11, 2009
Omalizumab (Genetical Recombination) ----- Xolair for s.c. injection	Novartis Pharma K.K.	March 13, 2009

Candesartan Cilexetil / Hydrochlorothiazide ECARD Combination Tablets LD, ECARD Combination Tablets HD	Takeda Pharmaceutical Company Limited	March 13, 2009
Zonisamide TRERIEF Tablets 25mg	Dainippon Sumitomo Pharma Co., Ltd.	March 13, 2009
Valsartan/Hydrochlorothiazide Co-DIO Combination Tablets MD, Co-DIO Combination Tablets EX	Novartis Pharma K.K.	March 13, 2009
Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3mg/0.23mL	Novartis Pharma K.K.	March 13, 2009
Nalfurafine Hydrochloride REMITCH CAPSULES 2.5µg	Toray Industries, Inc.	March 24, 2009
Azithromycin Hydrate ZITHROMAC SR Dry Syrup 2g for Adults	Pfizer Japan Inc.	April 6, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 50 Air 120 puffs	GlaxoSmithKline K.K.	April 6, 2009
Minodronic Acid Hydrate Bonoteo Tablets 1mg	Astellas Pharma Inc.	April 7, 2009
Minodronic Acid Hydrate RECALBON Tablets 1mg	Ono Pharmaceutical Co., Ltd.	April 7, 2009
Cetirizine Hydrochloride Zyrtec Dry Syrup 1.25%, Zyrtec tablets 5mg *1	UCB Japan Co. Ltd	April 22, 2009
Somatropin (genetical recombination) NORDITROPIN S injection 5mg and 10mg, Norditropin Nordiflex injection 5mg, 10mg and 15mg *4	Novo Nordisk Pharma Ltd.	April 22, 2009
Doxorubicin Hydrochloride DOXIL Injection 20mg *5	Janssen Pharmaceutical K.K.	April 22, 2009
Sodium Chloride/Potassium Chloride/Sodium Bicarbonate/Anhydrous Sodium Sulfate Niflec for internal use *6	Ajinomoto Pharma Co., Ltd.	April 22, 2009
Mosapride Citrate Gasmotin Tablets 2.5 mg and 5 mg, Gasmotin Powder *7	Dainippon Sumitomo Pharma Co., Ltd.	April 22, 2009
Sorafenib Tosilate Nexavar Tablets 200mg	Bayer Yakuhin, Ltd.	May 20, 2009
Valganciclovir Hydrochloride VALIXA Tablets 450mg	Mitsubishi Tanabe Pharma Corporation	May 20, 2009
Pemetrexed Sodium Hydrate Alimta Injection 500mg	Eli Lilly Japan K.K.	May 20, 2009
Freeze-dried cell culture derived Japanese encephalitis vaccine Jebik V	The Research Foundation for Microbial diseases of Osaka University	June 2, 2009
Atomoxetine Hydrochloride Strattera capsule 5mg, 10mg, and 25mg	Eli Lilly Japan K.K.	June 19, 2009
Fluticasone Furoate Allermist 27.5µg 56metered Nasal Spray	GlaxoSmithKline K.K.	June 19, 2009
Lapatinib Tosilate Hydrate Tykerb Tablets 250mg	GlaxoSmithKline K.K.	June 19, 2009
Telmisartan, Hydrochlorothiazide Micombi Combination Tablets AP and BP	Nippon Boehringer Ingelheim Co., Ltd.	June 23, 2009

Risperidone ----- RISPERDAL Consta Intramuscular Injection 25mg, 37.5mg, and 50mg	Janssen Pharmaceutical K.K.	June 23, 2009
Insulin Glulisine (Genetical Recombination) ----- APIDRA Inj. Cart, Inj. SoloStar, Inj. 100 units/mL	Sanofi-Aventis K.K	June 24, 2009

*1: An additional administration for “pediatrics”

*2: An additional indication for “remission of various symptoms of chronic obstructive pulmonary disease (COPD) (including chronic bronchitis and emphysema) (for patients who require concomitant use of inhaled corticosteroids and long acting inhaled beta-2 stimulant)”

*3: An additional indication for “prophylaxis of venous thromboembolisms in patients undergoing abdominal surgery who are at risk for thromboembolic complications”

*4: An additional indication for “replacement of endogenous growth hormone in adults with growth hormone hyposecretion (restricted to serious cases)”

*5: An additional indication for “treatment of patients with ovarian cancer whose disease has progressed after chemotherapy”

*6: An additional indication for “cleansing of the colon as a preparation prior to radiographic contrast barium enema”

*7: An additional indication for “adjunction with colonic cleansing agent for a preparation prior to radiographic contrast barium enema”

*8: An additional indication for “treatment of patients with unresectable hepatocellular carcinoma”

*9: An additional indication for “treatment of patients with cytomegalovirus infections associated with Acquired immunodeficiency syndrome, organ transplants (including haemopoietic stem cell transplants), or Malignant tumour”

*10: An additional indication for “treatment of patients with unresectable non-small cell lung cancer recurrent and advanced”

Reference 1. Information on oseltamivir phosphate (Tamiflu)

**<The brief summary of the results of the review
by the Subcommittee on Drug Safety (held on June 16, 2009)>**

The brief summary of the results of review on “oseltamivir phosphate (Tamiflu)” in the Subcommittee on Drug Safety Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council (held on June 16, 2009) is presented. Please refer to the “full text” of the results of the review and reference materials from the Subcommittee on Drug Safety available on the MHLW website (<http://www.mhlw.go.jp/>) in Japanese, as well.

Oseltamivir Phosphate (Tamiflu)

The subcommittee held meetings on April 4, June 16, November 11 and December 25, 2007 to discuss the relationship between the administration of oseltamivir phosphate (Tamiflu) and abnormal behavior and sudden death.

A hearing was conducted on June 16, 2007 to obtain statements of opinion from organizations collecting information on the safety of Tamiflu. In addition, investigations have been continuing on the reports on the status of reviews provided by the Oseltamivir Phosphate Non-clinical Working Group (Non-clinical WG) and Oseltamivir Phosphate Clinical Working Group (Clinical WG) on June 16, November 11 and December 25, 2007^(Note 1).

(Note 1) Refer to the Appendix “reference material” for the progress on the safety measures for Tamiflu.

Today, this subcommittee conducted an investigation of the review results reported by the Non-clinical WG and Clinical WG, as shown in Appendix 1 and 2, respectively. The results of the review by this subcommittee regarding the relationship between Tamiflu intake and abnormal behavior or sudden death are as follows.

<Editing note: The underlined materials are available at:

<http://www.mhlw.go.jp/shingi/2009/06/dl/s0616-5a.pdf> (Appendix “reference material”)

<http://www.mhlw.go.jp/shingi/2009/06/dl/s0616-5b.pdf> (Appendix 1)

<http://www.mhlw.go.jp/shingi/2009/06/dl/s0616-5c.pdf> (Appendix 2).>

- Today, this subcommittee received reports on results of non-clinical trials (animal experiments, etc.), clinical trials and epidemiological studies from the Non-clinical WG and Clinical WG.
- Regarding the possibility of Tamiflu increasing the risk of abnormal behavior associated with influenza, epidemiological studies by Hirota’s group showed that, no statistically significant difference was observed between Tamiflu-treated and untreated patients, when the target population was limited to teenage patients who exhibited serious abnormal behavior (abnormal behavior that may lead to an accident, etc.). However, experts in epidemiology and statistics respectively had different views on the validity of the statistical method used in this analysis. Given various limitations of the studies with regard to data collection and analysis, it was considered difficult to draw a concrete conclusion on the causality between Tamiflu and abnormal behavior, based only on the epidemiological analysis of the results of Hirota’s group
- According to analysis of the two epidemiological studies (carried out by Okabe’s group and Hirota’s group) it is further clarified that abnormal behavior may develop with the infection of influenza itself, regardless of Tamiflu administration.
The above findings, as well as the fact that there have been serious events including deaths due to falling over/falling off from a high place that were reported as adverse reactions associated with Tamiflu since implementation of preventative safety measures^(Note 2) in March 2007, indicate that the safety measures have a certain preventive effect. Meanwhile the study results obtained so far provide no substantial evidence to support the necessity of modifying the preventative safety measures for teenage patients. In light of this, the subcommittee has concluded that it is appropriate to continue with the current safety measures.
- Based on the above, the measures being taken for Tamiflu^(Note 2) are still valid at the present

time, and healthcare providers, patients and their families, etc. should be kept alerted. It is also considered appropriate to continue alerting the same groups regarding abnormal behavior, etc. associated with other anti-influenza virus drugs as well.

The current “PRECAUTIONS” doesn’t intend to prevent careful administration of Tamiflu to teenage patients of influenza with higher risk of severity due to complications, medical history, etc. The government should try to explain it in plain language Further, relevant academic societies and expert committees should be encouraged to provide advice from specialist’s point of view, based on risk- benefit considerations, on what situations Tamiflu etc. should be used in measures of H1N1 influenza.

(Note 2) Dear Healthcare Professional Letters dated March 20, 2007:

Abnormal behavior that have resulted in accidents such as falls have been reported in patients aged 10 to 19 years following administration of this drug, although the causal relationship to this drug is unknown. As a general rule, this drug should not be used in these patients for the above reason except that the patient is considered a high-risk patient based on complications and past history, etc.

When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, ①abnormal behavior may occur and ②caregivers should be careful not to let patients who are children/minors alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents. Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

- **The results of non-clinical studies (animal experiments, etc.) and clinical studies (so-called nocturnal ECG studies) did not appear to provide evidence for the causality between the Tamiflu administration and sudden death.**

[Summary of nonclinical studies (animal experiments, etc.)]

The results of the binding assay indicated that the estimated brain concentrations of Tamiflu (Oseltamivir phosphate, OP) and its active metabolite (Oseltamivir carboxylate, OC) following administration at a clinical dose were unlikely to affect CNS receptors and the ion channels, even with transporter defects or metabolic inhibition.

The report on the induction of jumping behavior in mice found that jumping behavior was not directly caused by the drug, the relationship between this phenomenon and the mechanism of action of OP was not clarified, and the given dose was high. Thus it was considered that there was insufficient evidence for determining the relationship with psychological/neurological symptoms and abnormal behavior in humans. Continual attention should be paid to ongoing relevant studies.

The report on decreased body temperature in mice administered intraperitoneally suggested a pharmacological effect on the brain stem etc. related to body temperature, although the relationship with other effects is unknown. Continual attention should be paid to relevant ongoing studies. However, reanalysis of the result of a rabbit Purkinje fiber action potential study did not suggest that oseltamivir had a cardiovascular effect that might lead to sudden death.

[Summary of clinical study (so-called nocturnal ECG study)]

The so-called nocturnal ECG study showed no significant effect of Tamiflu on ECGs.

- **The MHLW etc. should continue to collect information on the causality between the Tamiflu administration and abnormal behavior, etc. and take appropriate measures as necessary.**