# Pharmaceuticals and Medical Devices Safety Information

## No. 205 September 2004

### Table of Contents



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


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

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

**Translated by**
**Pharmaceuticals and Medical Devices Agency**

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


*This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).*

# Pharmaceuticals and Medical Devices Safety Information

## No. 205 September 2004

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

## [Outline of Information]

| No. | Subject | Measures | Outline of information | Page |
|---|---|---|---|---|
| 1 | **Reports on adverse reactions associated with influenza vaccines in FY2003** | | This section represents a summary of the reporting status etc. and safety measures for adverse reactions associated with the influenza vaccines in FY2003.<br>Estimated number of shipments of the influenza vaccines in FY2003 was approximately 14.63 million. Reported adverse reactions associated with the influenza vaccination in accordance with the Pharmaceutical Affairs Law were 162 cases and 259 events (26 events of injection site redness/swelling, etc., 18 events of pyrexia, 14 events of shock/anaphylactoid symptoms, 12 events of hepatic function disorder, 12 events of rash, etc., 9 events of loss of consciousness, etc., 7 events of arthralgia, 7 events of myalgia, 7 events of Guillain-Barre syndrome, 7 events of convulsion, 6 events of asthma, and 5 events of diarrhoea, etc.). | 3 |
| 2 | **Post-marketing safety measures for ticlopidine hydrochloride products and Cypher Stent** | | As for the safety measures for ticlopidine hydrochloride, MHLW has called for the proper use of ticlopidine hydrochloride in Pharmaceuticals Safety Information No. 156 (August 1999 edition) and ”Dear Healthcare Professional Letters” (June 30, 1999, July 23, 2002). In light of the approval of Cypher Stent, MHLW has notified related companies to ensure the proper use, and has asked prefectural and city governments, related academic society and organizations for corporation and dissemination of the information as a measure of safety for coronary stent treatment using this stent. This section presents the content of notice to alert healthcare professionals. | 8 |
| 3 | **Tacrolimus Hydrate (oral dosage form, injectable dosage form)** | *P*<br>*C* | 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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 204), together with reference materials. | 11 |
| 4 | **Sevoflurane (and 14 others)** | | Revision of PRECAUTIONS (No. 159) | 17 |

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

# 1

# Reports on adverse reactions associated with influenza vaccines in FY2003

## (1) Introduction

Influenza is classified into Category II Diseases according to the amendments of the Preventive Vaccination Law in 2001.

Category II Diseases places emphasis on prevention for the individual. As immunization for these diseases is mainly conducted for personal preventive purposes, as opposed to being a duty or obligation, vaccinations are given only when an individual chooses to receive one.

According to the Preventive Vaccinations Law, candidates for routine influenza vaccination are those who are aged 65 and older, and aged 60 and older and under aged of 65, who possess cardiac, renal, or respiratory dysfunction, and those who possess immune dysfunction due to human immunodeficiency virus (HIV).

The efficacy of the current influenza HA vaccination is recognized internationally. Its efficacy in preventing the disease in the elderly and particularly in preventing aggravation of the disease has been confirmed in Japan.

Known adverse reactions of the influenza vaccination include injection site redness, swelling, and pain, as well as systemic symptoms of pyrexia, chill, headache, general malaise, and vomiting. Normally, symptoms disappear within 2 to 3 days after vaccination. As well, rash, urticaria, erythema, and pruritus are also known to occur immediately or within a few days after vaccination. Shock, acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome, convulsion, hepatic function disorder/jaundice, and asthmatic attack are reported as serious adverse reactions.

This section represents a summary of the reporting status and safety measures on adverse reactions associater with the influenza vaccines in FY 2003.

## (2) Report, etc. on adverse reactions associated with influenza vaccines in FY2003

Estimated amount of shipments of the influenza vaccines in FY2003 was approximately 14.63 million vials. Marketing authorisation holders or healthcare providers etc. reported 162 cases and 259 events, including those for which causality with the pharmaceutical is unknown, as adverse reactions associated with the influenza vaccination in accordance with Article 77-4-2 of the Pharmaceutical Affairs Law.

Major reported adverse reactions consisted of 26 events of injection site redness/swelling, etc., 18 events of pyrexia, 14 events of shock/anaphylactoid symptoms, 12 events of hepatic function disorder, 12 events of rash, etc., 9 events of loss of consciousness, etc., 7 events of arthralgia, 7 events of myalgia, 7 events of Guillain-Barre syndrome, 7 events of convulsion, 6 events of asthma, 5 events of diarrhoea, 4 events of ADEM, 3 events of platelets decreased, 2 events of acute renal failure/nephrosis.

**Table 1** indicates the number of reported adverse reactions associated with influenza vaccination by outcome and according to age. The results of a review of the influenza vaccination by a committee consisting of specialists in infectious disease and viruses (hereafter, "vaccine adverse reaction review committee") showed that, among cases of death and sequelae, there were no cases strongly suspected to have been affected by the influenza vaccination. As for the review results, **Tables 2 and 3** respectively show cases of death and sequelae.

Aside from reports on adverse reactions based on the Pharmaceutical Affairs Law, a Vaccine Adverse Reaction Reporting System was established in accordance with amendments to the Preventive Vaccination Law in 1994. For reference, **Table 4** shows the number of events of reported adverse

reactions associated with the influenza vaccination (including events of uncertain causality) in FY 2003 reported through this system. This is intended based on Immunization Practices (November 7, 2001, No.1058, notification issued by the Director General of the Health Service Bureau of Ministry of Health, Labour and Welfare) for collecting the information of change in health conditions of the individuals in the form of periodic vaccinations in accordance with the Preventive Vaccinations Law, and providing the public a broad range of information,. Individuals targeted for reporting of adverse reactions from influenza vaccination according to the aforementioned system are those subject to routine vaccination, and differ from individuals targeted for reporting in reports on adverse reactions.

**Table 1 The number of reported adverse reaction cases associated with influenza vaccines based on the Pharmaceutical Affairs Law in FY2003**

| Age group | Total | | Recovery/ Remission | | Unrecovered | | Unknown | | Sequelae | | Death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| | 162 | | 119 | | 20 | | 11 | | 5 | | 7 | |
| | 74 | 88 | 50 | 69 | 10 | 10 | 6 | 5 | 2 | 3 | 6 | 1 |
| Under age of 10 | 35 | | 27 | | 6 | | 2 | | | | | |
| | 24 | 11 | 19 | 8 | 3 | 3 | 2 | 0 | | | | |
| 10s | 24 | | 20 | | 2 | | 2 | | | | | |
| | 10 | 14 | 7 | 13 | 2 | 0 | 1 | 1 | | | | |
| 20s | 5 | | 4 | | 1 | | | | | | | |
| | 1 | 4 | 1 | 3 | 0 | 1 | | | | | | |
| 30s | 12 | | 8 | | 1 | | 2 | | 1 | | | |
| | 4 | 8 | 3 | 5 | 0 | 1 | 1 | 1 | 0 | 1 | | |
| 40s | 15 | | 12 | | 1 | | 2 | | | | | |
| | 7 | 8 | 5 | 7 | 0 | 1 | 2 | 0 | | | | |
| 50s | 10 | | 7 | | 1 | | 1 | | | | 1 | |
| | 4 | 6 | 2 | 5 | 1 | 0 | 0 | 1 | | | 1 | 0 |
| 60s | 21 | | 14 | | 1 | | 2 | | 2 | | 2 | |
| | 8 | 13 | 4 | 10 | 1 | 0 | 0 | 2 | 1 | 1 | 2 | 0 |
| 70s | 19 | | 16 | | 1 | | | | 1 | | 1 | |
| | 7 | 12 | 5 | 11 | 0 | 1 | | | 1 | 0 | 1 | 0 |
| 80s | 17 | | 9 | | 5 | | | | 1 | | 2 | |
| | 7 | 10 | 4 | 5 | 2 | 3 | | | 0 | 1 | 1 | 1 |
| 90s | 3 | | 2 | | | | | | | | 1 | |
| | 1 | 2 | 0 | 2 | | | | | | | 1 | 0 |
| Unknown | 1 | | | | 1 | | | | | | | |
| | 1 | 0 | | | 1 | 0 | | | | | | |

**Table 2 Cases of death associated with influenza vaccination in FY2003**

| No. | Case summary of adverse reactions | Evaluation by experts |
|---|---|---|
| 1 | Male in 60s<br>Name of adverse reaction: bronchopneumonia, hepatic function abnormal<br>The patient had medical histories of interstitial lung disease and spinocerebellar disorder, in addition to a medical history of decreased respiratory function due to influenza infection. The patient fell cardiopulmonary arrest 6 days after the influenza vaccination and died while being transported by the ambulance. | Although the patient had a medical history of decreased respiratory function due to influenza infection, there is little possibility the vaccine would act as allergens even for an individual who had developed pneumonia due to influenza infection in the past. It might involve some kind of another infection since the CRP was high. Although death due to pneumonia was considered, there are no observations made actively suggesting the causality between influenza vaccine and the event based on |

| | | |
|---|---|---|
| | | the data available. |
| 2 | Male in 60s<br>Name of adverse reaction: pyrexia, acute cardiac failure<br>The patient was receiving haemodialysis (HD) due to chronic renal failure. The patient developed pyrexia with white blood cell count decreased 4 days after the vaccination. The patient died of respiratory and cardiac arrest the next day. | Pyrexia caused by the vaccination generally occurs within 1 to 2 days after the vaccination. In view of the value of CRP, it is considered that pyrexia occurred 4 days after the vaccination was caused by other factors. Possibility of infection by vaccination is excluded since influenza vaccine is an inactivated vaccine. It is also possible that the patient was complicated by infections for some reasons due to compromised immune function by the HD. It is more appropriate to assume that the cause of death was aggravation of the original disease or multi-organ failure due to infection unrelated from the vaccine and that causality with the influenza vaccine was unlikely. |
| 3 | Female in 80s<br>Name of adverse reaction: dyspnoea<br>The patient had underlying diseases of diabetes mellitus and hypertension. The patient experienced dyspnoea during sleeping 3 days after the vaccination and was transported by the ambulance. She fell cardiac arrest and died in spite of the intratracheal intubation. | Dyspnoea and cardiac arrest developed 3 days after the vaccination in this case. The possibility of shock or allergic reaction is unlikely since symptoms generally occur within the same day or 24 hours after the vaccination when caused by vaccine. In addition, serum creatinine level on the day of vaccination was high, which might suggest a renal failure-like state for some reasons. This may be considered to result in cardiac arrest. The causality with influenza vaccine is unlikely. |
| 4 | Male in 70s<br>Name of adverse reaction: death<br>The patient went near drowning in the bath 13 hours after the vaccination. Although the patient was transported by the ambulance, he died. The course of the event between the time of the vaccination and the near drowning remains unknown. | The time that elapsed after the vaccination was too long for shock or convulsion due to the vaccine. The causality between influenza vaccine and the event is unlikely although there are not enough data available to evaluate sufficiently. |
| 5 | Male in 80s<br>Name of adverse reaction: death<br>The patient had underlying diseases of cerebrovascular disorder. He failed to respond when his family member visited to wake him up 2 hours after the vaccination. The patient died in spite of the cardiac massage given by emergency home visit. | The causality with the vaccination cannot be denied due to the temporal relationship between the vaccination and the event. There is also a possibility that cerebrovascular disorder, the underlying disease, relapsed. Nevertheless, determination of cause of death is difficult since dissection was not performed. |
| 6 | Male in 90s<br>Name of adverse reaction: acute myocardial infarction<br>The patient had underlying diseases of large intestine carcinoma, anaemia, and cardiac disorder. The patient went an excited state and failed to remain sitting or standing position 9 hours after the vaccination and was transported by the ambulance. He was diagnosed with acute myocardial infarction and the condition was gradually aggravated. The patient died 15 hours after the vaccination. | The causality with the vaccination cannot be denied due to the temporal relationship between the vaccination and the death. However, as the patient was at an advanced age and had various kinds of serious underlying diseases, any evidence of adverse reactions cannot be detected. Therefore, it is difficult to determine the causality. |
| 7 | Male in 50s<br>Name of adverse reaction: pyrexia<br>The patient developed pyrexia 2 days after the vaccination. 23 days after the vaccination, he developed pneumonia and died of multi-organ failure. | The information is extremely limited and lacks grounds for assessment. It is impossible to assess the causality. |

**Table 3 Cases of sequelae associated with influenza vaccination in FY2003**

| No. | Case summary of adverse reactions | Evaluation by experts |
|---|---|---|
| 1 | Male in 70s<br>Name of adverse reaction: hemiplegia, dyslalia, convulsion, depressed level of consciousness<br>The patient developed left hemiplegia, dyslalia, and convulsion 16 days after the vaccination. On the following day, depressed level of consciousness progressed. The patient was diagnosed with encephalitis viral by MRI. | Although the patient was diagnosed with encephalitis viral based on pathological lesion in right temporal lobe found by MRI, it is unlikely that inactivated influenza vaccine would cause the encephalitis viral. The causality with influenza vaccination cannot be assessed due to lack of detailed information. |
| 2 | Female in 30s<br>Name of adverse reaction: myelitis transverse<br>The patient had medical histories of nasopharyngitis and asthma. She developed cough and pyrexia prior to the vaccination. The patient was taking amoxicillin, carbocisteine, d-chlorpheniramine maleate, and acetaminophen at the time of the vaccination. She developed urinary retention 4 days after the vaccination. Urinary retention was not improved and sensory disturbance occurred on the following day. The patient was diagnosed with acute disseminated encephalomyelitis (ADEM) by cerebrospinal fluid test and MRI. | It is considered that the symptoms occurred due to the underlying viral infection since the patient was vaccinated under poor health condition with symptoms of common cold present. However, ADEM is known as an adverse reaction of influenza vaccine, therefore, the causality cannot be denied. |
| 3 | Female in 80s<br>Name of adverse reaction: injection site pain<br>The patient had underlying diseases of hypertension and iron deficiency anaemia. The patient complained of pain on the injection site during movement and became unable to lift her arm 2 days after the vaccination. Although the pain was alleviated with fomentation, etc., it persisted after 5 months. | The causality between the vaccination and injection site pain cannot be denied because it was pain on the injection site. However, lack of objective information makes the assessment for the causality difficult. |
| 4 | Male in 60s<br>Name of adverse reaction: sick sinus syndrome<br>The patient experienced malaise from the day after the vaccination. 4 days after the vaccination, chest discomfort, pain, loss of consciousness, respiratory arrest, and cardiac arrest developed. The patient was diagnosed with sick sinus syndrome. | Malaise after the vaccination is a common adverse reaction. Electrocardiogram is required for accurate diagnoses of myocarditis. Although it is considered that sick sinus syndrome was associated with ischemic myocardial disorder in this case, causality between the vaccine and the event cannot be completely denied. |
| 5 | Female in 60s<br>Name of adverse reaction: leukoencephalomyelitis, depressed level of consciousness<br>The patient had underlying diseases of encephalopathy, Sjogren's syndrome, essential hypertension, and arrhythmia. She developed headache, bradykinesia, and hyporexia 16 days after the vaccination. The patient developed pyrexia, vomiting, and drowsiness and was transported by the ambulance. After consciousness disturbed persisted for several days, the patient recovered gradually. There were no findings of ADEM by MRI. | The interpretations of MRI findings of ADEM differ between the vaccinator and the consulting specialist. However, the possibility of adverse reaction of influenza vaccine cannot be denied if ADEM is confirmed. The causality remains unknown due to lack of information at this point. |

## (3) Safety measures for influenza vaccine

Vaccine adverse reaction review committee was conducted to assess the need to revise the package insert, etc. with regard to platelets decreased, acute renal failure/nephrosis, consciousness disturbed, diarrhoea, arthralgia, and myalgia, etc., reported as unknown adverse reactions.

As a result of the evaluation of each case including the cases collected prior to FY2002, despite the fact that the causality with the influenza vaccine cannot be denied for all the adverse reactions, the data

are not sufficient to state as adverse reactions under the section “Clinically Significant Adverse Reactions”, however, collection of the information will be continued.

**Table 4 Report on adverse reactions of influenza vaccines in FY2003 based on Immunization Practices**

| | Total | Recovery | Death | Serious | Hospitaliza-tion | Sequelae | Others | N/A |
|---|---|---|---|---|---|---|---|---|
| | 34 | 1 | 1 | | 8 | 1 | 17 | 6 |
| 1 Immediate systemic reaction | 5 | | | | 1 | | 4 | |
| 1A. Anaphylaxis | 3 | | | | 1 | | 2 | |
| 1B. General urticaria | 2 | | | | | | 2 | |
| 2 Encephalitis, encephalopathy | 1 | | 1 | | | | | |
| 3 Convulsion | | | | | | | | |
| 4 Movement disorder | | | | | | | | |
| 5 Other nerve disorders | 6 | | | | 4 | | 2 | |
| 6 Local abnormal swelling (over elbows) | | | | | | | | |
| 7 Rash generalized | 5 | | | | | | 3 | 2 |
| 8 Pyrexia of 39°C and higher | 1 | | | | | | 1 | |
| 9 Other abnormal reactions | 4 | 1 | | | 1 | | 1 | 1 |
| 10 Nonstandard reports | 12 | | | | 2 | 1 | 6 | 3 |
| 10A. Local reaction (redness and swelling, etc.) | 7 | | | | 1 | 1 | 3 | 2 |
| 10B. Systematic reaction (pyrexia, etc.) | 2 | | | | 1 | | 1 | |
| 10C. Others | 3 | | | | | | 2 | 1 |

# 2

# Post-marketing safety measures for ticlopidine hydrochloride products and Cypher Stent

As for the safety measures for ticlopidine hydrochloride, MHLW has called for the proper use of ticlopidine hydrochloride in Pharmaceuticals Safety Information No. 156 (August 1999 edition) and "Dear Healthcare Professional Letters" (June 30, 1999, July 23, 2002). In light of the approval of Cypher Stent, MHLW has called for reminding healthcare providers of the further alert.

As for proper use of ticlopidine hydrochloride products and Cypher Stent, MHLW has notified related companies to ensure the proper use, and have asked prefectural and city governments, related academic society and organizations for corporation and dissemination of the information as a measure of safety for coronary stent treatment using this stent under PFSB/ELD Notification No. 0730001-0730005, PFSB/SD Notification No. 0730001-0730005, and PFSB/GAD No. 0730001 dated July 30, 2004. This section presents the content of notice to alert healthcare professionals.

## (1) Outline

Drug-eluting coronary stent, "Cypher Stent," (approval No. 21600BZY00136) was approved in March, 2004. It is the first drug-eluting coronary stent in Japan and has the following features in comparison to conventional coronary stents.

① Pharmacological effect of the medically coated surface of the coronary stent reduces the coronary restenosis.

② It enables the stent treatment in small-sized veins (2.5 mm class).

Antiplatelet therapy is required for stent treatment. The standard period of time of the antiplatelet therapy for Cypher Stent is set to 3 months, which is longer than that of conventional coronary stent treatment (approximately 1 month) based on the data obtained from the clinical studies submitted for the application. For the antiplatelet treatment, ticlopidine hydrochloride products are recommended.

MHLW has been requesting healthcare providers, etc. to ensure the proper use for the prevention of serious adverse reactions such as thrombotic thrombocytopenic purpura (TTP) and agranulocytosis that may be caused by ticlopidine hydrochloride products. In response to marketing of the stent, MHLW is also notifying the related companies to ensure the proper use and is asking the prefectural and city governments, related academic society, and organizations for the cooperation and dissemination of information to promote the proper use.

## (2) Requests for proper use of ticlopidine hydrochloride products and Cypher Stent

For the prevention of clinically significant adverse reactions such as thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder due to ticlopidine hydrochloride products, following cautionary statements are included in "WARNING" section of the package insert of Cypher Stent. MHLW would like to request proper use of ticlopidine hydrochloride products and the stent with regard to the aforementioned points.

**<Warning>**

① This product should be used by physicians who are well-experienced in coronary angiography (CAG), PTCA, intracoronary stenting, and antiplatelet therapy and have taken the required trainings for the product.

② Long-term prognosis for the period exceeding 1 year after the stent placement has not been sufficiently observed at this point. Compared to non-drug coated bare metal stents, the Cypher Stent requires a longer administration period of ticlopidine hydrochloride products as antiplatelet therapy following the stent placement. Use of this stent with ticlopidine hydrochloride products increases risks of haemorrhage and serious adverse reactions. Therefore, physicians should be encouraged to carefully select appropriate patients before using this stent by balancing risks and benefits for each patient. In the selection of patients, the location of the target lesion (blood vessel), reference vessel diameter, lesion length and its characteristics, and the size of the myocardial area exposed to the risk of acute or subacute thrombosis should be considered.

③ Before use of the Cypher Stent, physicians should adequately advise the patients of the risks associated with the antiplatelet therapy following the stent placement as well as the characteristics of the stent (risks and benefits) and ensure that the patient is fully aware of the information given before using. Physicians should adequately instruct the patients to contact the physician if ischemic symptoms such as chest pain appear after the stent placement. In particular, physicians should inform the patient of the possible occurrence of life-threatening serious adverse reactions associated with the administration of ticlopidine hydrochloride products, and give the following instructions.

a) In principle, the patient should consult a physician once every 2 weeks since periodical blood test is required for the first 2 months after the initiation of administration.

b) The patient should contact a physician, etc. immediately if symptoms that suggest any adverse reactions occur.

④ In using the Cypher Stent, proper antiplatelet and anticoagulant therapy as well as periodical follow-up after the stent placement should be conducted. For antiplatelet therapy, in particular, premedicate the patient adequately beforehand so that full effect will be achieved at the time of stent placement. In addition, clinically significant adverse reactions such as thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder etc. may occur following administration of ticlopidine hydrochloride products. These symptoms have been reported to occur most commonly within 2 months after the initiation of administration, leading to death in some cases. Physicians should pay adequate attention to the following points.

a) For 2 months after initiating administration, physicians should be particularly alerted to the emergence of initial symptoms of the above-mentioned adverse reactions. In principle, blood count (including differential leukocyte count) and hepatic function tests should be performed once every 2 weeks. If these adverse reactions are observed, administration should be discontinued and appropriate measures should be taken. Physicians should conduct periodical blood test during the treatment period of the product and be alerted to these adverse reactions.

b) If thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and liver disorder etc. are suspected from the conditions of the patient during the administration of the product, physicians should conduct haemogram or liver function tests as necessary and take appropriate measures.

c) Physicians should prescribe the drug for 2 weeks at one time during the first 2 months after the initiation of the administration as a general rule.

⑤ Conduct the coronary stent placement only at the medical institutions where coronary-artery bypass can be operated expeditiously in case life-threatening complications may occur.

## (3) Requests on medication teaching of ticlopidine hydrochloride products

MHLW requests healthcare providers to pay attention to the following points at the time of medication teaching.

① Check the history of drug therapy of the patient prescribed ticlopidine hydrochloride product. Appropriate medication teaching such as recommending expeditious visits to the attending physician should be given, if any of the subjective symptoms below are observed.

a) Pyrexia
b) Sore throat
c) Haemorrhage from nose or gums
d) Haematuria or chromaturia (brown)
e) Become bruised (purple, red)
f) Skin or eye discoloration (yellow)
g) Eczema
h) Anorexia
i) Consciousness decreased
j) Serious fatigue

② In principle, for the patient who is newly prescribed ticlopidine hydrochloride product, ask the patient if she/he has been visiting the hospital once in every 2 weeks and has been receiving the blood test for the first 2 months from the initiation of administration and audit prescriptions and present inquiries to prescribing physicians, as necessary.

## (4) Outline of the instruction for companies

As a safety measure of the coronary stent treatment using Cypher Stent, MHLW has notified the related companies of thoroughness of its proper use.

① Proper use of Cypher Stent

a) <Warning> of (2) should be included in the package insert.
b) Patient handbook and informed consent form should be established, and thoroughly provide information to the medical institution with them to facilitate proper informed consent procedure to the patients.
c) In case of the patient transfer during the treatment with the stent, documentation regarding the patient is under the treatment with Cypher Stent, etc. should be created and distributes it to all the medical institutions where the stent has been marketed to accurately inform the attending physician at a new hospital.
d) Training sessions and briefings at medical offices, etc. should be held for the proper use of the stent and the sales should be limited only to the medical institutions that completed the trainings.
e) Periodical visits should be made to check if the patient handbook, etc. are properly managed.

② Proper use of ticlopidine hydrochloride products

Thoroughly notify all the medical institutions and dispensing pharmacies that prescribe ticlopidine hydrochloride products of the contents of <warning>.

## (5) Closing comments

There is a possibility of an increased risk of adverse reactions associated with ticlopidine hydrochloride products since longer administration of ticlopidine hydrochloride products is recommended for Cypher Stent compared to that of the conventional coronary stent. MHLW again requests all the healthcare providers for proper use of the product. Also, if you obtain information on adverse reactions relating to ticlopidine hydrochloride products or defects of Cypher Stent, please report to the Safety Division of the Pharmaceutical and Medical Safety Bureau within Ministry of Health, Labour and Welfare in accordance with article 77-4-2, 2 of the Pharmaceutical Affairs Law.

# 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. 204).

## 1 Tacrolimus Hydrate (oral dosage form, injectable dosage form)

| | |
|---|---|
| **Brand Name (name of company)** | Prograf Granules 0.2 mg and 1 mg, Prograf Capsules 0.5 mg, 1 mg, and 5 mg, Prograf Injection 5 mg (Toyama Fujisawa Co., Ltd.) |
| **Therapeutic Category** | Miscellaneous metabolism agents |
| **Indications** | ① Suppression of organ rejection in the following organ transplantation<br>Kidney transplantation, liver transplantation, heart transplantation, lung transplantation<br>② Suppression of graft rejection and GVHD in bone marrow transplantation<br>③ Systemic myasthenia gravis (in a case where the effect of steroids is insufficient or the administration is difficult because of adverse reactions in the treatment after thymectomy) (except Prograf Capsules 5 mg, Prograf Injection 5 mg) |

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

| | |
|---|---|
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Pancreatitis:**Pancreatitis may occur. Patients should be carefully monitored using periodic examinations or some other appropriate measures. If any abnormalities are observed, appropriate measures such as dose reduction or drug discontinuation should be taken. |
| **<Reference Information>** | Company report |

### 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 | Suppression of organ rejection in renal transplantation (malignant nephrosclerosis, nephrogenic anaemia, hypertension) | 12 mg (oral administration) 2 days<br>↓<br>2.4 mg (drip infusion) 2 days<br>↓<br>4-12 mg (oral administration) Unknown (continued for 3 months and more) | **Pancreatitis**<br>On day 3 of administration:<br>Live kidney transplantation was conducted due to malignant nephrosclerosis.<br>On day 14 of administration:<br>HUS developed. WBC 12300/mm$^3$, haematocrit (HCT) 32.1%, prothrombin time (PT) 9.8 seconds, LDH 2133 IU/L. The patient was treated with fresh frozen plasma (FFP).<br>On day 24 of administration:<br>Pancreatitis developed. Amylase (AMY) 1072 IU/L, lipase 214 IU/L. Treatment with urinastatin and gabexate mesilate was conducted. Blood concentration of this product was 16 ng/mL. | Company report |

| | | | | | |
|---|---|---|---|---|---|
| | | | | On day 90 of administration:<br>HUS improved. Pancreatitis recovered. WBC 5510/mm$^3$, HCT 29.2%, PT 19.4 seconds, LDH 654 IU/L.<br>On day 104 of administration:<br>AMY 341 IU/L, lipase 38 IU/L. | |
| | Concomitant medications: methylprednisolone, mycophenolate mofetil, gusperimus hydrochloride, sodium alginate, miconazole, nifedipine, ticlopidine hydrochloride, sulfamethoxazole/trimethoprim, doxazosin mesilate, aciclovir | | | | |

## Clinical Laboratory Values

| | | | 1 day before administration | On day 31 of administration | On day 97 of administration |
|---|---|---|---|---|---|
| RBC ($\times10^4$/mm$^3$) | | | 316 | 215 | 291 |
| Hb (g/dL) | | | 9.2 | 6.5 | 9.2 |
| HTC (%) | | | 29.3 | 20.9 | 28.8 |
| WBC (/mm$^3$) | | | 4700 | 7720 | 7400 |
| PLT ($\times10^4$/mm$^3$) | | | 18.7 | 12.4 | 33.1 |
| BUN (mg/dL) | | | 78.7 | 37.2 | 17.4 |
| Serum urate (mg/dL) | | | 7.4 | | 7.1 |
| AMY (IU/L) | | | 222 | 291 | 268 |
| FBG (mg/dL) | | | -- | -- | 91 |
| AST (GOT) (IU/L) | | | 15 | 13 | 18 |
| ALT (GPT) (IU/L) | | | 8 | 15 | 7 |
| Al-P (IU/L) | | | 98 | -- | 190 |
| LDH (IU/L) | | | 284 | 500 | 595 |
| γ-GTP (IU/L) | | | 9 | -- | 16 |
| Total bilirubin (mg/dL) | | | 0.2 | -- | 0.2 |
| Direct bilirubin (mg/dL) | | | 0.1 | | 0.0 |
| TP (g/dL) | | | 6.3 | -- | 6.7 |
| TC (mg/dL) | | | 232 | -- | 361 |
| NF (mg/dL) | | | 123 | -- | 196 |
| Na (mEq/L) | | | 136 | 136 | 133 |
| K (mEq/L) | | | 4.3 | 4.0 | 4.2 |
| Cl (mEq/L) | | | -- | 106 | 105 |
| Ca (mg/dL) | | | 9.1 | -- | 10.0 |
| Uranalysis | Glucose | | -- | (–) | -- |
| | Protein | | | (3+) | (3+) |
| | Urinary sediment | RBC | -- | 1-2/1 | 1/3-4 |
| | | WBC | -- | 2-3/1 | 2/1 |
| | | Epithelial cell | -- | Renal epithelial cells 1/6 | Renal epithelial cells 1-2/1 |
| | | Cast | | Hyaline cast 1-2/1<br>Granular cast 1/20 | Hyaline cast 1/1-2 |

RBC: Red Blood Cell
Hb: Haemoglobin
HTC: Haematocrit
WBC: White Blood Cell
PLT: Platelet
BUN: Blood Urea Nitrogen
AMY: Amylase
FBG: Fasting blood glucose
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
TP: Total protein
TC: Total cholesterol
NF: Neutral fat
Na: Sodium
K: Potassium
Cl: Chloride
Ca: Calcium

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | Remarks |
|---|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 2 | Female 40s | Suppression of graft rejection and GVHD in bone marrow transplantation (chronic myelocytic leukemia) | 1-1.5 mg (drip infusion) 17 days ↓ 4 mg (oral administration) 22 days | **Acute pancreatitis**<br>10 days before administration:<br>Unrelated bone marrow transplantation was conducted with busulfan and cyclophosphamide as pretreatment. Cyclosporine drip infusion was started for the suppression of GVHD. Methotrexate was additionally administered.<br>On day 1 of administration:<br>Ciclosporine was replaced by continuous drip infusion of this product due to skin and hepatic GVHD.<br>On day 4 of administration:<br>Methylprednisolone was added. GVHD tended to improve.<br>On day 8 of administration:<br>Herpes simplex genitalis developed. Aciclovir was orally administered. Blood concentration of this product was 19.2 ng/mL.<br>On day 12 of administration:<br>LDH was gradually elevated around this time.<br>On day 18 of administration:<br>Drip infusion was switched to oral administration.<br>On day 28 of administration:<br>The patient started experiencing queasy and occasional hypochondrium pain left around this time.<br>On day 29 of administration:<br>LDH was elevated to 1585 IU/L.<br>On day 31 of administration:<br>The patient was diagnosed with microangiopathy (Total bilirubin 3.5 mg/dL, direct bilirubin 2.3 mg/dL, LDH 1878 IU/L, erythrocyte fragmentation was observed in the peripheral blood). Administration of FFP was started.<br>On day 36 of administration:<br>TB 4.7 mg/dL, direct bilirubin 2.4 mg/dL, AST (GOT) 143 IU/L, ALT (GPT) 229 IU/L, LDH 1657 IU/L, cystitis haemorrhagic occurred. Herpes simplex genitalis improved around this time.<br>On day 39 of administration (day of discontinuation):<br>The patient complained of satiety. Diarrhoea improved. Weight increased (increased by 0.8 kg since the previous day) and ascites occurred. The patient underwent a state of disequilibrium from the night to the following morning.<br>1 day after discontinuation:<br>Total bilirubin,LDH, BUN, creatinine increased. Suddenly intensified abdominal distension followed by severe abdominal pain developed. Serum AMY and urine AMY were both high. As CT showed pancreatic enlargement, the patient was diagnosed with acute pancreatitis. Blood concentration of this product was 12.2 ng/mL. This drug was discontinued and gabexate mesilate at 2 g, plasma exchange, and continuous HD were started.<br>4 days after discontinuation:<br>Plasma exchange was conducted due to blood pressure decreased and continuous HD became unavailable. Only conservative therapy could be conducted thereafter. | Company report |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 7 days after discontinuation:<br>The patient died.<br>(cause of death: multi-organ failure, autopsy finding: acute severe pancreatitis) | |
| | Concomitant medications: methylprednisolone, lenograstim (Genetical recombination), cefozopran hydrochloride, aciclovir, ganciclovir | | | | |

## Clinical Laboratory Values

| | On day 1 of administration | On day 8 of administration | 1 days after discontinuation | 4 days after discontinuation |
|---|---|---|---|---|
| RBC ($\times 10^4/mm^3$) | 340 | 254 | 256 | 310 |
| Hb (g/dL) | 10.8 | 8.1 | 8.0 | 9.7 |
| HCT (%) | 30.4 | 22.3 | 21.8 | 28.2 |
| WBC ($/mm^3$) | 100 | 600 | 6200 | 4900 |
| PLT ($\times 10^4/mm^3$) | 1.8 | 0.3 | 2.9 | 0.5 |
| PT (%) | 141.0 | 112.0 | 38.0 | 45.0 |
| AST (GOT) (IU/L) | 69 | 64 | 281 | 233 |
| ALT (GPT) (IU/L) | 90 | 204 | 441 | 281 |
| Al-P (IU/L) | 250 | 239 | 293 | 271 |
| LDH (IU/L) | 366 | 549 | 1675 | 1421 |
| γ-GTP (IU/L) | 99 | 64 | 27 | 21 |
| Total bilirubin (mg/dL) | 2.1 | 2.2 | 15.3 | 12.0 |
| Direct bilirubin (mg/dL) | 1.1 | 0.8 | 9.8 | 7.9 |
| TP (g/dL) | 6.8 | 6.1 | 2.8 | 5.0 |
| Albumin (g/dL) | 3.6 | 3.3 | 1.8 | 3.2 |
| BUN (mg/dL) | 40.4 | 52.9 | 107.4 | 43.6 |
| Serum creatinine (mg/dL) | 2.01 | 1.91 | 3.43 | 1.96 |
| Na (mEq/L) | 132 | 133 | 133 | 137 |
| K (mEq/L) | 4.3 | 3.9 | 3.0 | 3.8 |
| Ca (mEq/L) | 4.3 | 3.8 | 4.6 | 2.6 |
| P (mEq/L) | 4.9 | 4.2 | 7.0 | 3.0 |
| CRP (mg/dL) | 1.48 | 1.28 | 3.82 | 8.0 |
| Blood glucose (mg/dL) | 111 | 120 | 308 | 167 |
| Serum AMY (IU/L) | -- | -- | 5984 | 500 |
| Urinary AMY (IU/L) | | | 1324 | |

RBC: Red Blood Cell
Hb: Haemoglobin
HCT: Haematocrit
WBC: White Blood Cell
PLT: Platelet
PT: Prothrombin Activity (%)
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
TP: Total Protein
BUN: Blood Urea Nitrogen
Na: Sodium
K: Potassium
Ca: Calcium
P: Phosphate
CRP: C-Reactive Protein
AMY: Amylase

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions | Remarks |
|---|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures | |
| 3 | Male 30s | Suppression of organ rejection in kidney transplantation (hypertension, HCV positive) | 18 mg (oral administration) 2 days ↓ 6 mg (drip infusion) 1 day ↓ 18 mg (oral administration) 3 days ↓ 1-17 mg (oral administration) Unknown (continued for 3 years and more) | **Acute pancreatitis**<br>On day 3 of administration:<br>Renal transplantation was implemented.<br>On day 909 of administration:<br>Clinical symptoms (abdominal pain, peritoneal irritation symptom) appeared. Blood test showed AMY 625 IU/L . The patient was diagnosed by abdominal CT scan with acute pancreatitis. Pancreatic pseudocyst was also observed.<br>On day 924 of administration:<br>The patient was hospitalized. Administration of nafamostat mesilate, citicoline, and ulinastatin were started. Cystostomy and intraperitoneal drainage were conducted due to aggravation of the symptoms considered to be caused by the abscess inside cyst. Dosage of this product was decreased.<br>On day 946 of administration:<br>The patient was discharged from the hospital.<br>On day 1119 of administration:<br>The symptoms improved. AMY was 238 IU/L. | Company report |
| | Concomitant medications: prednisolone, mizoribine, diltiazem hydrochloride, nicardipine hydrochloride, doxazosin mesilate | | | | |

## Clinical Laboratory Values

| | | On day 695 of administration | On day 1119 of administration |
|---|---|---|---|
| RBC ($\times 10^4/mm^3$) | | 707 | 529 |
| Hb (g/dL) | | 18.8 | 14.0 |
| HTC (%) | | 56.2 | 43.4 |
| WBC ($/mm^3$) | | 7600 | 12700 |
| PLT ($\times 10^4/mm^3$) | | 15.6 | 14.7 |
| Serum creatinine (mg/dL) | | 3.19 | 4.36 |
| BUN (mg/dL) | | 34.0 | 51.3 |
| Serum urate (mg/dL) | | 10.6 | 12.6 |
| AMY (IU/L) | | 74 | 238 |
| FBG (mg/dL) | | 89 | 92 |
| AST (GOT) (IU/L) | | 75 | 19 |
| ALT (GPT) (IU/L) | | 76 | 32 |
| Al-P (IU/L) | | 556 | 359 |
| LDH (IU/L) | | 201 | 170 |
| γ-GTP (IU/L) | | 118 | 33 |
| Total bilirubin (mg/dL) | | 0.55 | 0.34 |
| TP (g/dL) | | 6.4 | 6.2 |
| TC (mg/dL) | | -- | 197 |
| NF (mg/dL) | | | 107 |
| Na (mEq/L) | | 139 | 147 |
| K (mEq/L) | | 3.6 | 4.7 |
| Cl (mEq/L) | | 103 | 114 |
| Ca (mg/dL) | | 7.9 | 8.8 |
| Uranalysis | Glucose | (±) | (–) |
| | Protein | (3+) | (3+) |

| | | | | |
|---|---|---|---|---|
| | Urinary sediment | RBC | (+) | (–) |
| | | WBC | (+) | (–) |
| | | Epithelial cell | (+) | (–) |
| | | Cast | (±) | (–) |

RBC: Red Blood Cell
Hb: Haemoglobin
HTC: Haematocrit
WBC: White Blood Cell
PLT: Platelet
BUN: Blood Urea Nitrogen
AMY: Amylase
FBS: Fasting Blood Glucose
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
TP: Total Protein
TC: Total cholesterol
NF: Neutral fat
Na: Sodium
K: Potassium
Cl: Chloride
Ca: Calcium

# 4

# Revision of PRECAUTIONS

# (No. 159)

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. 204) (excluding those presented in "3. Important Safety Information" of this Bulletin.), together with reference materials.

## 1 <General anesthetics> Sevoflurane

| | |
|---|---|
| **[Brand Name]** | Sevofrane (Maruishi Pharmaceutical Co., Ltd.) |
| **[Careful Administration]** | Patients with a history of epilepsy |
| **[Important Precautions]** | In high concentration induction of this drug, electroencephalogram abnormal and movements abnormal have been reported especially under hyperventilation. Cautions should be exercised for patients' conditions when administering this drug. |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Convulsion, movements involuntary:** Convulsion and movements involuntary (primarily myoclonus like) may occur in the perioperative period. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as reduction of the dosage, discontinuation of administration, or concomitant use of other drugs should be taken. |
| **<Reference Information>** | Company report |

## 2 <Antipyretics and analgesics, anti-inflammatory agents> Lornoxicam

| | |
|---|---|
| **[Brand Name]** | Lorcam Tab. 2 mg and 4 mg (Taisho Pharmaceutical Co., Ltd.) |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Thrombocytopenia:** Since thrombocytopenia may occur, patients should be closely monitored through blood tests. If any abnormalities are observed, this drug should be discontinued and appropriate measures should be taken. |
| **<Reference Information>** | Company report |

## 3 <Bronchodilators> Beclometasone Dipropionate (oral inhalant)

| | |
|---|---|
| **[Brand Name]** | Becotide 50 Inhaler and 100 Inhaler (GlaxoSmithKline K.K.), and others |
| **[Adverse Reactions (clinically significant adverse reactions)]** | Although the possibility is low compared to systemic steroids, as **systemic reactions** (including Cushing's syndrome, Cushingoid symptoms, adrenal cortex hypofunction, childhood growth retardation, bone density decreased, cataract, and glaucoma) may occur associated with the administration of inhaled steroid, the dose of inhaled steroid should be adjusted to **the minimum** that controls asthma for each patient. Patients should receive **periodic examinations**, especially in cases of administrations of **high doses over long term**. If any systemic symptoms |

| | |
|---|---|
| | are observed, appropriate measures such as **tapering off this drug** should be taken **through observation** of the patient's **asthmatic conditions**. |
| **<Reference Information>** | Company report |

---

**4** **<Protein and amino acid preparations>**

## Elental P

| | |
|---|---|
| **[Brand Name]** | Elental P (Ajinomoto Pharma Co., Ltd.) |
| **[Important Precautions]** | Since vitamin deficiency, blood electrolytes decreased, trace element deficit may occur, replenish required as needed. In particular, concomitant administration of iron preparation, etc. can be effective if iron deficiency anaemia is confirmed. Selenium deficiency (cardiac function failed, nail discoloration (white), and muscular weakness, etc.) may occur during long-term administration. Carnitine decreased has been reported, too. |
| **<Reference Information>** | Company report |

---

**5** **<Blood and body fluid agents-Miscellaneous>**

## Aspirin (enteric coated tablet)

| | |
|---|---|
| **[Brand Name]** | Bayaspirin 100 mg (Bayer Yakuhin, Ltd.), and others |
| **[Important Precautions]** | Caution should be exercised for drug interaction with other antiplatelet drugs when administering patients with cerebral infarction. Careful administration is necessary for patients with persisting hypertension and sufficient blood pressure control should be conducted during administration. |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Haemorrhage:**<br><Haemorrhage intracranial such as cerebral haemorrhage><br>Haemorrhage intracranial such as cerebral haemorrhage (initial symptoms: headache, nausea/vomiting, consciousness disturbed, and hemiplegia, etc.) may occur. Patients should be carefully monitored. If such symptoms are observed, administration should be discontinued and appropriate measures should be taken.<br><pulmonary haemorrhage, haemorrhage of digestive tract, epistaxis, ocular fundus haemorrhage of, etc.><br>Pulmonary haemorrhage, haemorrhage of digestive tract, epistaxis, ocular fundus haemorrhage of, etc. may occur. Patients should be carefully monitored. If such symptoms are observed, administration should be discontinued and appropriate measures should be taken. |
| **<Reference Information>** | Company report |

---

**6** **<Blood and body fluid agents-Miscellaneous>**

## Aspirin/Dialuminate (81 mg Tablet)

| | |
|---|---|
| **[Brand Name]** | Bufferin 81 mg Tablets (Lion Corporation), and others |
| **[Important Precautions]** | Caution should be exercised for drug interaction with other antiplatelet drugs when administering patients with cerebral infarction. Careful administration is necessary for patients with persisting hypertension and sufficient blood pressure control should be conducted during administration. |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Haemorrhage:**<br><Haemorrhage intracranial such as cerebral haemorrhage><br>Haemorrhage intracranial such as cerebral haemorrhage (initial symptoms: headache, nausea/vomiting, consciousness disturbed, and hemiplegia, etc.) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.<br><haemorrhage of digestive tract, pulmonary haemorrhage, epistaxis, etc.> |

| | |
|---|---|
| | Haemorrhage of digestive tract, pulmonary haemorrhage, and epistaxis, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. |
| **<Reference Information>** | Company report |

---

**7** **<Blood and body fluid agents-Miscellaneous>**

## Ticlopidine Hydrochloride

| | |
|---|---|
| **[Brand Name]** | Panaldine Fine Granules 10%, Panaldine Tablets (Daiichi Pharmaceutical Co., Ltd.), and others |
| **[Warning]** | The patient should contact a physician, etc. immediately and follow the instruction, if symptoms that suggest any adverse reactions occur. |
| **[Important Precautions]** | Caution should be exercised for drug interaction with other antiplatelet drugs when administering patients with cerebral infarction. Careful administration is necessary for patients with persisting hypertension and sufficient blood pressure control should be conducted during administration. (See "Careful Administration" and "Interactions.") |
| **[Adverse Reactions (clinically significant adverse reactions)]** | Haemorrhage (haemorrhage intracranial such as cerebral haemorrhage (initial symptoms: headache, consciousness disturbed, and hemiplegia, etc.), serious haemorrhage such as haemorrhage of digestive tract) |
| **<Reference Information>** | Company report |

---

**8** **<Enzyme preparations>**

## Monteplase (Genetical recombination)

| | |
|---|---|
| **[Brand Name]** | Cleactor Inj. 400000, 800000, and 1600000 (Eisai Co., Ltd.) |
| **[Contraindications]** | "Patients with positive skin prick test" was omitted. |
| **<Reference Information>** | Company report |

---

**9** **<Antineoplastics-Miscellaneous>**

## Cladribine

| | |
|---|---|
| **[Brand Name]** | Leustatin Injection 8 mg (Janssen Pharmaceutical K.K.) |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Bone marrow depression**: pancytopenia, neutropenia, white blood cell decreased, platelets decreased, and anaemia (erythropenia, haemoglobin decreased, haematocrit value decreased) may occur or become aggravated and prolonged. Myelosuppressive effect of this product is most prominent for the first 1 month from initial administration. In particular, patient should be carefully monitored through blood test, etc. more than once a week for the first 8 weeks of initial administration. If any abnormalities are observed, appropriate measures should be taken. |
| **<Reference Information>** | Company report |

## 10 <Acting mainly on gram-positive and gram-negative bacteria>
## Fosfomycin Sodium (injectable dosage form)

| | |
|---|---|
| **[Brand Name]** | Fosmicin-S for Intravenous Drip Infusion (Meiji Seika Kaisha, Ltd.), and others |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Convulsions** may occur. If such symptoms occur, administration should be discontinued and appropriate measures should be taken. |
| **<Reference Information>** | Company report |

## 11 <Antivirals>
## Atazanavir Sulfate

| | |
|---|---|
| **[Brand Name]** | Reyataz Capsules 150 mg and 200 mg (Bristol Myers K.K.) |
| **[Important Precautions]** | Mild to moderate rash following the administration of this drug has been reported. Rash macular and papular rash generally occur within first 3 weeks of initial administration and usually disappear within 2 weeks while still continuing the administration. If severe rash occur or persists, administration should be discontinued. |
| **<Reference Information>** | Company report |

## 12 <Anthelmintics>
## Mebendazole

| | |
|---|---|
| **[Brand Name]** | Mebendazole Tablets 100 (Janssen Pharmaceutical K.K.) |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Shock/anaphylactoid symptoms:** Shock/anaphylactoid symptoms may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.<br>**Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome)**: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken. |
| **<Reference Information>** | Company report |

## 13 <X-ray contrast media>
## Iopromide

| | |
|---|---|
| **[Brand Name]** | Iopamiron 150, 300, and 370, Iopamiron 300 and 370 Syringe (Nihon Schering K.K.), and others |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Consciousness disturbed, syncope:** Consciousness disturbed and syncope without shock may occur. Patients should be carefully monitored by such as monitoring of consciousness level even after the exam and appropriate measures should be taken as required. |
| **<Reference Information>** | Company report |

## 14 <X-ray contrast media> Iopromide

| | |
|---|---|
| **[Brand Name]** | Proscope 150, 240, 300, and 370, Proscope 300 Syringe (Tanabe Seiyaku Co., Ltd.) |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Consciousness disturbed and syncope** without shock may occur. Patients should be carefully monitored by such as monitoring of consciousness level even after the exam and appropriate measures should be taken as required. |
| **<Reference Information>** | Company report |

## 15 <X-ray contrast media> Iomeprol

| | |
|---|---|
| **[Brand Name]** | Iomeron 300, 350, and 400, Iomeron 300 and 350 Syringe (Bracco-Eisai Co., Ltd.) |
| **[Adverse Reactions (clinically significant adverse reactions)]** | **Consciousness disturbed, syncope:** Consciousness disturbed and syncope without shock may occur. Patients should be carefully monitored by such as monitoring of consciousness level even after the exam. If any abnormalities are observed, appropriate measures should be promptly taken. |
| **<Reference Information>** | Company report |