Pharmaceuticals and Medical Devices Safety Information

No. 264 December 2009

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

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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

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No. 264 December 2009

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

[Outline of Information]

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

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

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

Safety measures for anaphylaxis and anaphylactoid symptoms associated with injectable antibiotics

1. Introduction

It is well recognized that injectable antibiotics and synthetic antibacterials (to be referred to as "injectable antibiotics" in the following) may cause shock or anaphylactoid symptoms (to be referred to as "anaphylaxis" in the following). Formerly, it was stated in the "Important Precautions" section of the package insert that "it is desirable to conduct a skin test beforehand" as a safety measure to predict the occurrence of anaphylaxis. Accordingly, intracutaneous testing as a type of skin test was performed prior to the use of injectable antibiotics.

However, in September 2004, an expert working group of the Pharmaceutical Affairs and Food Sanitation Council reviewed a proposal by the Japanese Society of Chemotherapy, a request by the Japan Antibiotics Research Association, concerning present descriptions in the package inserts used in Japan and overseas, and the current status of adverse reaction reports of anaphylaxis. In consequence, the working group came to the conclusion that there is little value in conducting intracutaneous testing as it is generally performed, because intracutaneous testing is not capable of fully efficiently predicting anaphylaxis.[1)] and because there are far more patients with false positive skin tests than there are patients with a true allergy and they are missing the opportunity to receive appropriate treatment. The working group also concluded that, as safety measures, it is more important to perform a careful questioning on medical history etc.; to detect anaphylaxis early; and to take immediate measures rather than relying on skin reactions test.

Based on these considerations, the following actions were taken to the marketing authorization holders (MAH) as of September 29, 2004: to delete the recommendation to conduct a skin test in the section of "Important Precautions" of the package insert, and to add precautions that a careful questioning should be performed, that anaphylaxis should be detected early, and that immediate measures should be taken. In addition, the number of incidents of adverse reactions of anaphylaxis was to be surveyed and reported to the Safety Division of the Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare (to be referred to as "Safety Division" in the following) for the first 3 years[2)].

The Pharmaceutical and Medical Devices Agency (to be referred to as "PMDA" in the following) has conducted a survey of the status of reports of adverse reactions of anaphylaxis submitted to the Safety Division by the marketing authorization holders since 2004, when the recommendation to conduct a skin test was withdrawn. PMDA in cooperation with experts has also reviewed the appropriateness of the withdrawal of the recommendation, the necessity for further safety measures against anaphylaxis. The results of the survey and review are presented in the following.

2. Status of adverse reaction reports on anaphylaxis and results of review of the necessity for safety measures

PMDA performed a survey of the adverse reaction reports on anaphylaxis associated with injectable antibiotics, which had been submitted between October 1, 1999 and September 30, 2008, to analyze the change in the incidence of anaphylaxis before and after the withdrawal of the recommendation to conduct a skin test.

In this survey, the period beginning on October 1 and ending on September 30 in the next year was defined as the one-year term of each year, in order to analyze the change in the incidence by year. PMDA

confirmed some parameters such as the number of treated patients in each term, the incidence and the change in the number of adverse reaction reports in this review. The number of treated patients in each term was estimated from the shipment amounts of injectable antibiotics, average duration of treatment, and average daily doses. The incidence was calculated by dividing the number of adverse reaction reports by estimated number of treated patients. However, since the review using the number of patients estimated from shipment amounts has its limitation[3)], these values were used for reference only.

According to the survey regarding the status of adverse reaction reports, it was found that sulbactam sodium/cefoperazone sodium, cefazolin sodium, and cefmetazole sodium had higher number of reports of adverse reactions and the incidence rate during the term after the withdrawal of the recommendation to conduct a skin test than in the year prior to the withdrawal. However, no difference in the status of the reports of adverse reactions before and after the withdrawal was confirmed for all other antibiotics.

As mentioned above, it has a limitation in the consideration that the trend of occurrence of anaphylaxis is estimated by the shipment amounts. Meanwhile, the usage pattern of antibiotics seems to have undergone changes over the entire period of the survey due to shortening of administration periods and other changes over time in accordance with the guidelines of the Japanese Society of Chemotherapy[4-9)]. In particular, the number of patients using antibiotics in recent years after the withdrawal of the recommendation to conduct a skin test is possibly higher than the estimated number of patients used in the present survey. Therefore, although it is difficult to discuss changes in the occurrence of anaphylaxis merely by comparing the incidence rates before and after the withdrawal of the recommendation, PMDA concluded that an obvious increase in the incidence rate of anaphylaxis could not be found after the withdrawal of the recommendation to conduct a skin test.

PMDA surveyed the patient's history of allergy, whether a skin test was conducted, and the results of the skin test in the adverse reaction reports of anaphylaxis associated with injectable antibiotics . Since anaphylaxis occurred in patients with negative skin reactions, the intracutaneous test is not a reliable measure to predict anaphylaxis in such cases. On the other hand, there were reports of adverse reactions of anaphylaxis associated with the intracutaneous test preparation after the recommendation to conduct a skin test had been withdrawn. Further survey of these cases in detail suggested that there were patients who were given the drug without a careful questioning and developed anaphylaxis, or patients who were given the drug before appropriate preparations were ready to detect anaphylaxis early and to take immediate measures, resulting in serious outcomes.

Based on the findings that anaphylaxis was also reported in subjects with a negative skin test and that no obvious increase in the incidence of anaphylaxis was observed after withdrawal of the recommendation to conduct a skin test, PMDA and the Safety Division concluded that it was not necessary to reconsider the decision to withdraw the recommendation for the time being.

The precautions "to perform a careful questioning, to detect anaphylaxis early and to take immediate measures" was described in the package insert at the same time as the withdrawal of the recommendation to conduct a skin test. However, there were reports of anaphylaxis that developed, as a result of inadequate implementation of these measures and reports of measures taken too late against anaphylaxis. In consideration of these events and the fact that anaphylaxis is an adverse reaction which occurs at a constant rate in association with the use of injectable antibiotics, it has been decided that it was necessary to emphasize the precautions "to perform a careful questioning, to detect anaphylaxis early and to take immediate measures" once again. It has been also decided to continue monitoring of reports of adverse reactions associated with sulbactam sodium/cefoperazone sodium, cefazolin sodium, and cefmetazole sodium etc. should be continued hereafter.

3. Safety measures hereafter

When using injectable antibiotics, healthcare providers are requested to perform a careful questioning, to prepare for early detection and treatment of anaphylaxis in accordance with the package insert as well as the "Guideline of Measures for Anaphylaxis Related to Administration of Antibiotics (2004)" established by the Japanese Society of Chemotherapy[10].

Precautions against anaphylaxis recommended in the package insert

Since there is no certain method of predicting the onset of anaphylaxis or anaphylactoid symptoms caused by antibiotics, the following measures should be taken:

- Perform a careful questioning on patient's medical history in advance. In addition, the history of allergy to antibiotics and other medication should be confirmed.
- Emergency measures against anaphylaxis should be prepared prior to administration.
- Patients should be kept rested throughout the period of administration and carefully monitored. In particular, patients should be carefully monitored immediately after the start of administration.

<References>

1) Japanese Journal of Chemotherapy. 2003; 51 (8): 497-506. (in Japanese)
2) Pharmaceuticals and Medical Devices Safety Information No. 206. Division of the Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare http://www.info.pmda.go.jp/iyaku_anzen/file/PMDSI206.pdf
3) GUIDELINE ON RISK MANAGEMENT SYSTEMS FOR MEDICINAL PRODUCTS FOR HUMAN USE. EMEA 2005
4) Japanese Journal of Chemotherapy. 2004; 52 (9): 474-485. (in Japanese)
5) Kyushu Pharmaceutical Society Bulletin. 2006; 60: 35-40 (in Japanese)
6) Antibiotics & Chemotherapy. 2005; 21 (11): 1639-1645 (in Japanese)
7) Journal of Japan Society for Surgical Infection. 2006; 3(3): 267-271 (in Japanese)
8) Journal of Japan Society for Surgical Infection. 2008; 5(2): 133-138 (in Japanese)
9) Acta Urologica Japonica. 2008; 54 (9): 587-591 (in Japanese)
10) Guidelines of Measures for Anaphylaxis Related to Administration of Antibacterials (2004) (in Japanese) http://www.chemotherapy.or.jp/journal/reports/hinai_anaphylaxis_gaiyo.pdf

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 October 27, 2009.

1 Salazosulfapyridine

Brand name (name of company)	Azulfidine EN Tablets 250 mg, 500 mg, Salazopyrin Tablets 500 mg, Salazopyrin Suppositories 500 mg (Pfizer Inc.) Azasurfan Enteric Tablets 500 mg (Choseido Pharmaceutical Co., Ltd.) Safildine-EN Tablets 500 (Shiono Chemical Co., Ltd.) Salazosulfapyridine Tablets 500 mg "Taiyo", Soaresin Tablets 250 mg (Taiyo Pharmaceutical Industry Co., Ltd.) Slama Tablets 500 mg (Nichi-Iko Pharmaceutical Co., Ltd.) Lanofen Tablets 500 mg (Taisho Pharm. Ind. Ltd.)
Therapeutic Category	Sulfonamides
Indications	(Azulfidine EN Tablets 250 mg, 500 mg, Azasurfan Enteric Tablets 500 mg, Safildine-EN Tablets 500, Soaresin Tablets 250 mg) Rheumatoid arthritis (Salazopyrin Tablets 500 mg, Salazosulfapyridine Tablets 500 mg "Taiyo", Slama Tablets 500 mg, Lanofen Tablets 500 mg) Ulcerative colitis, regional enteritis, nonspecific colitis (Salazopyrin Suppositories 500 mg) Ulcerative colitis

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis fulminant, hepatitis, hepatic function disorder, jaundice: Hepatitis, hepatic function disorder, and jaundice with marked elevations of AST (GOT) and ALT (GPT) may occur. It may cause hepatic failure or hepatitis fulminant Patients should be closely monitored through periodic hepatic function tests. If any abnormalities are observed, administration 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 denied) in about the last 3 years (April 1, 2006 to September 10, 2009):

- Hepatitis fulminant, hepatitis, hepatic function disorder, jaundice: 1 case (fatal)

The number of patients treated with Salazosulfapyridine for a year estimated by MAH: approximately 248,000 (March 2008 to February 2009)
Marketed in Japan in: September 1969

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Rheumatoid arthritis (chronic renal failure, hypertension, diabetes mellitus)	1 g for 8 days	**Hepatitis fulminant** 1 day before administration: The patient was admitted for chronic renal failure, hypertension, and diabetes mellitus. Day 1 of administration: Administration of salazosulfapyridine was started for the treatment of rheumatoid arthritis. Day 7 of administration: There were no abnormal findings on blood tests; no hepatic disorder was observed. Day 8 of administration (day of discontinuation): Breathing difficulty occurred suddenly. AST (GOT) and ALT (GPT) levels increased to 358 IU/L and 180 IU/L, respectively. Chest CT scan demonstrated marked ground-glass opacification and predominantly interstitial inflammatory changes. Though the KL-6 and SP-D levels were not much elevated (251 U/mL and 110 ng/mL, respectively), the patient was diagnosed with interstitial pneumonia with an ARDS pattern based on the course of disease and imaging findings. Administration of salazosulfapyridine was discontinued. 1 day after discontinuation: Her respiratory status worsened. The AST (GOT) and ALT (GPT) levels rapidly increased to 10700 IU/L and 3457 IU/L, respectively, and skin eruption occurred. The serum creatinine level increased to 4.42 mg/dL, suggesting decreased renal function. The potassium level was 6.7 mEq/L. Oliguria developed and acidosis progressed. Then, with AST (GOT) 13270 IU/L, ALT (GPT) 3432 IU/L, and potassium 7.0 mEq/L, the patient was transferred to the ICU. Continuous hemodialysis-filtration **(**CHDF**)** and steroid pulse therapy were begun. The patient showed asterixis and a coma scale was considered to be grade II or above. Artificial ventilation then became necessary, so that evaluation of coma scales became impossible. Hepatitis fulminant was diagnosed based on the above findings. 2 days after discontinuation: Her respiratory status worsened and her level of consciousness decreased further. Artificial ventilation was continued. AST (GOT): 15950 IU/L, ALT (GPT): 3698 IU/L, total bilirubin: 1.8 mg/dL. Plasma exchange was started while CHDF was continued. AST (GOT): 31791 IU/L, ALT (GPT) 7237 IU/L. Cardiac arrest then occurred. Cardiac massage was performed and DC (one of the electric shock) was delivered. Plasma exchange was discontinued, while CHDF was continued. The potassium level increased to 8.0 mEq/L showing significant acidosis, which could not be corrected. The patient was switched from CHDF to hem dialysis(HD). Low blood pressure and unstable hemodynamics were observed. The patient had a second cardiac arrest and did not respond to repeated emergency medical cares including cardiac massage. On request by the family members, all measures were discontinued and death was confirmed. Drug lymphocyte stimulation test (DLST): negative

				(salazosulfapyridine)
	Concomitant medications: omeprazol, olmesartan medoxomil, azelnidipine, prednisolone, senna/senna pod, teprenone, sulpiride, etizolam, flunitrazepam, fluvoxamine maleate, loxoprofen sodium hydrate, indometacin suppository, calcitriol			

Clinical Laboratory Values

	1 day before administration	8 days after administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation
RBC ($\times 10^4/mm^3$)	344	429	417	345
WBC ($/mm^3$)	12700	15100	11100	17300
PLT ($\times 10^4/mm^3$)	28.2	14.7	12.7	15.0
Total bilirubin (mg/dL)	0.2	0.1	0.8	1.8
AST (GOT) (IU/L)	13	358	10700	15950
ALT (GPT) (IU/L)	8	180	3457	3698
LDH (IU/L)	161	—	15120	—
γ-GTP (IU/L)	63	31	86	131
Total serum protein (g/dL)	7.5	7.2	6.2	5.8
BUN (mg/dL)	52	39.4	51	42.6
Serum creatinine (mg/dL)	2.01	3.47	4.42	4.16
Prothrombin time (%)	—	—	37.8	21.3
Ammonia (μg/dL)	—	—	—	195

RBC: Red blood cell count
WBC: White blood cell count
PLT: Platelet
AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)
ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)
LDH: Lactate dehydrogenase
γ-GTP: gamma-glutamyl transpeptidase
BUN: Blood urea nitrogen

2 Pethidine hydrochloride, pethidine hydrochloride/levallorphan tartrate

Brand name (name of company)	**Pethidine hydrochloride** Opystan, Opystan Injection 35 mg, 50mg (Mitsubishi Tanabe Pharma Corporation) Pethidine Hydrochloride Injection "Takeda" 35 mg, 50 mg (Takeda Pharmaceutical Co., Ltd.) **Pethidine hydrochloride/levallorphan tartrate** Pethilorfan Injection, Weak Pethilorfan Injection (Takeda Pharmaceutical Co., Ltd.)
Therapeutic Category	Synthetic narcotics
Indications	○Analgesia, sedation, and spasmolysis in severe pain ○Preanesthetic medication ○Anesthesia adjuvant ○Relief of labor pain (Opystan only) ○ Analgesia, sedation, and spasmolysis in severe pain

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

[Adverse Reactions (clinically significant adverse reactions)]

Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored. If decrease in blood pressure, dyspnoea, decreased consciousness etc. 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 September 2, 2009):

- Shock, anaphylactoid symptoms: 3 cases (including 1 fatality)

The number of patients treated with Pethidine hydrochloride, Pethidine hydrochloride/Levallorphan tartrate mixture for a year estimated by MAH: approximately 1,586,000 (October 1, 2008 to September 30, 2009)

Marketed in Japan in:

April 1961: Pethidine hydrochloride

April 1963: Pethidine hydrochloride/levallorphan tartrate

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Colonoscopy (Anaemia)	35 mg for 1 day	**Shock** 7 days before administration Hemoglobin: 10.0 g/dL 5 days before administration Early in the morning, the patient passed a large amount of melaena containing fresh blood and black stools. Due to rapid progression of anaemia (hemoglobin 6.1 g/dL), the patient was referred to our hospital by the hospital where he had been treated. Emergency endoscopy revealed multiple duodenal ulcers, one of which showed an exposed blood vessel with pulsatile bleeding. A diagnosis of bleeding duodenal ulcer was made and endoscopic hemostasis was performed successfully. The hemoglobin level had further decreased to 5.8 g/dL on admission. The patient received transfusion of 1600 mL of concentrated human red blood cells over 3 days beginning 5 days before administration of pethidine hydrochloride. Therapy involving rest, fasting, drip infusion, oxygen, hemostatic agent and anti-ulcer drug was continued, and the patient progressed favorably without any sign of rebleeding. 2 days before administration Oral food intake was resumed. 1 day before administration The hemoglobin level recovered to 9.4 g/dL and the patient was able to walk around in the hospital. Because the patient had melaena containing fresh blood before admission, an examination of the large intestine was scheduled for the following day. Approximately 5 hours before administration The patient began taking 2 L of sodium chloride/potassium chloride/sodium bicarbonate/anhydrous sodium sulfate. Approximately 1 hour before administration The stool output was confirmed to be clear with no particles of stool. Approximately 3 minutes before administration The patient was taken to the colonoscopy room, fully conscious.

				During administration Glucagon (genetical recombination) 1 mg, flunitrazepam 0.2 mg and pethidine hydrochloride 35 mg were administered intravenously as premedication for colonoscopy, then the colonoscope was introduced into the rectum and the examination was started. 1 minute after administration The percutaneous arterial oxygen saturation was 68% to 80%. Immediately thereafter, spontaneous respiration stopped. The examination was discontinued. The patient did not respond to repeated calls and thumps 2 minutes after administration The percutaneous arterial oxygen saturation suddenly fell to 38% and cyanosis developed. The pulse was not palpable and heart sounds ceased. With the help of doctors and outpatient nurses, intubation was performed and resuscitation was started immediately. At the same time, a peripheral intravenous line was placed and i.v. injections of flumazenil 0.25 mg to reverse the effects of flunitrazepam, and adrenalin 2 mg and atropine sulfate hydrate 0.5 mg for cardiotonic effects, and drip infusion of sodium bicarbonate 8.75 g for the treatment of acidosis were administered. 17 minutes after administration The heartbeat resumed. The blood pressure was 180/90 mmHg, and percutaneous arterial oxygen saturation was 83%. The pupils were normal and light reflex was present. However, the patient was in a state of coma without spontaneous breathing. 23 minutes after administration The patient was transferred to the recovery room and connected to artificial respiration. A central venous line was placed. As the blood pressure lowered, continuous infusion of dopamine hydrochloride 135 mg/3 hours was administered and the blood pressure recovered to 100 to 150 mmHg. No abnormal findings that might have caused the sudden changes were found on X-ray films or blood tests after the sudden changes. Because the sudden changes might have occurred in association with sudden development of concurrent diseases such as cardiac disease or stroke, the patient was referred to the previous hospital for examination, tests and treatment. 4 hours and 12 minutes after administration The patient was transferred to the hospital in an ambulance. After the transfer, special examination and tests were performed by the previous hospital and other medical institutions, however, no disease that might have caused the sudden changes was found. The patient remained in a coma without spontaneous respiration. Treatment including tracheotomy, artificial respiration, drip infusion and tube feeding was provided but the patient did not recover. Approximately 5 months after administration The patient died of complicated septic shock due to severe pneumonia.
	Concomitant medications: concentrated human red blood cells, glucagon (genetical recombination), flunitrazepam, sodium chloride/potassium chloride/sodium bicarbonate/anhydrous sodium sulfate, medical oxygen			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Colonoscopy (None)	35 mg for 1 day	**Anaphylactic shock** During administration The patient underwent colonoscopy periodically for examination of a large intestine polyp. The colonoscopy was also performed this time as a regular check up. Scopolamine butylbromide and diazepam injections were always used. Due to severe pain each time during colonoscopy, the patient requested use of a stronger analgesic than usual. The examination was started after i.v. injections of scopolamine butylbromide and diazepam, and 35 mg of pethidine hydrochloride was added because of severe pain. The patient started coughing intensely after i.v. injection of pethidine hydrochloride, and chest distress and difficulty speaking developed. 5 minutes after administration Pulse rate increased (120s/minute), and blood pressure and oxygen saturation decreased (90s mmHg and 70s%, respectively). The patient was considered to have anaphylaxis due to pethidine hydrochloride and was given i.m. injection of adrenalin 0.1 mg and i.v. injection of methylprednisolone sodium succinate 250 mg. The patient's condition gradually became stable. Detailed information on changes in vital signs is unknown.
	Concomitant medications: scopolamine butylbromide, diazepam			

3

Revision of PRECAUTIONS

(No. 211)

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 October 27, 2009 (excluding those presented in "2. Important Safety Information" of this Bulletin).

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1 **<Antipyretics and analgesics, anti-inflammatory agents>**

Indometacin (oral dosage form)

[Brand Name]	Inteban SP 25 and 37.5 (Dainippon Sumitomo Pharma Co., Ltd.) and others
[Adverse Reactions (clinically significant adverse reactions)]	**Gastrointestinal perforation, gastrointestinal haemorrhages, gastrointestinal ulcers, intestinal stenosis/obstruction, colitis ulcerative**

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2 **<Antipyretics and analgesics, anti-inflammatory agents>**

Indometacin (suppository)

[Brand Name]	Inteban Suppository 25 and 50 (Dainippon Sumitomo Pharma Co., Ltd.) and others
[Adverse reactions (clinically significant adverse reactions)]	**Gastrointestinal perforation, gastrointestinal haemorrhages, gastrointestinal ulcers, intestinal stenosis/obstruction, colitis ulcerative**

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3 **<Antipyretics and analgesics, anti-inflammatory agents>**

Indometacin farnecil

[Brand Name]	Infree Capsules 100 mg, Infree S Capsules 200 mg (Eisai Co., Ltd)
[Adverse reactions (clinically significant adverse reactions)]	**Gastrointestinal perforation, gastrointestinal haemorrhages, gastrointestinal ulcers, colitis haemorrhagic, intestinal stenosis/obstruction, colitis ulcerative:** Gastrointestinal perforation, gastrointestinal haemorrhages, gastrointestinal ulcers, colitis haemorrhagic, or intestinal stenosis/obstruction may occur. If any of the symptoms are observed, administration should be discontinued and appropriate measures should be taken. Colitis ulcerative has been reported in association with indometacin, which is the active metabolite of this drug.

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4 **<Antipyretics and analgesics, anti-inflammatory agents>**

Proglumetacin maleate

[Brand Name]	Miridacin Tablet 90 mg (Taiho Pharmaceutical Co., Ltd.)

[Adverse reactions (clinically significant adverse reactions)]	**Gastrointestinal perforation, gastrointestinal haemorrhages, gastrointestinal ulcers:** Gastrointestinal perforation, gastrointestinal haemorrhages, or gastrointestinal ulcers may occur. If any of the symptoms are observed, administration should be discontinued and appropriate measures should be taken.
[Clinically significant adverse reactions (active metabolite)]	Intestinal stenosis/obstruction, colitis ulcerative

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5 **<Antihypertensives>**

Lisinopril hydrate

[Brand Name]	Zestril Tablets 5, 10, and 20 (AstraZeneca K.K.), Longes Tablets 5 mg, 10 mg, and 20 mg (Shionogi & Co., Ltd.) and others
[Adverse reactions (clinically significant adverse reactions)]	**Syndrome of inappropriate ADH secretion (SIADH)**: The syndrome of inappropriate ADH secretion (SIADH) accompanied by hyponatraemia, blood hyposmosis, increased sodium excretion into the urine, hypersthenuria, convulsions, or consciousness disturbed may occur. In such cases, administration should be discontinued and appropriate measures such as restricting fluid intake etc. should be taken.

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6 **<Miscellaneous cardiovascular agents>**

Lanthanum carbonate hydrate

[Brand Name]	Fosrenol Chewable Tablets 250 mg and 500 mg (Bayer Yakuhin, Ltd.)
[Precautions of dosage and administration]	Because this product is hard to be dissolved when swallowed without chewing, patients should be instructed to completely chew up the tablet and swallow this product with saliva or a small amount of water. Patients who have difficulty in chewing up (such as elderly patients) should take this product after crushing the tablet.
[Precautions in use]	**Oral administration**: This product should be swallowed after chewing up the tablet completely.

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7 **<Anticoagulants>**

Parnaparin sodium

[Brand Name]	Lowhepa 100 U/mL Syringe 20 mL, 150 U/mL Syringe 20 mL, 200 U/mL Syringe 20 mL, and 500 U/mL Vial 10 mL for dialysis (Ajinomoto Co., Inc.) and others
[Adverse reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if any abnormalities including blood pressure decreased, consciousness decreased, dyspnoea, cyanosis or urticaria occur, administration should be discontinued and appropriate measures should be taken.

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8 **<Antivirals>**

Zanamivir hydrate

[Brand Name]	Relenza (GlaxoSmithKline K.K.)
[Adverse reactions (clinically significant adverse reactions)]	**Oculomucocutaneous syndrome (Stevens-Johnson Syndrome), toxic epidermal necrolysis (TEN, Lyell syndrome), erythema multiforme:** Serious skin disorders such as oculomucocutaneous syndrome (Stevens-Johnson Syndrome), toxic epidermal necrolysis (TEN, Lyell syndrome), or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities occur, administration should be discontinued and appropriate measures should be taken.

4

List of products subject to Early Post-marketing Phase Vigilance

(As of December 1, 2009)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
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 5 mg, 10 mg, and 25 mg	Eli Lilly Japan K.K.	June 19, 2009
Fluticasone Furoate Allermist 27.5 μg 56 metered Nasal Spray	GlaxoSmithKline K.K.	June 19, 2009
Lapatinib Tosilate Hydrate Tykerb Tablets 250 mg	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 25 mg, 37.5 mg, and 50 mg	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
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion 100[*1]	Mitsubishi Tanabe Pharma Corporation	July 7, 2009
Etanercept (Genetical Recombination) ENBREL 25 mg Syringe for S.C. Injection[*2]	Wyeth K.K.	July 7, 2009
Somatropin (Genetical Recombination) Growject injection 1.33 mg, 8 mg, BC 8 mg[*3]	JCR Pharmaceuticals Co., Ltd.	July 7, 2009
Follitropin alfa (Genetical Recombination) Gonalef 75, Gonalef Pen 450 and 900[*4]	Merck Serono Co., Ltd.	July 7, 2009
Levofloxacin Hydrate CRAVIT TABLETS 250 mg, 500 mg, Fine Granules 10%	Daiichi Sankyo Company, Limited.	July 7, 2009
Clozapine CLOZARIL Tablets 25 mg, 100 mg	Novartis Pharma K.K.	July 29, 2009
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 OPTHALMIC SOLUTION 0.03%	Senju Pharmaceutical Co., Ltd.	October 5, 2009
Paroxetine hydrochloride hydrate Paxil Tablets 10 mg and 20 mg*5	GlaxoSmithKline K.K.	October 16, 2009
Interferon-beta FERON Injections 1 x 10^6, and, 3 x 10^6, and 6 x 10^6 IU *6	Toray Industries, Inc.	October 16, 2009
Ribavirin REBETOL Capsules 200 mg*7	Schering-Plough K.K.	October 16, 2009
Voglibose BASEN Tablets 0.2 and BASEN OD Tablets 0.2*8	Takeda Pharmaceutical Company Limited	October 19, 2009
Bevacizumab (genetical recombination) AVASTIN Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL*9	Chugai Pharmaceutical Co., Ltd.	November 6, 2009

*1: An additional indication for "treatment of patients with rheumatoid arthritis which is not adequately responsive to conventional therapies (including prevention of structural damage to joints)"

*2: An additional indication for "treatment of patients with polyarticular-course juvenile idiopathic arthritis (only for cases which are not adequately responsive to conventional therapies)"

*3: An additional indication for "treatment of patients with replacement of endogenous growth hormone in adults with growth hormone hyposecretion (restricted to serious cases)"

*4: An additional indication for "ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders or polycystic ovarian syndrome"

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

*6: 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"

*7: 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"

*8: 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)"

*9: An additional indication for "treatment of patients with advanced or recurrent, inoperable non-squamous non-small cell lung cancer"