Pharmaceuticals and Medical Devices Safety Information

No. 216 August 2005

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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.
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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,
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. 216 August 2005

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	**Serious health hazards in the use of bone cement**		In response to occurrence of blood pressure decreased and shock etc. resulting from the use of bone cement, MHLW has alerted healthcare providers by presenting examples of serious case reports and the content of revisions to PRECAUTIONS section of package inserts in "Pharmaceutical Adverse Reaction Information No. 116" issued in September 1992, "Pharmaceuticals Safety Information No. 147" issued in March 1998, and "Pharmaceuticals and Medical Devices Safety Information No. 165" issued in March 2001. Thereafter, as there have been reports of blood pressure decreased, shock, and pulmonary embolism, etc. resulting in death due to the use of bone cement in high-risk patients and where monitoring by an anesthetist is not conducted etc., MHLW has decided to present the content of these reports and to alert healthcare providers etc. again on risks and proper use.	3
2	**Effects on implantable medical devices (cardiac pacemakers and cardioverter defibrillators) by new system mobile phone terminals and RFID devices**		With regard to effects on implantable cardiac pacemakers and implantable cardioverter defibrillators (ICDs) (hereinafter referred to as "implantable medical devices") by mobile phone terminals etc., awareness was promoted in Pharmaceuticals Adverse Events Information 3 times in the past. As for the effects of antitheft devices etc. on implantable medical devices awareness was promoted in Pharmaceuticals and Medical Devices Safety Information 4 times in the past. As the result of a study relating to the effects of electoromagnetic waves emitted from new-type mobile phone terminals on implantable medical devices conducted by Ministry of Internal Affairs and Communications (MIC) in 2004, the current guideline that "mobile phone terminals should be separated from the implant site of cardiac pacemakers at a distance of approximately 22 cm and more" was confirmed to be appropriate. In addition, regarding the effects of electoromagnetic waves emitted from RFID devices (fixed types and module types) on implantable medical devices, it was confirmed that such effects can be avoided by separating the devices at a distance of 22 cm and more, as was confirmed for the hand-held RFID in 2003. At this time, MHLW has decided to present the content of these reports and to alert healthcare providers etc. again on risks and proper use. In addition, as guidelines for the prevention of such effects have been released which are based on the survey results of various electoromagnetic wave devices collected by MIC until 2004, is also be presented.	12
3	**Sodium Valproate (and 2 others)**	*P* *C*	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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 215), together with reference materials.	23
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D: Distribution of Dear Healthcare Professional Letters *P*: Revision of PRECAUTIONS *C*: Case Reports

1

Serious health hazards in the use of bone cement

Nonproprietary name Brand name (name of company)	Generic name	Brand name (name of company)
	Bone cement	Endurance Bone Cement (Johnson & Johnson K.K.) Orthoset High Viscosity Bone Cement (Wright Medical Technology, Inc.) Orthoset Low Viscosity Bone Cement (Wright Medical Technology, Inc.) Osteobond Copolymer Bone Cement (Zimmer K.K.) Surgical Simplex (Stryker Japan K.K.) Zimmer Bone Cement (Zimmer K.K.) Cemex RX (Sata Corporation) Cemex System (Sata Corporation)
Category	Medical Supplies 4 orthopedic article	
Indications	Fixation of artificial joints etc.	

(1) Course

If joint damage such as femoral neck fracture or rheumatoid arthritis etc. occurs, femoral head replacement involving decapitation of the bone head (upper end of femora) and replacement with an artificial bone head, or artificial joint replacement involving replacement of the entire joint with an artificial joint is performed. At this time, it is sometimes necessary to inject an acrylic resin called "bone cement" into living bone in order to affix the implant material such as the artificial joint to the living bone. However, as serious blood pressure decreased, shock, and pulmonary embolism etc. resulting in death may occur as adverse reactions during surgery which uses bone cement, MHLW has alerted healthcare providers by presenting examples of serious case reports and the content of revisions to PRECAUTIONS section of package inserts in "Pharmaceutical Adverse Reaction Information No. 116" issued in September 1992, "Pharmaceuticals Safety Information No. 147" issued in March 1998, and "Pharmaceuticals and Medical Devices Safety Information No. 165" issued in March 2001.

(2) Precautionary notifications etc. issued to date

The content of the "Warning" section of the current package inserts of relevant bone cement companies which are based on serious case reports during the use of bone cement are indicated below:

1) Compared to other patients, as the risk of resulting in blood pressure decreased, and in particular to serious cardiovascular failure is high for patients with cardiovascular disorders, patients in poor general condition, patients with metastasis of malignant tumor to the femur, elderly patients, osteoporosis patients, patients receiving adrenocorticosteroids, patients with decreased circulatory blood volume, low oxygen patients, and obese patients, the product should only be used when it is judged that the benefits of using bone cement outweigh the risks.

2) The product should be used under conditions in which there is sufficient circulatory blood volume and as far as possible when the patient's general condition is good.

3) The product should be used while being monitored by an anesthetist etc. capable of taking emergency actions in case of sudden drop in blood pressure and serious cardiovascular failure. Also, while continuing to monitor changes in the patient's blood pressure etc., necessary preparations should be made so that immediate treatment can be performed if serious cardiovascular failure should occur.

4) In order to prevent the absorption of unpolymerized monomers into the blood stream which may lead to the myocardial depression etc., take sufficient time to mix the bone cement and do not apply the cement until it has sufficiently polymerized.

5) When injecting the product in the medullary cavity of long bones (femur etc.), make sure to adequately remove bone marrow tissue (bone marrow, bone fragments, and blood) which may cause embolism.

6) When filling low-viscosity bone cement into the femoral cavity using a cement gun, seal the distal medullary cavity with a plug in order to minimize as much as possible the entry of unpolymerized monomers and bone marrow contents into the cardiovascular system.

7) As increased internal pressure within the medullary cavity of the femur during the filling of bone cement will affect respiration and circulation, caution should be exercised to minimize intramedullary pressure such as by temporarily inserting a pressure reduction tube.

(3) Recent numbers of case reports etc.

In a 4 year period from April 2001 to the end of March 2005, 37 serious domestic cases including those resulting in death due to the use of bone cement have been reported by relevant companies and medical institutions. The following table indicates sales quantities and reported number of cases per year investigated by the relevant bone cement companies. However, as the number of applications of bone cement in a single case was not constant, sales quantities do not directly reflect actual number of cases utilizing bone cement.

	Sales quantity	Reported number of cases
FY2001	Approx. 82000	11
FY2002	Approx. 94000	4
FY2003	Approx. 83500	10
FY2004	Approx. 83800	12

(4) Analysis of reported cases

Of the 37 serious domestic cases (including 32 fatal cases) including those resulting in death from the use of bone cement reported by the relevant bone cement companies and medical institutions during the 4 year period from April 2001 to the end of March 2005, with the exception of 5 cases for which detailed information could not be obtained due to non-cooperation by medical institutions, case analysis was been conducted toward 32 cases (refer to **Table 1**) and their contents have been briefly outlined.

1) Therapeutic purpose

In all cases, bone cement was injected for the purpose of affixing replacement material to the femur during femoral head replacement in patients with femoral neck fracture etc.

2) Age, etc.

Patient age was between 69 and 96, with average age approx. 83. According to sex, there were 30 women, 1 man, and 1 unknown case.

3) Period from the date of injury until surgery

The period from the date of injury until the date of surgery has been confirmed in 8 cases, and were between 3 and 9 days.

4) Medical history

Of 32 cases, there were 12 cases of cardiovascular disorders (thoracic aortic aneurysm, heart valve disease, myocardial infarction, angina pectoris etc.), 11 cases of osteoporosis, 3 cases of rheumatism, and 1 case of obesity (with medical history of hypertension and diabetes mellitus) with respect to which precautions have been entered in the "Warning" section of package inserts.

5) Monitoring by an anesthetist

Of the 32 cases, 25 cases of surgery were confirmed to have been conducted with monitoring by an anesthetist, there were 4 cases in which an anesthetist was not present, and 3 unknown cases due to investigative difficulties.

6) Changes in blood pressure

Decreased blood pressure was confirmed in all cases. Most of the cases for which blood pressure values before surgery and blood pressure values after bone cement injection were known, included dramatic declines in blood pressure including unmeasurable levels immediately after injection.

7) Outcomes, etc.

Among the 32 cases subject for analysis, 27 cases resulted in death and 3 cases were judged to have suffered consciousness disorder (unrecovered). In addition, of the fatal cases, 7 cases were confirmed by autopsy etc. to have suffered fat embolism or blood clot in the lungs etc.

8) Procedure, etc.

A cement gun*[1] was used in all cases with the exception of 2 cases. A cement plug*[2] was used in all cases with the exception of 1 case in which one was not used and 1 unknown case. A vent tube*[3] was not used in 22 cases, with the exception of 5 cases for which one was used and 5 unknown cases. Also, a pressurizer*[4] to increase the pressure of the cement was not used in 23 cases, with the exception of 4 cases in which one was used and 5 unknown cases. As for the washing of the medullary cavity, washing was conducted through pulse washing in 12 cases, through syringe in 9 cases, by another method in 10 cases, and there were 2 unknown cases.

<Explanation of terms>

*1 Cement gun: a device used to fill the medullary cavity with bone cement using a syringe.

*2 Cement plug: a plug used to seal the distal medullary cavity to prevent excessive filling of bone cement into the medullary cavity.

*3 Vent tube: a tube used to vent air from the medullary cavity during bone cement filling.

*4 Pressurizer: a pressurizing device used to ensure that the cement fills the medullary cavity without leaving any gaps or spaces.

(5) Summary and future post-marketing safety measures etc.

From the results of our analysis of reported cases, numerous cases in which the product was used in high risk patients were confirmed. There were some cases which were not monitored by an anesthetist and cases of embolism due to blood clots etc. Moreover, as the results of X-ray etc. tests in 11 of the above cases showed that the cement plug had shifted to the distal end of the femur including 1 reported case that the plug was established too proximally at time of initial placement, the selection of an appropriate plug size and its appropriate placement is necessary so that the bone cement does not shoot past the cement plug into the medullary cavity. In addition, as prolonged immobility can be raised as a risk factor for thrombosis and pulmonary embolism, in the event of fractures, it is desirable that surgery be performed soon after the injury is sustained.

In addition to observing the aforementioned points of caution, caution should be exercised for the contents of the PRECAUTIONS section of package inserts for bone cement products.

(6) Application toward compression fracture of spine

Although bone cement which is currently approved under the Pharmaceutical Affairs Law is indicated for the “fixation of bone and implant materials during replacement arthroplasty”, there have recently been occasional reports of bone cement being injected into the affected location of a osteoporosis-induced compression fracture of spine during percutaneous vertebroplasty. In Japan, MHLW has just recently received reports of fatal cases who experienced decreased blood pressure and went into shock immediately after bone cement was injected into the affected location of a compression fracture of spine during vertebroplasty from medical institutions. It is requested that medical institutions issue medical device safety information reports in accordance with article 77-4-2-2 of the Pharmaceutical Affairs Law in the event of serious adverse events occurring during the use of bone cement in these therapies, even when causality with bone cement cannot be denied. In addition, as the US FDA and the UK MHRA (former MDA) have been alerting healthcare providers and have issued safety information in this regard in 2003 and 2004, a brief overview of their contents is provided below.

(Summary)

According to safety information issued by the FDA etc., among patients for whom bone cement was used to treat compression fracture of spine caused by osteoporosis etc. (Vertebroplasty and Kyphoplasty), there have been reports of nerve root pain, soft tissue injury, pulmonary embolism, cardiac failure, and death etc. accompanying leakage of bone cement. It is also stated that a comparative clinical study etc. has not been conducted to confirm the long-term safety and efficacy of this treatment method.

In addition, according to the same safety information, while a contrast agent is mixed into the bone cement to sharpen X-ray images, guidelines have not been established with respect to hardening time, durability, and safety of bone cement relative to blending ratio with a contrast agent, and warning of unforeseen dangers is included.

Table 1-1. List of reported cases of adverse events

Item \ Case		1	2	3	4	5	6	7	8
Therapeutic purpose		Fracture in proximal femur	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture/trochanter fracture	Fracture of the femur	Femoral neck fracture/trochanter fracture	Femoral neck fracture
Sex		Female	Female	Female	Female	Female	Female	Female	Female
Age		79	82	87	80	92	91	69	82
Period from the date of injury until surgery		Unknown	Unknown	Unknown	On day 6	Unknown	Unknown	Unknown	Unknown
Medical history	Cardiovascular disorder	○	○				○		
	Osteoporosis			○		○		○	○
	Rheumatism		○						
	Cerebrovascular disorder				○			○	
	Diabetes mellitus				○	○			
	Others	○			○	○	○	○	
Constitution	Obesity								
Anesthesia	Site	General	Spinal	Spinal	Spinal	Spinal	General	Spinal	Unknown
	Monitoring by anesthetist	Yes	Unknown	Yes	Yes	Yes	Yes	Yes	Yes
Blood pressure	Preoperative blood pressure	170/60	162/88	154/92	160/100	148/90	120/75	130/60	Unknown
	Diastolic blood pressure after bone cement injection	Unmeasurable	Unmeasurable	90/50	80/50	Unknown	Unknown	130/80	Unknown
Adverse event	Blood pressure decreased	○	○	○	○	○	○	○	○
	Pulmonary etc. embolism	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
	Death	○	○	○	○	○	○	○	○
Procedure etc.	Cement injection method	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun
	Use of cement plug	Yes	Yes	Yes	Yes	Yes	No	Yes	Unknown
	Use of vent tube	No	Unknown	Unknown	Yes	No	No	No	Unknown
	Use of pressurizer	No	Unknown	No	No	No	Unknown	No	Unknown
	Medullary cavity washing	Syringe	Pulse	Syringe	Pulse	Dropper washing	Pulse	Brush	Unknown
Reporter		Company	Company	Company	Company	Company	Company	Company	Company

Table 1-2. List of reported cases of adverse events

Item \ Case		9	10	11	12	13	14	15	16
Therapeutic purpose		Femoral neck fracture/trochanter fracture	Femoral neck fracture/trochanter fracture	Femoral neck fracture	Femoral neck fracture/trochanter fracture	Femoral neck fracture/trochanter fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture
Sex		Female	Female	Female	Female	Female	Female	Female	Female
Age		79	80	91	75	86	92	80	83
Period from the date of injury until surgery		Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Medical history	Cardiovascular disorder					○	○		
	Osteoporosis	○	○		○	○			
	Rheumatism								
	Cerebrovascular disorder								
	Diabetes mellitus		○						
	Others	○	○	○		○		○	
Constitution	Obesity								
Anesthesia	Site	Spinal	Unknown	Spinal	Spinal	Unknown	Spinal	General	Spinal
	Monitoring by anesthetist	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Blood pressure	Preoperative blood pressure	120/65	138/80	100/55	152/90	130/80	160/92	Unknown	210/90
	Diastolic blood pressure after bone cement injection	100/60	Unmeasurable	48/28	40/25	Unknown	Unknown	Unknown	130/66
Adverse event	Blood pressure decreased	○	○	○	○	○	○	○	○
	Pulmonary etc. embolism	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	○	Unknown
	Death	(consciousness disorder)	○	○	(consciousness disorder)	○	○	○	○
Procedure etc.	Cement injection method	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun
	Use of cement plug	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Use of vent tube	No	No	Unknown	No	No	No	No	No
	Use of pressurizer	No	No	No	Yes	No	No	No	No
	Medullary cavity washing	Syringe	Dropper/Gauze washing	Pulse	Pulse	Pulse	Washing	Pulse	Washing
Reporter		Company	Company	Company	Company/ Medical institution	Company	Company	Company	Company

Table 1-3. List of reported cases of adverse events

Item \ Case		17	18	19	20	21	22	23	24
Therapeutic purpose		Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture/trochanter fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture
Sex		Female	Female	Female	Female	Male	Female	Female	Female
Age		83	81	80	87	96	82	88	79
Period from the date of injury until surgery		Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	On day 6	Unknown
Medical history	Cardiovascular disorder	○	○		○		○	○	
	Osteoporosis								
	Rheumatism			○	○				
	Cerebrovascular disorder						○		○
	Diabetes mellitus		○						
	Others		○	○	○				
Constitution	Obesity		○						
Anesthesia	Site	Unknown	Spinal	Unknown	Unknown	Spinal	Spinal	General	General
	Monitoring by anesthetist	Yes	Yes	No	Yes	Yes	Unknown	Yes	Yes
Blood pressure	Preoperative blood pressure	135/75	Unknown	130/60	Unknown	110/65	120/60	126/60	120/50
	Diastolic blood pressure after bone cement injection	Unknown	Unknown	85/45	Unknown	Unknown	Unknown	70/35	46/15
Adverse event	Blood pressure decreased	○	○	○	○	○	○	○	○
	Pulmonary etc. embolism	Unknown	○	Unknown	○	Unknown	Unknown	Unknown	○
	Death	○	○	○	○	○	(consciousness disorder)	○	
Procedure etc.	Cement injection method	Cement gun	Cement gun	Cement gun	Cement gun	Manual	Cement gun	Cement gun	Cement gun
	Use of cement plug	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Use of vent tube	No	No	No	Yes	No	No	No	No
	Use of pressurizer	No	No	No	No	No	No	No	No
	Medullary cavity washing	Washing	Pulse	Washing	Pulse/Syringe	Syringe	Pulse	Washing	Washing
Reporter		Company	Company	Company	Company	Company	Company	Company	Company

Table 1-4. List of reported cases of adverse events

Item \ Case		25	26	27	28	29	30	31	32
Therapeutic purpose		Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture	Femoral neck fracture
Sex		Female	Female	Female	Female	Female	Female	Unknown	Female
Age		84	85	69	88	88	82	82	86
Period from the date of injury until surgery		Unknown	On day 6	On day 9	On day 3	Unknown	On day 9	On day 4	On day 7
Medical history	Cardiovascular disorder							○	○
	Osteoporosis						○	○	○
	Rheumatism								
	Cerebrovascular disorder		○						
	Diabetes mellitus	○						○	
	Others		○	○	○				
Constitution	Obesity								
Anesthesia	Site	Unknown	Spinal	General	Spinal	Unknown	Spinal	General	Spinal
	Monitoring by anesthetist	Yes	No	Yes	No	Unknown	Yes	Yes	Yes
Blood pressure	Preoperative blood pressure	Unknown	118/59	Unknown	200/60	Unknown	Unknown	165/130	140/56
	Diastolic blood pressure after bone cement injection	Unknown	69/24	130/65	Unknown	Unknown	Unknown	80/50	Unmeasurable
Adverse event	Blood pressure decreased	○	○	○	○	○	○	○	○
	Pulmonary etc. embolism	○	Unknown	○	Unknown	Unknown	Unknown	Unknown	○
	Death	○	○		○	○	○	○	○
Procedure etc.	Cement injection method	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Cement gun	Manual
	Use of cement plug	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Use of vent tube	Yes	Yes	No	Yes	Unknown	No	No	No
	Use of pressurizer	No	Yes	Yes	Unknown	Unknown	No	Yes	No
	Medullary cavity washing	Syringe	Syringe	Washing	Pulse	Unknown	Pulse	Syringe	Syringe
Reporter		Company	Company	Company/ Medical institution	Company/ Medical institution	Company	Company	Company	Company

(References)

FDA
http://www.fda.gov/cdrh/safety/bonecement.html

2

Effects on implantable medical devices (cardiac pacemakers and cardioverter defibrillators) by new system mobile phone terminals and RFID devices

With regard to effects on implantable cardiac pacemakers and implantable cardioverter defibrillators (ICDs) (hereinafter referred to as "implantable medical devices") by mobile phone terminals etc., awareness was promoted in Pharmaceutical Adverse Reaction Information No. 136 (March 1996 issue), No. 137 (May 1996 issue), No. 143 (June 1997 issue). As for the effects of antitheft devices etc. on implantable medical devices awareness was promoted in Pharmaceuticals Safety Information No. 155 (June 1999 issue), and Pharmaceuticals and Medical Devices Safety Information No. 173 (January 2002 issue), No. 190 (June 2003 issue), and No. 203 (July 2004 issue).

Ministry of Internal Affairs and Communications (MIC) has been implementing studies relating to the effects of electromagnetic waves on medical devices since 2000. In 2004, a study relating to the effects of electromagnetic waves emitted from new-type mobile phone terminals (hereafter, "new type mobile phone terminals") on implantable medical devices were conducted, and the current "Guidelines for the usage of mobile phone terminals etc. for preventing the effect of electromagnetic waves on electrical medical devices" [March 1997, the Conference for Countermeasures for the Issues of Unnecessary Electromagnetic Waves (the current "Electromagnetic Compatibility Conference Japan (EMCC)")] which states that "mobile phone terminals should be separated from the implant site of cardiac pacemakers at a distance of approximately 22 cm and more" was confirmed to be appropriate.

In addition, regarding the effects of electromagnetic waves emitted from RFID devices*[1] (fixed types and module types) on implantable medical devices, it was confirmed that such effects can be avoided by separating the devices at a distance of 22 cm and more, as was confirmed for the hand-held RFID in 2003.

At this time, MHLW has decided to present the content of these reports and to alert healthcare providers etc. again on risks and proper use. In addition, as guidelines for the prevention of such effects have been released as "Guidelines for Preventing the Effects of Electromagnetic Waves From Various Types of Device on Implantable Medical Devices" which are based on the survey results of various electromagnetic wave devices collected by MIC until 2004, is also be presented.

(1) Background

It has been described that a summary of the effects of electromagnetic waves emitted from mobile phone terminals etc. on implantable medical devices and medical devices used inside medical institutions in No. 179 of this bulletin. And a summary of the effects of electromagnetic waves emitted from RFID devices (gate types and hand-held types) on implantable medical devices has been presented in issue No. 203 of this bulletin.

At this time, as the results of the investigation conducted by MIC in 2004 on the effects of electromagnetic waves emitted from new-type mobile phone terminals on implantable medical devices, and the effects of electromagnetic waves emitted from RFID devices (fixed types and module types) on implantable medical devices have been released, the content of the investigation is presented to medical institutions, healthcare professionals, and medical device manufacturers etc.

(2) Overview of the study

MIC investigated the effects of electromagnetic waves emitted from mobile phone terminals used in newly introduced mobile phone services and the effects of electromagnetic waves emitted from currently used typical RFID devices on typical implantable medical devices currently in use by establishing worst-case test scenarios wherein these effects would become the most prominent. With respect to the RFID, as a continuation of investigations conducted in 2003 on gate-type RFID devices and hand-held RFID devices, investigations on the fixed-type RFID and the module-type RFID were conducted.

The following is a list of the types and numbers of devices employed in the study.

1) Wave emission source

① Mobile phone terminal

With the cooperation of mobile telephone companies, a study was conducted on the following mobile phone terminals:

a) CDMA2000 1X/CDMA2000 1xEV-DO (800 MHz band): 3 models

b) CDMA2000 1X/CDMA2000 1xEV-DO (2 GHz band): 2 models

② RFID[note]

With cooperation from the Japan Automatic Identification Systems Association, a study was conducted on the following RFID devices:

a) Fixed-type RFID devices: 45 models

b) Module-type RFID devices: 16 models

Note: The study targeted RFID devices selected by the Japan Automatic Identification Systems Association and which are used in normal environments such as public facilities and business districts. RFID devices which are used only in controlled areas such as inside factory compounds where the general public cannot enter (RFID devices exclusively used in controlled areas) were not targeted for investigation.

2) Implantable medical devices

With the cooperation of the Pacemaker Committee, a study was conducted on the following implantable medical devices:

① Implantable cardiac pacemakers: 33 models

② ICDs: 7 models

(3) Overview of study results

1) Effects of mobile phone terminals on implantable medical devices

① Effects of CDMA2000 1X/CDMA2000 1xEV-DO (800 MHz band) mobile phone terminals on implantable medical devices

a) With respect to the cardiac pacemaker, a possible effect on the pacing pulse was confirmed*[2]. This effect can be recovered and restored to normal by moving the mobile phone terminal away from the pacemaker. The furthest distance apart at which this effect was confirmed was 8 cm.

b) With respect to the pacemaker function of the IDCs *[3], a possible effect on the pacing pulse was confirmed. This effect can be recovered and restored to normal by moving the mobile phone terminal away from the pacemaker. The furthest distance apart at which this effect was confirmed was 2 cm.

In addition, an effect on the defibrillating function*[4] of the ICD was not confirmed.

② Effects of CDMA2000 1X/CDMA2000 1xEV-DO (2 GHz band) mobile phone terminals on implantable medical devices

a) With respect to the cardiac pacemaker, a possible effect on the pacing pulse was confirmed. This effect can be recovered and restored to normal by moving the mobile phone terminal away from the pacemaker. The furthest distance apart at which this effect was confirmed was 1 cm.
b) With respect to the ICD, effects on the pacemaker function or the defibrillating function were not confirmed.

Note: In this study, testing was performed under stringent conditions, such as by setting the transmission output of the mobile phone terminal to maximum so that the effects on implantable medical devices would be largest. Consequently, it is not appropriate to compare the study results (furthest distance away at which an effect was confirmed) with mobile phone calling systems under normal communication conditions.

2) Effects of RFID devices on implantable medical devices

① The effects of fixed-type RFID devices on implantable medical devices

a) With respect to the cardiac pacemaker, a possible effect on the pacing pulse was confirmed. This effect can be recovered and restored to normal by moving the fixed-type RFID away from the pacemaker. The furthest distance apart at which this effect was confirmed was 14 cm.
b) With respect to the pacemaker function of the ICD, a possible effect on the pacing pulse was confirmed. This effect can be recovered and restored to normal by moving the fixed-type RFID away from the ICD. The furthest distance apart at which this effect was confirmed was 6 cm.
In addition, with respect to the defibrillating function of the ICD, production of unnecessary defibrillation shocks*[5] was confirmed. The furthest distance apart at which this effect was confirmed was 6 cm.

② The effect of the module-type RFID devices on implantable medical devices

a) With respect to the cardiac pacemaker, a possible effect on pacing pulse was affected when the antennae region of the module-type RFID was placed in close proximity with the pacemaker was confirmed. This effect could be recovered and restored to normal by moving the module-type RFID away from the pacemaker.
b) With respect to the ICD, effects on the pacemaker function or the defibrillating function were not confirmed.

(4) Cautions for patients with implantable medical devices

1) Mobile phone terminals etc.

From the results of the study conducted this time, it was confirmed that the level of effect by CDMA2000 1X/CDMA2000 1xEV-DO (800 MHz band) and CDMA2000 1X/CDMA2000 1xEV-DO (2 GHz band) mobile phone terminals on implantable medical devices was smaller compared to the level of effect produced by mobile phone terminals investigated in 1997 for which a policy was stipulated to "separate the devices by approximately 22 cm and more". However, considering the mobile phone terminal models currently in use, it is surmised that existing guideline measures to prevent the effect of mobile phone terminals on implantable medical devices are appropriate even now, and it is necessary to caution all relevant parties to continue to observe existing guideline (22 cm).

2) RFID devices

From the results of this study, it is necessary to caution against bringing fixed-type RFID and module-type RFID to within a 22 cm proximity of implantable medical devices, as was determined for hand-held RFID devices.

(5) Request for medical institutions

Based on the results of this report, it is requested that all relevant healthcare providers continue to instruct patients to observe existing policy (22 cm) with respect to electromagnetic waves emitted from

new-type mobile phone terminals etc. As well, with respect to electromagnetic waves emitted from RFID devices (fixed types and module types), although it has not been ascertained as to which RFID systems affect implantable medical devices in particular, from the perspective of preventing health hazards to people with medical device implants, it is requested that all relevant healthcare providers instruct patients not to bring the antennae region of fixed-type RFID devices and module-type RFID devices to within a 22 cm proximity of the implant site. It is also requested that instruction be adequately provided to parents and guardians if the patient is a child.

<Explanation of terms>

*1 RFID (Radio Frequency Identification) device: Device that uses non-contact communications between a tag fitted with an IC and a reader/writer to read and write the data on the tag. It is used in a wide variety of fields, including distribution, inventory control, and settlement of products, etc.
Furthermore, the following types of device exist based on reader/writer configuration:
- Gate type: the reader/writer is established in a gate configuration
- Hand-held type: the reader/writer is a hand-held device that can be carried around
- Fixed type: the reader/writer is used in a stationary condition
- Module type: the reader/writer is built-into a printer etc.

*2 Effect on pacing pulse: The following conditions occur due to effects from external electromagnetic waves.
a) When a cardiac pacemaker etc. is generating a pacing pulse at a set cycle, a condition occurs where the pacing pulse is inhibited due to the effects of an external electromagnetic wave, or there is displacement of the set cycle.
b) When the pacing pulse of a cardiac pacemaker etc. is inhibited, a condition occurs where a pacing pulse is generated due to effects from external electromagnetic waves.

*3 Pacemaker function of ICDs: As an ICD normally functions as an implantable cardiac pacemaker, “pacemaker function” refers to this function.

*4 Cardioverter defibrillation function of ICDs: Refers to the function of an ICD emitting a strong electric shock to stop ventricular fibrillation (a type of fatal arrhythmia where the heart suffers sudden convulsions) when ventricular defibrillations are detected.

*5 Unnecessary defibrillation shock: A phenomenon where the defibrillating function of the ICD activates without actual ventricular fibrillation. This phenomenon may have a recovery effect on patient in immediately aggravating the patient’s condition.

(6) Others

MHLW has introduced the attached “Guidelines For Preventing the Effects of Electromagnetic Waves From Various Types of Device on Implantable Medical Devices” issued dated on August 2005 based on the results of the studies implemented in 2004 or before by MIC.

(References)

Guidelines For Preventing the Effects of Electromagnetic Waves From Various Types of Device on Implantable Medical Devices

(Ministry of Internal Affairs and Communications (MIC), August 2005)

In recent years, the use of various kinds of devices which utilize electromagnetic waves [mobile phone terminals, PHS terminals, wireless card (non-contact IC cards) systems, electronic article surveillance (EAS) terminals, RFID devices (electronic tag), and wireless LAN devices] by the general public is rapidly growing. Ministry of Internal Affairs and Communications (MIC) has conducted a study in order to prevent the effects of electromagnetic waves emitted from these devices on implantable medical devices and has recently released the results of this study.

This guideline is based on the results of the study conducted until 2004 and have been compiled for the purpose of preventing the effects of electromagnetic waves emitted from these devices on implantable medical devices*.

Cooperation from related organizations etc. was obtained in conducting this study, and while targets for the study were selected to cover typical types of devices found in the market at the time of the study, the study was not designed to include all types of devices in the market. As well, as new types of devices are being marketed, these points should be fully considered when making use of this guideline.

* "Guidelines relating to the use of mobile phone terminals to prevent the effect from electromagnetic waves on electrical medical devices" were issued in 1997 by Conference for Countermeasures for the Issues of Unnecessary Electromagnetic Waves [comprised of members of academia, relevant ministries and agencies, and industrial association etc.; the current Electromagnetic Compatibility Conference Japan (EMCC)], which also covered electrical medical devices used by medical institutions. Later, as mobile phone terminals operating on a new standard are now in use etc., we are now confirming the suitability of pertinent sections in this guideline relating to the effect of electromagnetic waves emitted from mobile phone terminals and PHS terminals on implantable medical devices from the aforementioned study. The guidelines which have been compiled this time include these points which have been confirmed.

1 Guidelines for preventing the effects of electromagnetic waves from mobile phone terminals and PHS terminals on implantable medical devices

A Any person with an implantable medical device should keep mobile phone terminals at least approximately 22 cm away from the area where the device is implemented when using or carrying the mobile phone terminal.
Take adequate attention in crowded place as mobile phone terminals may be used nearby.

B Any person with an implantable medical device should take the same action as the mobile phone terminals in A is required when using PHS terminals.

(As PHS terminals on the implantable medical device when approached closely is not completely unaffected, and it is not easy to distinguish between PHS terminals and mobile phone terminals by appearance, it is desirable to treat them in the same manner as in the mobile phone terminals in the preventative sense.)

C It is desirable for people carrying mobile phone terminals or PHS terminals to turn them off in areas where there is a possibility of being close proximity to person with an implantable medical device (e.g. in crowded trains).

2 Guidelines for preventing the effects of electromagnetic waves from wireless card (non-contact IC card) systems on implantable medical devices [note]

A Any person with an cardiac pacemaker should keep the reader/writer (antenna) of wireless card systems approximately at least 12 cm and more away from the area where the device is implemented.

B Although it is not necessary for person with ICDs to be especially concerned about wireless card systems in daily life, close contact of the reader/writer (antenna) of a wireless card system with the area where the device is implanted should be avoided.

C As for the manufacturers of wireless card systems, it is effective to make the reader/writer (antenna) parts clearly recognizable for the prevention of the effects. Additionally, it is effective to keep the mode in repetitive magnetic field as much as possible since the effect increases in intermittent magnetic field mode.

Note: Wireless card (non-contact IC card) systems covered by this guideline consist of a remote reader (reader/writer) and IC card which transmits/receives data using low-intensity electromagnetic waves emitted from the reader, which is used in transportation facilities and access controls, etc.

3 Guidelines for preventing the effects of electromagnetic waves from EAS on implantable medical device [(note)]

A Any person with an implantable medical device should quickly pass straight through the center of the passage without pausing around the area where EAS devices are installed and where EAS stickers (figure below) are attached.

B Any person with an implantable medical device should not stay around the EAS devices or lean on these devices.

C Any person with an implantable medical device should immediately consult their physician if they feel any change in their physical condition.

D Further safety investigations should be conducted by relevant organizations in order to reduce the effects of EAS devices on implantable medical devices.

Figure. EAS sticker

Note: Electronic Article Surveillance (EAS) devices covered by this guideline refer to devices designed to prevent shoplifting by sounding an alarm when goods attached with the sensor label or tag pass through a corresponding sensor without being checked through by a cashier.

∗ Permission to use the EAS sticker in the above Figure was obtained from the Japan Association of Electronic Article Surveillance Machines.

4 Guidelines for preventing the effects of electromagnetic waves from RFID devices (electronic tags) on implantable medical devices [note 1]

(1) Gate type RFID devices [(note 2)]

A Any person with an implantable medical device should pass straight through the center of the passage without pausing around area where gate-type RFID devices are installed and where RFID stickers (figure 1) are attached.

B Any person with implantable medical devices should not stay around the gate-type RFID devices or lean on these devices.

C Any person with implantable medical devices should immediately consult their physician if they feel any change in their physical condition.

D Further safety investigations should be conducted by relevant organizations in order to reduce the effects of gate-type RFID devices on implantable medical devices.

(2) Hand-held type, fixed type, and module type RFID devices [note 2]

A The operator of a hand-held RFID device should keep the antenna region of the device away from the implanted site of the medical device at a distance of at least 22 cm.

B Patients implanted with an implantable medical device should keep the antenna region of a fixed or module-type RFID away from the implanted site of the medical device at a distance of at least 22 cm.

C Further safety investigations should be conducted by relevant organizations in order to minimize the effects of hand-held type, fixed type, and modular type RFID devices on implantable medical devices.

For gate type RFID devices

For other types of RFID devices

Figure 1. RFID stickers

Note 1: RFID devices referred to here are those used in general environments such as in public facilities and business districts. RFID devices (dedicated RFID devices for controlled areas) used in the controlled areas inaccessible by the general public such as inside factory are excluded. In addition, in order to prevent the outflow of dedicated RFID devices for controlled areas into general environments, it is prescribed by JAISA that precautions should be included in the user manual etc. and that a special sticker indicating “dedicated RFID for controlled areas” be attached (figure 2).

Figure 2. Special sticker for the dedicated RFID devices for controlled areas

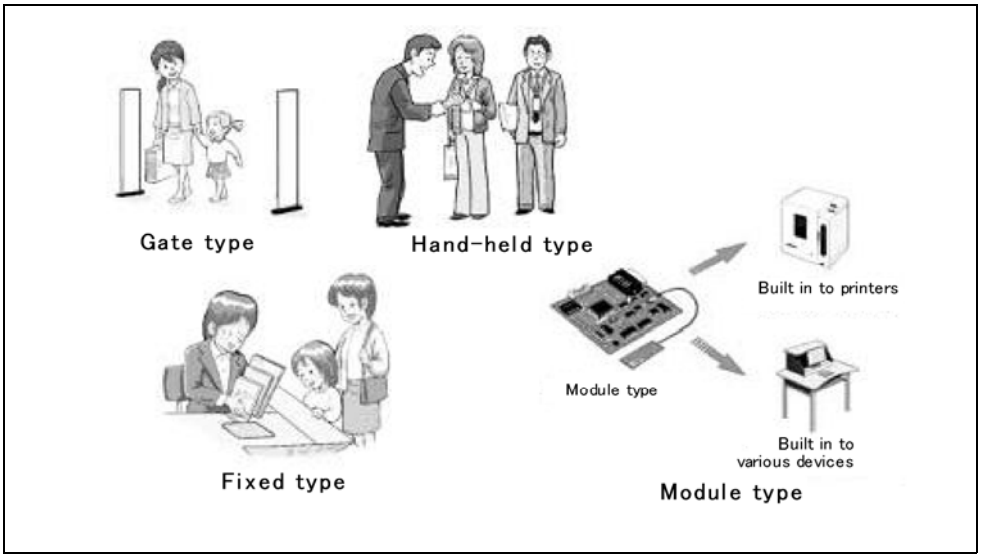

Figure 3. Types of RFID devices

Note 2: RFID devices are categorized as follows based on reader/writer configuration:
Gate type: the reader/writer is established in a gate configuration
Hand-held type: the reader/writer is a hand-held device that can be carried around
Fixed type: the reader/writer is used in a fixed condition
Module type: the reader/writer is built-into a printer etc.

* Permission to use the stickers in Figures 1 and 2 has been obtained from the Japan Automatic Identification Systems Association.

5 Measures for preventing the effects of electromagnetic waves from wireless LAN devices on implantable medical devices

A Since the implantable medical device affected by wireless LAN devices was only 1 model, all the users of this particular model had alerted based on the investigation result through medical institutions with the cooperation of Ministry of Health, Labour and Welfare.

B Therefore, people implanted with implantable medical device who have not been notified at this point are not required of special attention towards wireless LAN devices.

Reference 1

Investigative Research Reports etc. Used as the Basis for Compiling This Guideline

1 "Guidelines for the usage of mobile phone terminals etc. for preventing the effect of electromagnetic waves on electrical medical devices" (March 1997, the Conference for Countermeasures for the Issues of Unnecessary Electromagnetic Waves)
URL: http://www.arib.or.jp/emcc/ (in Japanese)
Study period: FY1995–FY1996
Devices emitting electromagnetic waves targeted by this study: mobile phone terminals, PHS terminals etc.

2 "Investigative research report on the effect of electromagnetic waves on medical devices etc." (March 2001)
URL: http://www.soumu.go.jp/joho_tsusin/pressrelease/japanese/sogo_tsusin/010515_1.html (in Japanese)
Study period: FY2000
Devices emitting electromagnetic waves targeted by this study: mobile phone terminals, PHS terminals

3 "Investigative research report on the effect of electromagnetic waves on medical devices etc." (March 2002)
URL: http://www.soumu.go.jp/s-news/2002/020702_3_1.html (in Japanese)
Study period: FY2001
Devices emitting electromagnetic waves targeted by this study: mobile phone terminals, PHS terminals

4 "Investigative research report on the effect of electromagnetic waves on medical devices etc." (March 2003)
URL: http://www.soumu.go.jp/s-news/2003/030620_1b.html (in Japanese)
Study period: FY2002
Devices emitting electromagnetic waves targeted by this study: wireless card devices and EAS devices

5 "Investigative research report on the effect of electromagnetic waves on medical devices etc." (March 2004)
URL: http://www.soumu.go.jp/s-news/2004/040618_2.html#mokuji (in Japanese)
Study period: FY2003
Devices emitting electromagnetic waves targeted by this study: EAS devices, wireless LAN devices, and RFID devices

6 "Investigative research report on the effect of electromagnetic waves on medical devices etc." (March 2005)
Study period: FY2004
Devices emitting electromagnetic waves targeted by this study: mobile phone terminals, RFID devices

Reference 2

Study Targets and Study Periods

1 Mobile phone terminals and PHS terminals	Study period
Analog type (800 MHz)	FY1995-FY1996
PDC (800 MHz)	FY1995-FY1996 FY2000-FY2001
PDC (1.5 GHz)	FY1995-FY1996 FY2000 -FY2001
W-CDMA (2 GHz)	FY2000-FY2001
cdmaOne/CDMA2000 1X (800 MHz)	FY2000-FY2001
CDMA2000 1X/CDMA2000 1xEV-DO (800 MHz, 2 GHz)	FY2004
PHS (1.9 GHz)	FY1995-FY1996 FY2000-FY2001

2 Wireless card systems	Study period
Proximity type (13.56 MHz)	FY2002
Vicinity type (13.56 MHz)	FY2002

3 EAS devices	Study period
Magnetic type (200 Hz-14 kHz)	FY2002-FY2003
Electromagnetic type (1.8-8.2 MHz, 2.4 GHz)	FY2002-FY2003
Magnetic cipher cards (22-37.5kHz)	FY2002-FY2003
Acoustic-magnetic type (58 kHz)	FY2002-FY2003
Complex type (electromagnetic + magnetic cipher type) (22-37.5 kHz, 8.2 MHz)	FY2002-FY2003

4 RFID devices	Study period
Gate type (125 kHz, 134.2 kHz, 135 kHz, 500 kHz, 13.56 MHz)	FY2003
Hand-held type (125 kHz, 134.2 kHz, 135 kHz, 13.56 MHz, 300 MHz, 2.4 GHz)	FY2003
Fixed type (125 kHz, 134.2 kHz, 135 kHz, 13.56 MHz, 300 MHz, 2.4 GHz)	FY2004
Module type (125 kHz, 134.2 kHz, 135 kHz, 13.56 MHz, 300 MHz)	FY2004

5 Wireless LAN devices	Study period
IEEE802.11 (2.4 GHz)	FY2003
IEEE802.11b (2.4 GHz)	FY2003
IEEE802.11g (2.4 GHz)	FY2003
IEEE802.11a (5 GHz)	FY2003

3

Important Safety Information

This section presents contents of revisions, reference materials 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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 215).

1 Sodium Valproate

Brand Name (name of company)	Esdouble Tablets 200 mg (Toyo Pharmar Co., Ltd.) Epirenat Sustained Release Granules 40%, Epirenat Tablets, Epirenat Syrup (Fujinaga Pharm Co., Ltd.) Sanoten Tablets (Tatsumi Kagaku Co., Ltd.) Cebotval Tablets (Kyowa Pharmaceutical Industry Co., Ltd.) Selenica-R Granules, Selenica-R Tab. 200 mg (Nikken Chemicals Co., Ltd.) Cereb Syrup (Ohta Pharmaceutical Co., Ltd.) Depakene Fine Granules 200 and 400, Depakene Tablets 100 and 200, Depakene R Tablets 100 and 200, Depakene Syrup (Kyowa Hakko Kogyo Co., Ltd.) Hyserenin Fine Granules 20, Hyserenin Fine Granules 40%, Hyserenin Tablets 100 and 200 (Nippon Organon K.K.) Valpram R Granules (Kobayashi Pharmaceutical Co., Ltd.) Sodium Valproate Fine Granules 20% "EMEC" (Sannova Co., Ltd.) Valerin Tablets 100 and 200 mg, Valerin Syrup (Dainippon Pharmaceutical Co., Ltd.)
Therapeutic Category	Antiepileptics, psychotropics
Indications	Treatment of various types of epilepsy (petit mal, focal attack, psychomotor seizure, and mixed seizure) and personality and behavior disorders accompanying epilepsy (dysphoria, irascible etc.) Treatment of manias and manic-depressive illness

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]

Since hypersensitivity syndrome may occur, patients should be monitored carefully. If patients present with rash, pyrexia or other initial symptoms which are followed by swollen glands, hepatic function disorder, increased white blood cell count, increased eosinophil count or appearance of atypical lymphocytes, administration should be discontinued, and appropriate measures should be taken. Precautions are required for potential relapse or protraction of symptoms including rash, pyrexia and hepatic function disorder.

Since inappropriate antidiuretic hormone secretion (SIADH) may occur, patients should be carefully monitored. If hyponatraemia, blood hyposmosis, increased urine sodium, hypersthenuria, etc. occur, water restriction or other appropriate measures should be taken.

<Reference Information>

Company report

Number of related adverse reaction reports since the initial marketing (approximately 30 years)

(exclusive of "causality could be denied" and inclusive of "causality is unknown")

- Hypersensitivity syndrome: 10 cases (no fatal case)
- Inappropriate antidiuretic hormone secretion (SIADH): 5 cases (no fatal case)

The number of patients treated with Sodium Valproate for a year estimated by MAH (Marketing Authorisation Holder): approximately 550000 (FY 2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 20s	Bipolar affective disorder [manic depressive illness] (none)	600 mg 17 days ↓ 800 mg 14 days ↓ (no administration for 2 days) ↓ 800 mg 3 days	**Hypersensitivity syndrome** On day 1 of administration: The patient was hospitalized for treatment of bipolar affective disorder. Administration of this drug at 600 mg and lithium carbonate at 600 mg etc. was started. On day 18 of administration: Dosages of this drug and lithium carbonate were respectively increased to 800 mg. On day 30 of administration: Malaise and pyrexia of 37.3°C were confirmed. On day 31 of administration (day of discontinuation): Pyrexia increased to 38°C level, erythaema appeared on the torso, and elevated transaminase, platelets decreased, decreased eosinophils were confirmed. Administration of applied drugs was discontinued. 1 day after discontinuation: Atypical lymphocytes 1.0% were detected. 2 days after discontinuation (on day 1 of readministration): Body temperature did not fall, swollen lymph nodes of cervical and opisthotic, anasarca were confirmed. Atypical lymphocytes were 6.0%. Administration of 800 mg of this drug was started again to treat psychomotor excitability. On day 3 of readministration (day of discontinuation of readministration): Administration of this drug was discontinued again. 1 day after discontinuation of readministration: Atypical lymphocytes were 7.0%. 2 days after discontinuation of readministration: Atypical lymphocytes were 4.0%. 4 days after discontinuation of readministration: IV infusion of betamethasone, glycyrrhizin/glycine/cysteine was started (for 6 days). 10 days after discontinuation of readministration: As general condition worsened, the patient was transferred to another hospital. CPAP (continuous positive airway pressure) was implemented (for 4 days), and the condition gradually improved. Approx. 1 and a half months after discontinuation of readministration: The patient recovered from symptoms. Patch test: this drug (positive), lithium carbonate (negative) DLST: this drug (positive), lithium carbonate (positive) HHV-6 IgG: 2560 times, HHV-6 DNA PCR (+)	Company report
	Concomitant medications: lithium carbonate, chlorpromazine hydrochloride, biperiden hydrochloride, etizolam, non-pyrazolone drug for reducing cold symptoms				

Clinical Laboratory Values

	On day 1 of administration	1 day after discontinuation	1 day after discontinuation of readministration	9 days after discontinuation of readministration	15 days after discontinuation of readministration	Approx. 1 and a half months after discontinuation of readministration:
WBC (/mm^3)	8530	6110	15780	3560	5700	5540
Eosinophils (%)	0.7	6.0	13.0	0.0	--	12.1
Atypical lymphocytes (%)	--	1.0	7.0	1.0	--	--
PLT ($\times 10^4$/mm^3)	31.1	10.4	11.0	19.0	--	26.8
AST (GOT) (IU/L)	18	183	244	39	71	35
ALT (GPT) (IU/L)	17	389	434	102	126	41
LDH (IU/L)	187	459	816	393	--	191

WBC: White Blood Cell
PLT: Platelet
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 80s	Epileptic seizure (diabetes mellitus)	800 mg approx. 3 years and 7 months	**Inappropriate antidiuretic hormone secretion** On day 1 of administration: Administration of this drug to treat absence attacks was started (loss of consciousness). Approx. 4 months after administration: Blood test confirms serum sodium level 129 mEq/L (approx. 1 year before starting administration of this drug, serum sodium was 140 mEq/L), thereafter serum sodium levels were remain low between 126–135 mEq/L. Approx. 3 years and 7 months after administration: The patient was hospitalized for careful examination. Serum sodium 128 mEq/L, plasma osmolality 270 mOsm/kg, urinary osmolality 345 mOsm/kg，urinary sodium 132 mEq/day, antidiuretic hormones 0.5 pg/mL, no dehydration, no oedema. The patient was diagnosed with inappropriate antidiuretic hormone secretion (SIADH) associated with this drug and administration of this drug was discontinued. 49 days after discontinuation: Improvement of antidiuretic hormones 0.7 pg/mL, serum sodium 135 mEq/L.	Company report
	Concomitant medications: gliclazide, difenidol hydrochloride				

Clinical Laboratory Values

	Approx. 1 year before administration	Approx. 4 months after administration	Approx. 2 years 9 months after administration	Approx. 3 years 7 months after administration	49 days after discontinuation
Creatinine (mg/dL)	0.9	0.8	0.9	0.8	0.9
BUN (mg/dL)	17	13	18	16	18
Serum sodium (mEq/L)	140	129	128	128	135
Serum potassium (mEq/L)	3.7	4.1	4.5	4.6	4.3
Serum chloride (mEq/L)	105	96	96	98	103
Plasma osmolality (mOsm/kg)	--	--	264	270	285
Antidiuretic hormones (Vasopresin) (pg/mL)			1.6	0.5	0.7
Urinary sodium (mEq/day)	--	--	--	132	--
Plasma osmolality (mOsm/kg)	--	--	491	345	401

BUN: Blood Urea Nitrogen

2 Pranoprofen (oral dosage form)

Brand Name (name of company)	Iteopan Tab. (Towa Pharmaceutical Co., Ltd.) ELICAPRIC Tablets (Shiono Chemical Co., Ltd.) Cesflan Tablets (Choseido Pharmaceutical Co., Ltd.) Niflan Tablets (Mitsubishi Pharma Corporation), Niflan Syrup (Dojin Iyaku-kako Co., Ltd.) Noipain Capsules (Nichi-iko Pharmaceutical Co., Ltd.) Pranoprofen Solution 1.5% MEEK (Kobayashi Kako Co., Ltd.) Pransus Syrup (Hisamitsu Pharmaceutical Co., Inc.) Prandfen Tablets (Nipro Pharma Corporation) Mabul Capsules (Taisho Pharmaceutical Industries, Ltd.) Rupock Tablets (Toyo Pharmar Co., Ltd.)
Therapeutic Category	Antipyretics and analgesics, anti-inflammatory agents
Indications	(tablets, capsules, solutions) ① Anti-inflammation and pain relief of the following diseases: Chronic rheumatoid arthritis, arthrosis deformans, low back pain, cervico-omo-brachial syndrome, dental periostitis, gouty attack ② Pyretolysis and pain relief for the following diseases: Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanying acute bronchitis) ③ Anti-inflammation and pain relief after injury, minor operation, and odontectomy (syrup) Pyretolysis of the following diseases: Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanying acute bronchitis)

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia, eosinophilic pneumonia:** Interstitial pneumonia and eosinophilic pneumonia may occur. If symptoms of pyrexia, cough, or dyspnoea etc. are observed, administration should be discontinued and examinations such as chest X-ray and blood tests etc. should be performed immediately and appropriate measures such as administration of adrenocortical hormones should be taken.
<Reference Information>	Company report Number of related adverse reaction reports since the initial marketing (approximately 25 years) (exclusive of "causality could be denied" and inclusive of "causality is unknown") • Interstitial pneumonia, eosinophilic pneumonia: 6 cases (no fatal case) The number of patients treated with Pranoprofen for a year estimated by MAH: approximately 1.7 million (April 1, 2004-March 31, 2005)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 50s	Common cold (cervical spondylosis, hyperlipidaemia, hypertension)	225 mg 6 days	**Interstitial lung disease** The patient received treatment for hypertension from 15 years ago, and treatment for cervical spondylosis from approximately 6 months ago. On day 1 of administration: The patient had symptoms of pyrexia, cough, and sputum. She received administration of this drug, ofloxacin during out-patient visit to another hospital (leukocyte count 5400/mm^3). Pyrexia persisted thereafter. On day 6 of administration (day of discontinuation): The patient was diagnosed with pneumonia by chest X-ray (white blood cell count 11450/mm^3). Medication was switched to sulbenicillin sodium injection and tosufloxacin tosilate. 2 days after discontinuation: Fosfomycin sodium was added to regimen. 6 days after discontinuation: Medication was switched to cefotiam hydrochloride and sparfloxacin. The symptoms persisted. 9 days after discontinuation: The patient was examined at this department. After hospitalization, minocycline hydrochloride was administered, and oxygen administration was started. 10 days after discontinuation: Transbronchial lung biopsy performed using bronchoscope confirmed interstitial pneumonia. While drug-induced pneumonia was suspected based on the progress and condition was observed, there was no pyrexia thereafter and the symptoms were gradually improved (white blood cell count 5560/mm^3, LDH 1015 IU/L). 34 days after discontinuation: As DLST test (this drug 203%, ofloxacin 121%) was positive for this drug, the patient was diagnosed with drug-induced pneumonia by this drug. 37 days after discontinuation: WBC and LDH became 4350/mm^3 and 335 IU/L, respectively. 38 days after discontinuation: The patient recovered.	Company report
	Concomitant medications: zaltoprofen, eperisone hydrochloride, diclofenac sodium, cisapride, ofloxacin, alprazolam, pravastatin sodium, methyldopa, pindolol, ranitidine hydrochloride				

Clinical Laboratory Values

	On day 1 of administration	On day 6 of administration (day of discontinuation)	8 days after discontinuation	10 days after discontinuation	37 days after discontinuation
WBC (/mm^3)	5400	11450	6700	5560	4350
LDH (IU/L)	--	--	--	1015	335

WBC: White Blood Cell LDH: Lactate Dehydrogenase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 40s	Upper respiratory inflammation (none)	225 mg 3 days	**Acute eosinophilic pneumonia** On day 1 of administration: This drug etc. was administered by a nearby physician to treat upper respiratory inflammation. On day 3 of administration (day of discontinuation): Pyrexia, cough, and dyspnoea developed. 1 day after discontinuation: The patient was examined by the nearby physician and drug administration was discontinued. 2 days after discontinuation: The patient was admitted to this hospital. At the hospitalization, eosinophils 28%, PaO_2 60 mmHg, chest X-ray: Kerley B line, bilateral pleural effusion. Ceftazidime, minocycline hydrochloride were applied and the patient steadily recovered. Leukocyte migration inhibition test performed later was positive for this drug. Eosinophils increased to 39% with BAL (bronchoalveolar lavage). TBLB (transbronchial lung biopsy) showed eosinophilic infiltration into alveolar space.	Company report
	Concomitant medications: tipepidine hibenzate, cefcapene pivoxil hydrochloride				

Clinical Laboratory Values

	2 days after discontinuation	11 days after discontinuation
Body temperature (°C)	37	
WBC (/mm^3)	8300	5700
Eosinophil fractionation (%)	28	5
CRP (mg/dL)	2.7	--

WBC: White Blood Cell CRP: C-Reactive Protein

3 Hochuekkito

Brand Name (name of company)	OHSUGI Hochuekkito Extract Granules (Takasago Yakugyo Co., Ltd.) Kanebo Hochuekkito Extract Fine Granules (Kanebo, Ltd.) KOTARO Hochuekkito Extract Fine Granules (Kotaro Kampo Seiyaku Co., Ltd.) Sakamoto Hochuekkito Extract Granules (Sakamoto Kampow Pharmaceutical Inc.) Sanwa Hochuekkito Extract Fine Granules (Sanwa Shoyaku Co., Ltd.) JPS Hochuekkito Extract Granules [dispensing] (JPS Seiyaku Co., Ltd.) JUNKOU Hochuekkito Extract Fine Granules for Ethical Use (Kowa Yakutsu Co., Ltd.) Taikodo no Hochuekkito Extract Granules, Hochuekkito Extract Powder (Taikoseido Seiyaku Co., Ltd.) TSUMURA Hochuekkito Extract Granules for Ethical Use (Tsumura & Co.) TEIKOKU Hochuekkito Extract Granules (Teikoku Kampo Seiyaku Co., Ltd.) TOYO Hochuekkito Extract Granula Subtilae (Toyo-yakuko Corporation) Hochuekkito Extract Granules T (TOA Pharmaceuticals Co., Ltd.) Honomi Hochuekkito N Extract Granules (Zaiseido Yakuhin Co., Ltd.) Honzo Hochuekkito Extract Granules–M (Honzo Co., Ltd.)
Therapeutic Category	Kampo medicines
Indications	**KOTARO Hochuekkito Extract Fine Granules** Decreased gastrointestinal function accompanied by fatigue and malaise, or accompanied by headache, chills, night sweat, atonic haemorrhage etc. Tuberculous disease and increased stamina after illness, gasterasthenia,

	anaemia, summer emaciation, delicate constitution, hypotension, scrofulosis, haemorrhoids, anal prolapse. **Sanwa Hochuekkito Extract Fine Granules** The following symptoms/conditions of patients having poor stamina and slightly anaemic, decreased gastrointestinal function, fatigue and malaise, anorexia, and night sweat: Debility after illness or after operation, increased stamina in chest disease, anaemia, hypotension, summer emaciation, gasterasthenia, decreased gastrointestinal function, hyperidrosis **TSUMURA Hochuekkito Extract Granules for Ethical Use** The following symptoms/conditions of patients having delicate constitution, reduced digestive functions, and severe fatigability of limbs: Summer emaciation, reinforcement of physical strength after illness, tuberculosis, anorexia, gastroptosis, cold, hemorrhoid, anal prolapse, uterine prolapse, impotence, hemiplegia, and hyperidrosis **Others** The following symptoms/conditions of patients having lack of vigor, decreased gastrointestinal function, and easily fatigued: Delicate constitution, fatigue and malaise, debility after illness, anorexia, night sweat

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia:** If pyrexia, cough, dyspnoea, abnormal chest sound (crepitations) etc. occur, administration should be discontinued. Immediately perform a chest X-ray and undergo examinations, and appropriate measures such as administration of an adrenocortical hormone preparation should be taken. Patient should be instructed to discontinue administration and immediately contact a physician if pyrexia, cough, and dyspnoea, etc. occur..
<Reference Information>	Company report Number of related adverse reaction reports since the initial marketing (approximately 21 years) (exclusive of "causality could be denied" and inclusive of "causality is unknown") • Interstitial pneumonia: 5 cases (1 fatal case) The number of patients treated with Hochuekkito for a year: approximately 140000 (FY 2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 80s	Anorexia (asthma bronchial, osteoporosis)	7.5 g 170 days	**Interstitial pneumonia** On day 1 of administration: Administration of this drug for anorexia was started. In the 5th month of administration: The patient experienced shortness of breath during exertion. On day 169 of administration: Cyanosis of the hands and fingers developed. On day 170 of administration (day of discontinuation): Administration of this drug was discontinued. 1 day after discontinuation**:** The patient was examined by nearby physician. Blood gas PaO_2 35.5 (room air), $PaCO_2$ 42.3 (room air). Prominent interstitial shadow in both lung fields was observed by chest X-ray, and the patient was referred and hospitalized in this hospital on the same day. Chest X-ray and CT scan taken at the time of hospitalization revealed preponderance of ground-glass, reticular shadow of the bilateral upper lobes. Drug-induced, mycoplasma, or opportunistic infection was initially suspected. Meropenem trihydrate 0.5 g × 2 and minocycline hydrochloride 100 mg × 2 (10 days), and methylprednisolone sodium succinate 1000 mg (3 days) pulse therapy was started. 4 days after discontinuation: As improvement in blood gas and chest X-ray was not confirmed, 500 mg of cyclophosphamide was administered. Thereafter, 100 mg of cyclophosphamide was administered 6, 8, and 10 days after discontinuation. 6 days after discontinuation: Body temperature gradually increased (pyrexia). WBC count increased daily. 9 days after discontinuation: As there was consciousness clouding, pyrexia at 38°C level, blood pressure decreased to 80–100/50–60 mmHg, sepsis was suspected. No improvement in the interstitial shadow was observed in chest X-ray. 10 days after discontinuation: Consciousness level was III-300, respiration was significantly worsened. 11 days after discontinuation: The patient died.	Company report
	Concomitant medications: theophylline, bifidus preparation, sucralfate, menatetrenone, magnesium oxide, calcium lactate, alfacalcidol				

Clinical Laboratory Values

	1 day after discontinuation	6 days after discontinuation	9 days after discontinuation	10 days after discontinuation
WBC (/mm^3)	10100	14400	16400	27100
LDH (IU/L)	560	638	--	939
CRP (mg/dL)	5.48	3.84	13.31	14.23

WBC: White Blood Cell CRP: C-Reactive Protein
LDH: Lactate Dehydrogenase

Blood gas (0_2 10 L/minute)

	1 day after discontinuation	6 days after discontinuation	9 days after discontinuation	10 days after discontinuation
pH	7.498	7.442	7.221	7.127
PaO_2 (torr)	92.9	84.1	68.2	60.9
$PaCO_2$ (torr)	44.4	52.8	69.8	91.0

PaO_2: Partial Pressure Arterial Oxygen $PaCO_2$: Partial Pressure of Carbon Dioxide in Artery

Immune serum test

	2 days after discontinuation
RA test	negative
Antinuclear antibodies	negative
Anti-DNA antibodies	negative
Immune complex (μEq/mL)	<1.5
Complement CH_{50} (CH_{50} units)	32.7

RA: Rheumatoid Arthritis

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 80s	Constipation (hypertension, neurogenic bladder, cerebrovascular dementia, cerebral infarction)	7.5g 1119 days	**Interstitial pneumonia** On day 1 of administration: Administration of this drug for constipation was started. On day 933 of administration: The patient experienced mild shortness of breath (not experienced at time of initial examination). On day 1085 of administration: Malaise, breathing difficulty, anorexia was indicated. On day 1098 of administration: The patient received out-patient examination because of pyrexia, epigastric pain, and breathing difficulty were aggravated. Sputum expectoration and cough was both (–). Chest X-ray revealed mild interstitial shadow around both lung fields, accumulation of pleural effusion. Pleural changes were (+). Although IV infusion of antibiotics was given, there was unclear aggravation in symptoms (CRP 30.0 mg/dL). Although symptoms slightly improve with drip infusion of hydrocortisone sodium succinate, the patient did not completely recover. On day 1119 of administration (day of discontinuation): Administration of this drug was discontinued. 2 days after discontinuation: Medication was changed to methylprednisolone sodium succinate and pulse therapy was conducted. CRP and symptoms improved. 5 days after discontinuation: Pyrexia resolved, shortness of breath showed improvement tendency.	Company report
	Concomitant medications: ticlopidine hydrochloride, nisoldipine, imipramine hydrochloride, tamsulosin hydrochloride, fluvastatin sodium, furosemide				

Clinical Laboratory Values

	On day 1098 of administration	On day 1111 of administration	2 days after discontinuation	7 days after discontinuation
WBC (/mm^3)	11500	13400	9000	11700
Eosinophils (%)	1	1	0	1
LDH (IU/L)	511	395	315	372
CRP (mg/dL)	30.0	28.0	6.1	2.4

WBC: White Blood Cell CRP: C-Reactive Protein
LDH: Lactate Dehydrogenase

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Revision of PRECAUTIONS

(No. 168)

This section presents details of revisions to PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 215) (excluding those presented in "3. Important Safety Information" of this Bulletin), together with reference materials.

1 <Antiepileptics, psychotropics> Carbamazepine

[Brand Name] Tegretol Fine Granules 50%, Tegretol Tablets 100 mg and 200 mg (Novartis Pharma K.K.), and others

[Adverse Reactions (clinically significant adverse reactions)]

Aplastic anaemia, pancytopenia, white blood cell decreased, agranulocytosis, haemolytic anaemia, aplasia pure red cell, platelets decreased: Serious blood disorder may occur. Patients should be carefully monitored through periodic haematologic examinations, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Hypersensitivity syndrome: Initial symptoms of pyrexia and rash, followed by serious delayed symptoms of hypersensitivity accompanied by organ disorders such as swollen lymph nodes, arthralgia, white blood cell increased, pulmonary eosinophilia, appearance of atypical lymphocytes, splenohepatomegalia, and hepatic function disorder may occur. In addition, as recurrence or prolongation of rash, pyrexia, and hepatic function disorder etc. may occur, patients should be carefully monitored for these signs. Symptoms often accompanied by virus reactivation such as human herpes virus type 6 (HHV-6). If such symptoms are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

2 <Antispasmodics> Tizanidine Hydrochloride

[Brand Name] Ternelin Granules 0.2%, Ternelin Tablets 1 mg (Novartis Pharma K.K.), and others

[Contraindications] Patients receiving fluvoxamine or ciprofloxacin

[Interactions (precautions for concomitant use)] Fluvoxamine, ciprofloxacin

<Reference Information> Company report

3 <Hyperlipidaemia agents> Colestimide

[Brand Name] Cholebine Granules 70%, Cholebine Mini 83%, Cholebine 500 mg Tablets (Mitsubishi Pharma Corporation)

[Careful Administration] Elderly or patients with swallowing difficult

[Important Precautions] Patients should be instructed to take this product with careful attention to the following, since it was reported that this product was accidentally sucked into the airway, where it became swollen, resulting in dyspnoea.

1) Instruct patients to take this product with a sufficient amount of water (about 200 mL). Also instruct patients to take more water if it remains in the back of the throat.

2)Instruct patients to take this product with water at room temperature or cold water because this product may become swollen if it is taken with warm water (hot water, warm tea, etc.) and it may become difficult or impossible to swallow it.

3)Instruct patients to swallow this product promptly because this product may become swollen if it is kept in the mouth for a long time and it may become difficult or impossible to swallow it.

4)Instruct patients to take tablets one-by-one at a time.

<Reference Information> Company report

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

[Brand Name] Anderm Ointment, Anderm Cream (Teikoku Seiyaku Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Contact dermatitis:** Dermatological symptoms such as itching, redness/erythaema, swelling, oedema, and blisters/erosion etc. may occur in the site of application and may affect the whole body and become serious. If any abnormalities are observed, administration should be discontinued immediately and appropriate measures should be taken.

<Reference Information> Company report

5 <Hemostatics> Polidocanol

[Brand Name] Aethoxysklerol 1% Injection (Sakai Chemical Industry Co., Ltd.)

[Important Precautions] Administration of this drug may cause esophageal haematom. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures should be taken.

<Reference Information> Company report

6 <Antidiabetic agents> Metformin Hydrochloride

[Brand Name] Glycoran Tablets (Nippon Shinyaku Co., Ltd.), Melbin Tablets (Sumitomo Pharmaceuticals Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder, jaundice:** Hepatic function disorder with significant elevations of AST (GOT), ALT (GPT), Al-P, γ-GTP levels, and bilirubin levels etc. and jaundice may occur. Patients should be carefully monitored and if any any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

7 <Kampo medicines> Shoseiryuto

[Brand Name] Kanebo Shoseiryuto Extract Fine Granules (Kanebo, Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Interstitial pneumonia:** If pyrexia, cough, dyspnoea, abnormal chest sound (crepitations) etc. occur, administration should be discontinued. Immediately perform a chest X-ray and undergo examinations, and appropriate measures such as administration of an adrenocortical hormone preparation should be taken. Patient should be instructed to discontinue administration and immediately contact a physician if pyrexia, cough, and dyspnoea, etc. occur..

<Reference Information> Company report

8 <Synthetic antibacterials> Ciprofloxacin, Ciprofloxacin Hydrochloride

[Brand Name] Ciproxan-I.V. 200 mg and 300 mg, Ciproxan Tablets 100 mg and 200 mg (Bayer Yakuhin, Ltd.), and others

[Contraindications] Patients receiving tizanidine hydrochloride

[Interactions (contraindications for concomitant use)] Tizanidine hydrochloride

<Reference Information> Company report

9 <Antivirals> Oseltamivir Phosphate

[Brand Name] Tamiflu Capsules 75, Tamiflu Dry Syrup 3% (Chugai Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Hemorrhagic colitis**: Hemorrhagic colitis may occur. If any abnormalities such as bloody stool, bloody diarrhea, etc., are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

10 <Miscellaneous non-main therapeutic purpose agents> Nicotine

[Brand Name] Nicotinell TTS 30, 20, and 10 (Novartis Pharma K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Anaphylactoid reactions:** Anaphylactoid reactions accompanied by general symptoms such as hypotension, tachycardia, dyspnoea, urticaria, angioedema etc. may occur. In such cases, appropriate measures such as drug discontinuation should be taken.

<Reference Information> Company report

11 Over the counter drugs
Bufexamac-containing Preparations

[Brand Name] Makkukaramira Cream (Fukuchi Pharmaceutical Co., Ltd.), Romana Cream (Toko Pharmaceutical Industrial Co., Ltd.)

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.

If the following symptoms are observed after taking this drug.

In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.

Contact dermatitis: Rash/redness, itching, swelling, rash etc. may occur on the application site and spread over the entire body and become serious.

<Reference Information> Company report

12 Over the counter drugs
Shoseiryuto

[Brand Name] TSUMURA Kampo Shoseiryuto Extract Granules, and others

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.

If the following symptoms are observed after taking this drug

In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.

Interstitial pneumonia: Shortness of breath, dyspnoea, pyrexia accompanying cough may occur.

<Reference Information> Company report

13 Over the counter drugs
Hochuekkito

[Brand Name] TSUMURA Kampo Hochuekkito Extract Granules, and others

[Counseling] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.

If the following symptoms are observed after taking this drug

In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.

Interstitial pneumonia: Shortness of breath, dyspnoea, pyrexia accompanying cough may occur.

<Reference Information> Company report

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List of products subject to Early Post-marketing Phase Vigilance

(As of August 1, 2005)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Pralmorelin Hydrochloride / Ghrp Kaken 100 for Injection	Kaken Pharmaceutical Co., Ltd.	February 25, 2005
Aluminum Potassium Sulfate/Tannic Acid / Zione Injection/Lidocaine, Zione Injection	Mitsubishi Pharma Corporation	March 15, 2005
Epinastine Hydrochloride / Alesion Dry Syrup 1%	Nippon Boehringer Ingelheim Co., Ltd.	March 23, 2005
Etanercept (Genetical recombination) / Enbrel 25 mg for s.c. Injection	Wyeth K.K.	March 30, 2005
Oxaliplatin / Elplat for Injection 100 mg	Yakult Honsha Co., Ltd.	April 6, 2005
Tacrolimus Hydrate / Prograf Capsules 0.5 mg and 1 mg*[1]	Astellas Pharma Inc.	April 11, 2005
Emtricitabine / Emtriva Capsules 200 mg	Japan Tobacco Inc.	April 19, 2005
Emtricitabine/Tenofovir Disoproxil Fumarate / Truvada Tablets	Japan Tobacco Inc.	April 19, 2005
Rosuvastatin Calcium / Crestor Tablets 2.5 mg and 5 mg	AstraZeneca K.K.	April 27, 2005
Bosentan Hydrate / Tracleer Tablets 62.5 mg	Actelion Pharmaceuticals Japan Ltd.	June 10, 2005
Tamibarotene / Amnolake Tablets 2 mg	Toko Pharmaceutical Industrial Co., Ltd.	June 13, 2005
Tocilizumab (Genetical recombination) / Actemra for Intravenous Infusion 200	Chugai Pharmaceutical Co., Ltd.	June 13, 2005
Adenosine / Adenoscan Injection 60 mg	Daiichi Suntory Pharma Co., Ltd.	June 21, 2005
Voriconazole / Vfend Tablets 50 mg and 200 mg, Vfend 200 mg IV for Intravenous Use	Pfizer Japan Inc.	June 27, 2005
Luliconazole / Lulicon Cream 1%, Lulicon Solution 1%	Pola Chemical Industries, Inc.	July 20, 2005

Note) Subject to additional indication etc.

*1: An additional indication for "Rheumatoid arthritis (only for cases which are not adequately responsive to conventional therapies"