Pharmaceuticals and Medical Devices Safety Information

No. 203 July 2004

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Pharmaceuticals and Medical Devices Safety Information

No. 203 July 2004

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

[Outline of Information]

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

1

Serious skin disorders caused by pharmaceuticals

(1) Introduction

Skin disorders are commonly known to occur as adverse reactions of drugs. Among the serious skin disorders, there are the Stevens-Johnson syndrome (SJS) (oculomucocutaneous syndrome) and toxic epidermal necrolysis (TEN).

SJS and TEN have been explained regarding their pathology in Pharmaceuticals and Medical Devices Safety Information No. 163 (November 2000 issue) and No. 177 (May 2002 issue). It has been also described the details matter of adverse reactions reported to Ministry of Health and Welfare (at that time) between 1997 and 2000. MHLW has decided to remind them based on the cases of adverse reaction reported to MHLW afterwards, although there may be some parts including the contents regarding SJS and TEN in No. 163 and No. 177.

(2) About Stevens-Johnson syndrome (oculomucocutaneous syndrome), toxic epidermal necrolysis (TEN)

SJS (oculomucocutaneous syndrome) is synonymous with erythema exsudativum multiforme major (EEMM), and toxic epidermal necrolysis is identified as the most severe among the skin disorders[1)].

TEN is also referred to as Lyell syndrome. Disorders that demonstrate similar symptoms include staphylococcal scalded skin syndrome (SSSS) and graft versus host disease (GVHD) after blood transfusions.

The incidence of these disorders is extremely low, consisting of approximately 1 to 6, 0.4 to 1.2 [2, 3)] for every 1 million people per year. After developing these disorders, there are some cases of resulted in poor prognosis, and even after skin symptoms have become in remission, disorders with the eyes and respiratory tract may still remain.

1) Initial symptoms and clinical course

The initial symptoms of SJS are pyrexia and erythema (target lesion, etc.) distributed symmetrically mainly around the back surface of joints, which rapidly increase in the amount. Increase in severity of erythema is resulting in the development and fusion of blisters and erosions. They often accompany enanthema of the eyes, oral mucosa, and vulva, and are demonstrated by increased white blood cell, increased red blood cell, sedimentation rate, CRP positive, etc. in test findings. Diagnosis is not difficult, as Erythema multiforme exudativum-type skin eruptions (target lesions) and rapid distribution of enanthema over an extensive area occur together with general symptoms such as pyrexia. With complications such as respiratory disorders (pneumonia, etc.) and liver disorder, it has been reported that the mortality rate of SJS is 6.3%[4)].

On the other hand, TEN causes symptoms of pyrexia and erythaema over an extensive area such as the axilla, vulva, and torso, followed by rapid blister formation which can be easily broken (Nikolsky's sign) together with general erosion. These symptoms resemble burns second degree, and pain is significant. Clinical laboratory tests often confirm abnormal blood, liver and electrolyte findings. They are often complicated by multi-organ failure (liver disorder, renal disorder, respiratory disorder, gastrointestinal disorder etc.), and it has been reported that mortality rate is also high, between 20%-30%[4, 5)].

2) Pathogenesis and mechanisms

These disorders are considered to be allergic skin reactions (type III allergy reactions) that might be caused by infectious diseases by various viruses and bacteria such as the herpes simplex virus, mycoplasma pneumoniae, bacteria, or fungi, drugs, foods, endocrine abnormalities, malignant tumors and physical stimuli. These skin disorders are often caused by drugs, and it has been reported in some literature that 59% of SJS cases are estimated to have been caused by drugs[4)] and 90% and more of TEN cases are estimated to have been caused by drugs[4, 5)]. The onset mechanisms of these skin disorders are not yet clear, and it is also extremely difficult to predict the onset before administration of drugs.

3) Causative drugs

There are a wide range of causative drugs including antibiotic preparations, antipyretics, analgesics, and anti-inflammatory agents, antiepileptics, antigout agents, sulfonamides, peptic ulcer agents, hypnotic sedatives/anxiolytics, psychotropics, therapeutic agents for glaucoma, muscle relaxants, hypertensive agents and the others[2, 4-7)].

4) Treatment

If initial symptoms such as pyrexia and rashes are confirmed in the case of drug-induced SJS or TEN, the most important and best treatment is to immediately discontinue administration of the drug suspected to be the cause. However, attention is necessary as there are cases where symptoms increase in severity and develop into SJS and TEN even if administration is discontinued. In general, if SJS and TEN occur, systemic administration of glucocorticoids or vitamins, or plasma exchange therapy, in addition to administration of antibiotics for the purpose of preventing secondary infections is carried out. External antibiotics and external glucocorticoids are used on the skin surface. For mucosal surfaces, treatment of apertural area such as gargling and eye washing are performed together with the above[6-8)]. It is recommended that these treatments be performed at a hospital possessing dermatological department inpatient facilities[9, 10)].

(3) Adverse reactions reported to MHLW from FY2001 to FY2003 (until the shift to electronic reports)

Adverse reactions reports were received by pharmaceutical companies on paper, but those reports have been received electronically by the system established on October 27, 2003. Here is the summary regarding the reports that were received after 2001, before the electronic reporting system was established (a period of approximately 2 years and 7 months until October 26, 2003). During this period, there were 72409 reports on adverse reaction reported directly to MHLW from medical institutions based on the pharmaceuticals and medical devices safety information reporting system and company reports from companies according to the Pharmaceutical Affairs Law. From among these reports, 1064 reports (approximately 1.5%), concerned adverse reactions of SJS or TEN, and from among these approximately 5%, or 58 reports, suspected that OTC drugs were included in the suspected drugs of SJS or TEN. Among the 1064 reports, 702 cases (approximately 66%), consisted of “remission” or “recovered” as the outcome, 66 cases (approximately 6%) were “not recovered” at the time of the report, 62 cases (approximately 6%) resulted in some form of sequelae, and 106 cases (approximately 10%) resulted in drug-related deaths. The remaining 128 cases (approximately 12%) died of causes not related to drugs, or consisted of unclear outcomes. When comparing these figures to those reported in the 4 years between April 1, 1997 and March 31, 2001 that were introduced in No. 163 and No. 177, there was no large divergence in the occurrence trends or outcomes. Please note that these reported cases include duplicate cases as well as cases where a causality with the drug is not clear.

Table 1 Most numerously reported suspected drugs (according to drug)

Carbamazepine
Allopurinol
Diclofenac sodium
Levofloxacin
Loxoprofen sodium
Zonisamide
Azithromycin hydrate
Cefdinir
Cefcapene pivoxil hydrochloride
Clarithromycin

(based on the case reports from April 1, 2001 to October 26, 2003)

Table 2 Most numerously reported suspected drugs (according to therapeutic category)

Antibiotics
Antipyretics and analgesics, anti-inflammatory agents
Antiepileptics
Combination cold remedy
Antigout agents
Peptic ulcer agents
Synthetic antibacterials
Sulfonamides
Hyperlipidaemia agents
Psychotropics

(based on the case reports from April 1, 2001 to October 26, 2003)

There were 283 ingredients reported as the suspected drug, and the items and therapeutic category for pharmaceuticals widely reported are shown in **Tables 1 and 2**. Upon comparing the drugs widely reported, what is prominent is that non-steroidal anti-inflammatory drugs (NSAIDs) were reported often, and that there is no large difference as compared to past trends. With regard to the order of the number of reports, since the volume of sales of each drug and the usage method, usage frequency, concomitant medications, primary diseases, and complications, etc. differ depending on the cases, please note that it is not possible to make simple comparisons.

(4) Conclusion

Although the incidences of SJS or TEN are extremely rare, once they occur, some cases might result in fatal outcomes from complications of multi-organ failure, etc. As well, SJS and TEN are serious skin disorders where disorders in the eyes and respiratory tract, etc. remain even if skin symptoms become in remission. These skin disorders, although they are very rare, have the possibility of occurring regardless of the individual or drug. Therefore, the most important and best treatment is to discontinue administration of suspected drugs when eruptions caused by drugs occur, in addition to conducting a medical examination through an interview before administering a drug. When a rash etc. accompanied by a hyperthermia is observed after administration of a drug, discontinue administration of the suspected drug immediately, and if the onset of SJS or TEN is suspected, it is necessary to introduce the patient to a dermatologic specialist.

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2

Effects of electromagnetic waves from antitheft devices, etc. on medical devices

MHLW has alerted healthcare providers about the effects on implantable cardiac pacemakers and implantable cardioverter defibrillators (ICDs) by antitheft devices, etc. in the Pharmaceuticals and Medical Devices Safety Information No. 155 (June 1999 issue), No. 173 (January 2002 issue), and No. 190 (June 2003 issue).

Ministry of Internal Affairs and Communications (MIC) has been implementing "Study on the Effects of Electromagnetic Waves on Medical Equipment" for 2 years starting in 2002. The Association of Radio Industries and Businesses (hereinafter referred to as "the Association") recently gathered results from a survey on the effects of electromagnetic waves emitted from antitheft devices, etc. on implantable medical devices (cardiac pacemakers and ICDs). Based on the results of this study, it was confirmed that the guidelines introduced in Pharmaceuticals and Medical Devices Safety Information No. 173 are valid. MHLW has therefore decided to promote awareness again among healthcare providers, etc. by introducing the contents of relevant reports in this bulletin.

(1) Background

Pharmaceuticals and Medical Devices Safety Information No. 190 has described an interim report of the effects on implantable cardiac pacemakers and ICDs by electromagnetic waves emitted from antitheft devices [referred to as "EAS (Electronic Article Surveillance)" in the report of the Association].

MIC recently released the reports on 1) antitheft devices, 2) RFID devices (radio frequency identification devices) (excluding fixed types) and 3) wireless LANs (local area networks), which were made by the "Investigative Research Committee for Effects of Electromagnetic Waves on Medical Devices, etc." established in the Association, to which this survey was commissioned, MHLW has introduced details of the contents of the report to medical institutions, healthcare professionals, and marketing authorisation holders of medical devices, etc.

<Explanation of terms>

1) An antitheft device is a device that detects various types of tags that are attached to a product when the product passes the device through non-contact communication. There are various types of antitheft devices, including a electromagnetic type, magnetic type, magnetic cipher type, acoustomagnetic type, and compound type. As configurations for antitheft devices, there are gate types and ceiling types, as well as types where the device is embedded into the ceiling of floor.
2) RFID device is a device that records information in electronic circuits and make intercommunication through non-contact communication possible. Such devices exchange information through intercommunication of electromagnetic waves between the detection device and tags fitted with IC chips and antennas. RFID devices are used in logistics and inventory management, settlement of products, etc. Based on the configuration of the detection devices, RFID devices are broadly classified into a gate type, hand-held type, and fixed type.
3) Wireless LANs use wireless media with electromagnetic waves of 2.4 GHz or 5.4 GHz, making transmission rates of approximately 1 Mbps to 54 Mbps possible for computers and peripheral devices. They represent a data communication system that enables for direct communication within an area that is geographically limited, such as an office, floor, or group of buildings.

(2) Overview of the study

This survey was carried out for antitheft devices, RFID devices, and wireless LANs by the same evaluation method used for the evaluation of the effects of electromagnetic waves emitted from antitheft devices and wireless card systems on implantable medical devices (cardiac pacemakers and ICDs) implemented in 2002.

1) Effects of antitheft devices on implantable medical devices

The effects of antitheft devices on implantable medical devices was surveyed through the following 4 tests, using a total of 40 devices including 15 electromagnetic-type, 14 magnetic-type, 7 magnetic cipher-type (including 2 floor-type and 2 ceiling-type), 3 acoustomagnetic-type, and 1 compound-type antitheft devices as devices subject to testing, and 28 implantable cardiac pacemakers (48 modes) and 7 ICDs (10 modes) that are representative of the products distributed before 1995 and after 1999, in order to cover the models that are currently used, as medical devices subject to testing.

<Test 1>

Test description: A situation where a person with an implantable medical device passes through the center of the antitheft detection device was reproduced, and the distance from the center of the gates that had an effect on the medical device is measured.

<Test 2>

Test description: In order to reproduce the situation where a person with an implantable medical device turns around inside the gates, the person approached the gates that were transmitting electromagnetic waves up to a distance of 20 cm while turning around inside the gates. The expression condition of the effects on the medical devices depending on the difference of the rotation angle in relation to the gates and the distance from the gates was measured.

<Test 3>

Test description: A situation where a person with an implantable medical device approaches the gate itself (transmitter-receiver board) closely at a distance (within 20 cm) where they cannot turn their body between the gates was reproduced, and the distance from the gate that affected the medical device was measured.

<Test 4>

Test description: Using implantable medical devices that were affected in <Test 1>, a situation where a person with an implantable medical device approaches the area around the gate (transmitter-receiver board) from the outside the gate was reproduced, and the distance from the gate that affected the medical devices was measured from an angle immediately lateral to the gate, 45 degrees from the gate and 90 degrees from the gate.

2) Effects of RFID devices on implantable medical devices

A survey on the effects on medical devices was conducted, using the same implantable medical devices as those in 1) as medical devices subject to testing and 10 gate-type and 21 hand-held type RFID devices (total of 31 devices) as devices subject to testing.

Taking the structural characteristics of RFID devices into consideration, for gate-type RFID devices the effects were surveyed using the same method as that used for antitheft devices in 1). For hand-held type RFID devices, the effects on implantable medical devices were surveyed using the following 2 types of testing methods.

<Test A>

Test description: A situation where the hand-held type RFID device is moved close to the body of the person was reproduced, and while gradually moving the hand-held RFID device away from the person after holding it in close proximity once, the distance at which there were no more effects was measured.

<Test B>

Test description: In order to survey the sensitivity of the implantable medical device at which there are no more effects on the device, if effects were observed in <Test A>, the sensitivity of the implantable medical device was reduced sequentially, and the same test as in Test A was performed until effects could not be observed.

3) Effects of wireless LANs on implantable medical devices

A survey on the effects on medical devices was conducted, using the same implantable medical devices as those in 1) as medical devices subject to testing and 8 access points for all types of wireless LANs and 8 wireless LAN mobile devices (total of 16 devices) as devices subject to testing.

The same testing method as that for hand-held type RFID devices in 2) was used.

(3) Overview of survey results

1) Effects of antitheft devices on implantable medical device

① Implantable cardiac pacemakers

With regard to gate-type antitheft devices, some form of effect was observed in a combination of 177 testing modes (10.2%) for Test 1, 671 testing modes (38.8%) for Test 2, and 797 testing modes (46.1%) for Test 3, as indicated in the table below. Most of the observed effects were temporary, and conditions returned to normal as the person stepped away from the gates.

For the floor-type antitheft devices, some form of effect was observed in 3 testing modes (3.1%). Effects were not observed with the ceiling-type antitheft device.

	Test 1	Test 2	Test 3	Test 4
Interference rate	10.2%	38.8%	46.1%	—
Maximum interference distance	275 cm	—	—	280 cm

Note 1: Interference rate signifies the percentage of the implantable cardiac pacemaker modes that were affected.

Note 2: Maximum interference distance refers to the maximum distance at which the implantable cardiac pacemaker was affected.

In Tests 2 and 3, there were cases where the program was reset (maximum interference distance: 25 cm).

② ICDs

With regard to gate-type antitheft devices, some form of effect on the pacemaker function was observed in a combination of 5 testing modes (1.4%) for Test 1, 34 testing modes (9.4%) for Test 2 and 59 testing modes (16.4%) for Test 3, as indicated in the table below. Most of the observed effects were temporary, and conditions returned to normal as the person stepped away from the gates.

In addition, some form of effect on the defibrillation function was observed in a combination of 13 testing methods (3.6%) in Test 2 and 29 testing modes (8.1%) in Test 3. Most of the observed effects were temporary, and conditions returned to normal as the person stepped away from the gates.

With the floor-type and ceiling-type antitheft devices, effects on neither the pacemaker function nor the defibrillation function were observed.

<Pacemaker function>

	Test 1	Test 2	Test 3
Interference rate	1.4%	9.4%	16.4%
Maximum interference distance	65 cm	—	—

<Defibrillation function>

	Test 1	Test 2	Test 3
Interference rate	0%	3.6%	8.1%
Maximum interference distance	—	—	—

Note 1: Interference rate signifies the percentage of the ICD modes that were affected.
Note 2: Maximum interference distance refers to the maximum distance at which the ICD was affected.

In Test 2 and Test 3, effects that caused unnecessary defibrillation shock were confirmed in 29 testing modes (8.1%) for 5 models. The maximum interference distance for these cases was 42.5 cm, and the angle in relation to the gate was 90 degrees (when the person was facing the gate).

2) Effects of RFID devices on implantable medical devices

① Implantable cardiac pacemakers

With regard to gate-type RFID devices, some form of effect was observed in a combination of 5 testing modes (1.0%) for Test 1, 22 testing modes (4.6%) for Test 2, and 89 testing modes (18.5%) for Test 3, as indicated in the table below. Most of the observed effects were temporary, and conditions returned to normal as the person stepped away from the gates.

For hand-held type RFID devices, the maximum interference distance was 15 cm, and some form of effect was observed in 50 testing modes (5.0%), but there were no cases where the program was reset.

	Test 1	Test 2	Test 3
Interference rate	1.0%	4.6%	18.5%
Maximum interference distance	50 cm	—	—

Note 1: Interference rate signifies the percentage of the implantable cardiac pacemaker modes that were affected.
Note 2: Maximum interference distance refers to the maximum distance at which the implantable cardiac pacemaker was affected.

② ICDs

For gate-type RFID devices, some form of effect was observed in 4 testing modes (4.0%) for Test 3, as indicated in the table below. Most of the observed effects were temporary, and conditions returned to normal as the person stepped away from the gates. Effects were observed in both the pacemaker function and defibrillation function in a state where the person was in close proximity to the gates. For the defibrillation function, an effect where unnecessary defibrillation shock occurred was observed.

For the hand-held type RFID device, the maximum interference distance was 2 cm and some form of effect was observed in 7 testing modes (3.3%) for the pacemaker function, whereas for the defibrillation function, the maximum interference was 1 cm and an effect in which unnecessary defibrillation shock occurred was observed in 5 testing modes (2.4%). Most of the observed effects were temporary, and conditions returned to normal as the person stepped away from the gates.

<Pacemaker function>

	Test 1	Test 2	Test 3
Interference rate	0%	0%	4.0%
Maximum interference distance	—	—	0 cm

<Defibrillation function>

	Test 1	Test 2	Test 3
Interference rate	0%	0%	4.0%
Maximum interference distance	—	—	0 cm

Note 1: Interference rate signifies the maximum distance at which the affected ICD was affected.
Note 2: Maximum interference distance refers to the maximum distance at which the ICD was affected.

3) Effects of wireless LANs on implantable medical devices

① Implantable cardiac pacemakers

For wireless LAN access points, the maximum interference distance was 6 cm, and some form of effect was observed in 4 testing modes (1.0%). For the mobile device, the maximum interference distance was 1 cm or less, and some form of effect was observed in 4 testing modes (1.0%).

② ICDs

No effects were observed for either the wireless LAN access points or the mobile devices.

(4) Cautions for patients with implantable medical devices

1) Antitheft devices

In this research, it is not made clear exactly which type of device has a particular effect on implantable medical devices, but since effects were observed in approximately 10% of combinations of antitheft devices and implantable cardiac pacemakers when the person passed through the middle of the gates, approximately 40% when the person came close to the gate while turning between the gates, and nearly 50% when the person came very close to the gate (transmitter-receiver board), it is important for patients with implantable cardiac pacemakers to move away from the area between the gates as quickly as possible.

When in between the gates, there appears to be a higher tendency of the implantable medical devices being affected, if the person orients his/her chest and back towards the gates (transmitter-receiver board), such as twisting his/her body between the gates. When cutting across gates, it is recommended for patients with implantable medical devices to do so in a straight manner and facing forward. This is particularly important, as unnecessary defibrillation shock was observed at a distance of 42.5 cm and an angle of 90 degrees in relation to the gate for ICDs (it is confirmed that in a state where the person is facing straight forward, no shock occurs as long as he/she does not come with 1/4 of the distance of the installation width of the gates).

As it is indicated that implantable medical devices are affected at the same distance regardless of whether the person is between or outside of the gates, it is necessary to warn patients not to come close to antitheft devices as much as possible even if they are standing outside of the gates.

2) RFID devices

In this research conducted in 2003, gate-type and hand-held type RFID devices were investigated.

For gate-type RFID devices, effects for the combination of RFID devices and implantable cardiac pacemakers were observed as follows: approximately 1% when the person passed the center of the area between the gates, approximately 5% when the person changed his/her orientation while in the center of the area between the gates, and approximately 20% when the person came very close to the gate (transmitter-receiver board). In addition, as unnecessary defibrillation shock was observed in ICDs that were in very close proximity of the gate, and since distinguishing between RFID devices from antitheft devices in terms of external appearance is difficult, the same precautions as for antitheft devices in 1) are considered as being necessary.

For hand-held types, since unnecessary defibrillation shocks were observed with ICDs at a distance of 1 cm, and also since it is easily possible to bring these types of RFID devices close to human bodies because they are hand held, it is necessary to take precautions not to place RFID devices within 22 cm of implantable medical devices inadvertently.

3) Wireless LANs

The effects that were observed with the wireless LANs that are currently in distribution were all for the same implantable cardiac pacemaker, and patients using this model have already been warned by the concerned company to promote awareness. For other implantable medical devices, although effects were not observed, it is appropriate to continue exercising the general caution of not bringing implantable medical devices unnecessarily close to objects that emit electromagnetic waves.

(5) Request for medical institutions

In this time, results from investigation on antitheft devices, RFID devices (excluding fixed types), and wireless LANs are introduced. However, with regard to antitheft devices for which the percentage of effects was particularly high, it was not made clear in this investigation exactly which type of device has a particular effect on implantable medical devices. From the perspective of preventing heath hazards for people with implantable medical devices, MHLW requests that it be made thoroughly clear to patients to adhere to the following items and if the patient is a child, MHLW also requests that the child's caregivers be thoroughly informed as well.

- Any person with implantable medical devices should not stop between the gates of antitheft devices or come into close proximity of the gates unnecessarily, such as leaning on the gates.
- If it is inevitable that one must pass through antitheft devices, etc., do so by rapidly and by passing through the middle of the area between the gates while facing straight ahead.
- For gate-type RFID devices, take the same precautions as for antitheft devices, since distinguishing between gate-type RFID devices from antitheft devices in terms of external appearances is difficult.
- With regard to hand-held type RFID devices, take precautions not to allow hand-held RFID devices to come within 22 cm of implantable medical devices unnecessarily.

3

Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 202), together with reference materials.

1 Monoethanolamine Oleate

Brand Name (name of company)	Oldamin for Injection (Fuji Chemical Industry Co., Ltd.)
Therapeutic Category	Hemostatics
Indications	Haemostasis of oesophageal varices haemorrhage and sclerosing/involution of oesophageal varices

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

[Important Precautions]

Acute respiratory distress syndrome and pulmonary oedema due to effusion towards areas other than those that are considered target areas may occur. Hemodynamics in treated areas should be monitored, and caution should be exercised for effusion towards areas other than the varices oesophageal.

[Adverse Reactions (clinically significant adverse reactions)]

Acute respiratory distress syndrome, pulmonary oedema: Acute respiratory distress syndrome and pulmonary oedema may occur. Patients should be carefully monitored. If rapidly advanced dyspnoea, hypoxemia, and bilateral diffuse infiltration shadows confirmed by chest X-ray are observed, appropriate measures, such as respiratory management and circulatory management, 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 70s	Oesophageal varices (hepatic cirrhosis, diabetes mellitus, hypertension)	[as oldamin for injection (10%)] 3.5 mL Once	**Pulmonary embolism, adult respiratory distress syndrome** Medical history: Segmental resection of right lung On day 1 of administration: As endoscopic sclerotherapy, 7 ml of the 5% solution was injected into varicose vein for the treatment of oesophageal varices. There were no leaks outside of the varicose vein. Drug was in stasis for 5 minutes in balloon of proximal end. Thrombin was sprayed when removing the needle. Immediately after removing the endoscope, dry cough and dyspnoea developed. Oxygen inhalation was conducted during the operation, and continued afterwards as well (3 L/min.). SaO_2 decreased to 80% from 100%. High dose of steroids were administered, and the patient was transferred under the control of ICU. Diffuse granular shadows for both lungs were confirmed in the chest X-ray test. 3 days after administration: The symptoms such as dyspnoea disappeared.	Company report
	Concomitant medications: iopamidol				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 70s	Oesophageal varices (hepatic cirrhosis, chronic hepatitis C, gastric varices, osteoporosis)	[as oldamin for injection (10%)] 5.25 mL Once	**Pulmonary oedema** Approx. 4 years before administration: Hepatic cirrhosis and oesophageal varices were suggested. 11 days before administration: The patient was hospitalized for the purpose of endoscopic sclerotherapy for oesophageal varices. There was perforating veins penetrating the muscularis propria in the esophagus. 7 days before administration: Ligation of esophageal varices was carried out. Though sclerotherapy was continued, it was discontinued since the drugs leaked out of the vessels. On day 1 of administration: As endoscopic sclerotherapy, 0.5 mL (extravascular) and 7.0 mL (intravascular) of the 5% solution was injected into the oesophageal varices. The flow of the solution into the vessel was confirmed through fluoroscopic imaging, and it was also confirmed that there was no excessive flow towards the hepatic side. Shortly after the injection, facial flush, wheezing, and chest pain developed. As a result, treatment was continued after deairing 20 mL of air from the esophageal balloon.	Company report

				At this time, the oxygen saturation was 98%. After injecting 0.5 mL (extravascular) of the solution, chest pain developed and 5 mg of midazolam was intravenously injected. The oxygen saturation decreased to 85% to 87%, and 3 L of oxygen was administered through the nose. In addition, 0.5 mL (extravascular) and 2 mL (intravascular) of the solution were injected, and since there was no improvement in oxygen saturation, 10 mg of flumazenil was intravenously administrated immediately after this drug was injected. Oxygen saturation improved to 93% to 95%, and the needle holes were astricted twice with a balloon. 30 minutes after administration: Immediately after removing the endoscope, the patient complained of respiratory discomfort, and cyanosis, pink-colored foamy sputum were confirmed. 40 minutes after administration: Oxygen saturation was 70% and did not improve, decrease in state of consciousness was confirmed. Endotracheal intubation was immediately conducted, pure oxygen was used for ventilation. Diffuse infiltrative shadows were confirmed in both lungs (more prominent in left lung) in chest X-ray. No significant changes in echocardiography. Cardiogenic pulmonary oedema and embolism lung were negative, and the patient was diagnosed with pulmonary oedema. 1 hour after administration: The patient was transferred to ICU. Although she was put on an artificial respirator, oxygen saturation was poor at 85%. Assisted ventilation using PEEP was carried out. Blood pressure decreased and the patient went into shock. Steroid pulse therapy and administration of ulinastatin and dopamine hydrochloride were performed. 2 hours and 30 minutes after administration: Increase in partial pressure O_2 confirmed. 2 days after administration: Tubes removed, the patient transferred to general ward. 32 days after administration: The patient was discharged from the hospital.	
	Concomitant medications: iopamidol, lidocaine, lactated Ringer's solution, pentazocine, hydroxyzine hydrochloride, scopolamine butylbromide, midazolam, flumazenil				

2 Clarithromycin

Brand Name (name of company)	Klaricid Tablets 50 mg for Pediatric Use, Klaricid Tablets 200 mg, Klaricid Dry Syrup for Pediatric Use (Abbott Japan Co., Ltd.) Clarith Tab. 50 for Pediatric, Clarith Tab. 200, Clarith Dry Syrup for Pediatric (Taisho Pharmaceutical Co., Ltd.)
Therapeutic Category	Acting mainly on gram-positive bacteria and mycoplasma
Indications	(For Klaricid Tablets 50 mg for Pediatric Use, Klaricid Dry Syrup for Pediatric Use, Clarith Tab. 50 for Pediatric, Clarith Dry Syrup for Pediatric) General infectious diseases Clarithromycin-susceptible microorganisms: *Staphylococcus sp., Streptococcus sp., (excluding enterococci), Branhamella catarrhalis, Haemophilus influenzae, Bordetella pertussis, Campylobacter sp., Mycoplasma sp.,* and *Chlamydia sp.* ○ Folliculitis, erysipelas, cellulites, lymphangitis (lymphadenitis), felon, suppurative paronychia, subcutaneous abscess, hidradenitis, acne conglobata, infected skin atheroma, chronic pyoderma, superficial secondary infections such as traumatic injury, thermal burn, and surgical wound ○ Laryngopharyngitis, acute bronchitis, tonsillitis, chronic bronchitis, pneumonia, pulmonary suppuration ○ Campylobacter enterocolitis ○ Scarlet fever ○ Pertussis ○ Otitis media ○ Sinusitis Disseminated mycobacterial infection associated with acquired immunodeficiency syndrome (AIDS) (For Klaricid Tablets 200 mg and Clarith Tab. 200) General infectious diseases The following infectious diseases resulting from clarithromycin-susceptible *Staphylococcus sp., Streptococcus sp., (excluding enterococci), Peptostreptococcus sp., Branhamella catarrhalis, Haemophilus influenzae, Campylobacter sp., Mycoplasma sp., and Chlamydia sp.* ○ Folliculitis, furuncle, furunculosis, carbuncle, erysipelas, cellulitis, lymphangitis (lymphadenitis), felon, suppurative perionychia, subcutaneous abscess, hidradenitis, acne conglobata, infected skin atheroma, chronic pyoderma, perianal abscess, superficial secondary infections such as traumatic injury, thermal burn, and surgical wound ○ Laryngopharyngitis, acute bronchitis, tonsillitis, chronic bronchitis, diffuse panbronchiolitis, bronchiectasis (during infectious episode), secondary infection of chronic respiratory disorders, pneumonia, pulmonary suppuration ○ Non-gonococcal urethritis ○ Campylobacter enterocolitis ○ Cervicitis ○ Otitis media, sinusitis ○ Periodontitis, pericoronitis, jaw inflammation Disseminated mycobacterial infection associated with acquired immunodeficiency syndrome (AIDS) Helicobacter pylori infection in gastric ulcers or duodenal ulcer

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

[Contraindications]	Patients receiving administration of pimozide, ergotamine, and cisapride
[Interactions (contraindications for concomitant use)]	(terfenadine was omitted) Ergotamine (ergotamine tartrate, dihydroergotamine mesilate)
[Interactions (precautions for concomitant use)]	Calcium antagonist (nifedipine, verapamil hydrochloride, etc.)
[Adverse Reactions (clinically significant adverse reactions)]	**Fulminant hepatitis, hepatic dysfunction, jaundice, hepatic failure:** Since fulminant hepatitis, hepatic dysfunction with increased AST (GOT), ALT (GPT), γ-GTP, LDH, Alk-phos, and/or the like, jaundice, and/or hepatic failure may occur, patients should be closely monitored. If any abnormalities are observed, this drug should be discontinued and appropriate therapeutic action take. **Thrombocytopenia, pancytopenia, hemolytic anemia, leukopenia, agranulocytosis:** Since thrombocytopenia, pancytopenia, hemolytic anemia, leukopenia, and/or agranulocytosis may occur, patients should be closely monitored (e.g., with periodical blood tests). If any abnormalities are observed, this drug should be discontinued and appropriate therapeutic action taken. **Pseudomembranous colitis, hemorrhagic colitis**: Since serious colitis (pseudomembranous colitis, hemorrhagic colitis, etc.) may occur, patients should be closely monitored. If any abnormalities (abdominal pain, frequent diarrhea, etc.) are observed, this drug should be discontinued and appropriate therapeutic action taken. **Convulsion**: Since convulsion (tonic-clonic convulsion, myoclonus, sudden attack of loss of consciousness, etc.) may occur, patients should be closely monitored. If any abnormalities are observed, this drug should be discontinued and appropriate therapeutic action taken. **Allergic purpura**: Since allergic purpura may occur, patients should be closely monitored. If any abnormalities are observed, this drug should be discontinued and appropriate therapeutic action taken. **Acute renal failure**: Since acute renal failure may occur, patients should be closely monitored. If any abnormalities (abnormal renal function tests [e.g., increased blood creatinine], oliguria, etc.) are observed, this drug should be discontinued and appropriate therapeutic action 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	Male 80s	Chronic respiratory failure (chronic emphysema, zinc deficiency disorder)	200 mg 21 days	**Anaemia haemolytic autoimmune** 56 days before administration: The patient had cold symptoms. Cefditoren pivoxil was prescribed. 28 days before administration: The patient visited the hospital and received consultation. He complained of physical deconditioning. Anorexia also deleloped at the same time. 15 days before administration: Gastroscope was carried out: Only 1 polyp was found. On day 1 of administration: The patient visited the hospital and received consultation. Physical deconditioning persisted, and the patient complained of headaches.	Company report

				Starting this day, medication was switched to the erythromycin used in the past, and this drug was started to prescribe. On day 13 of administration: The patient was hospitalized in the department of internal medicine. Symptoms of headache and anorexia, etc. persisted. Due to increased LDH and bilirubin, and a decrease in haptoglobulin, the patient was diagnosed with haemolytic anaemia. As direct Coombs test and indirect Coombs test were both positive, the symptom was diagnosed as being autoimmune. On day 19 of administration: The symptoms continued after hospitalization, anemia was not improved. On day 21 of administration (day of discontinuation): Administration of this drug was discontinued. 19 days after discontinuation: The symptoms gradually improved. Test values also showed improvements in haemoglobin. 42 days after discontinuation: Lymphocyte migration inhibition test was conducted. This drug: positive, cefditoren pivoxil, famotidine: negative 52 days after discontinuation: The symptoms nearly disappeared, and the patient was discharged from the hospital.	
	Concomitant medications: cefditoren pivoxil, famotidine, pentoxifylline, triazolam, vitamin-B complex, sodium picosulfate, theophylline, procaterol hydrochloride, ipratropium bromide, zinc sulfate				

Clinical Laboratory Values

	56 days before administration	On day 1 of administration	On day 13 of administration	19 days after discontinuation	63 days after discontinuation
RBC ($\times 10^4/mm^3$)	447	331	257	315	420
Haemoglobin (g/dL)	14.6	10.5	8.8	10.5	13.4
Haematocrit (%)	43.0	32.7	27.3	33.5	40.2
Reticulocyte (‰)	—	—	64.7	9.8	—
LDH (IU/L)	324	1093	1008	439	—
Total bilirubin (mg/dL)	0.8	1.6	1.1	0.4	—
Haptoglobulin (mg/dL)	—	—	5	—	—
Direct Coombs test	—	—	(+)	—	—
Indirect Coombs test	—	—	(+)	—	—

RBC: Red 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 60s	Upper respiratory inflammation (none)	400 mg 8 days	**Clonic convulsion of upper body** Approx. 10 months before administration: As clonic convulsions developed during treatment at Hospital A for upper respiratory inflammation (including macrolide antibiotics), the patient underwent head testing with CT and MRI at Hospital B, but no abnormalities were confirmed. Although drip infusion was given, the symptoms did not improve (department of psychiatry/neurology). Cause was unclear. The symptoms disappeared after 2 to 5 days after abandoning treatment. On day 1 of administration: Treatment for upper respiratory inflammation was initiated at Hospital C (this hospital). On day 8 of administration (day of discontinuation): Clonic convulsions (continuation of movement where both shoulders moved up and down [1 movement/0.2 to 0.3 seconds]) started to develop. Since the symptoms were the same as those from 10 months ago, and since the patient did not complain very much of pain, administration was discontinued. On day 10 to 13 of administration: The symptoms disappeared.	Company report
	Concomitant medications: kakkonkajutsubuto extract, Kikyoto extract, lysozyme hydrochloride, dihydrocodeine phosphate/dl-methylephedrine hydrochloride/chlorpheniramine maleate				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female Under age of 10	Suspected mycoplasma infection (acute bronchitis)	200 mg 3 days	**Allergic purpura** 7 days before administration: Cough developed. 5 days before administration: Slight fever of 37.5°C, cough intensified during night. 3 days before administration: Mild pharynx redness of was confirmed. Theophylline, carbocisteine, procaterol hydrochloride, and cefroxadine were prescribed, and the administration was started around noon. 1 day before administration: Hyperthermia of 38.4°C developed. On day 1 of administration: Rale in chest was confirmed, abnormality was also confirmed in chest X-ray test. The patient was diagnosed with acute bronchitis. Mycoplasma pneumonia was suspected as the cause, and this drug was prescribed taking inhalation of theophylline into consideration.	Company report

				On day 3 of administration (day of discontinuation): The patient had no pyrexia, and cough improved, but starting around noon, a rash on mandible developed, and the patient complained of abdominal pain. This drug was administered until around noon. 2 days after discontinuation: Abdominal pain persisted, rash on lower limbs also developed. 4 days after discontinuation: The patient visited the pediatric department in this hospital, and was diagnosed with allergic purpura. Injection of infusion fluid, tranexamic acid, and carbazochrome sodium sulfonate were initiated. 5 days after discontinuation: The patient did not complain of abdominal pain. 10 days after discontinuation: Rash (bleeding spots) disappeared. 18 days after discontinuation: No particular problems were observed afterwards.	
	Concomitant medications: cefroxadine, carbocisteine, procaterol hydrochloride, theophylline				

Clinical Laboratory Values

	4 days after discontinuation	12 days after discontinuation	18 days after discontinuation
Platelet ($\times 10^4/mm^3$)	53.4	37.6	29.1
Bleeding time (min. sec.)	2.30	—	—
Time when coagulation started (min. sec.)	4.30	—	—
Time when coagulation ended (min. sec.)	9.30	—	—
Factor XIII (%)	79	—	—
PT (sec.)	11.9	—	—
APTT (sec.)	34.1	—	—
Rumpel-Leede sign	+ (6 signs)	3+	—

PLT: Platelet APTT: Activated Partial Thromboplastin Time
PT: Prothrombin time

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Male 60s	Bronchitis (chronic nephritis, bronchial asthma, cardiac failure, lung cyst)	400 mg 11 days	**Acute renal failure** 17 days before administration: The patient was hospitalized for dyspnoea and hypoxemia resulting from lung cyst and bronchitis. After hospitalization, bronchitis improved through administration of this drug after cefoperazone sodium (2 g × 10 days). On day 4 of administration: Since hypoxemia did not recover sufficiently, the patient was discharged from the hospital under the condition of home oxygen therapy. On day 7 of administration: Urine output decreased, dyspnoea exacerbated, and development of anasarca.	Company report

				On day 8 of administration: The patient visited this hospital, and was confirmed to have significant hypoxemia (PO_2 69.8 mmHg, PCO_2 59.0 mmHg under administration of O_2 at 5 L/min.) and cardiac failure. Thus, intravenous furosemide was used, but since diuresis was insufficient (urine volume 1250 mL/day), dobutamine hydrochloride and dopamine hydrochloride were also used. On day 9 to 10 of administration: Although the above diuretics were used, urine volume was 500 mL/day; oliguria. On day 11 of administration (day of discontinuation): Cardiac failure did not improve, creatinine increased to 4.3 mg/dL and haemodialysis (drainage: 2.3 kg) was performed. Administration of this drug was discontinued. Urine volume was 900 mL/day. 1 day after discontinuation: Urine volume was 1300 mL/day. 2 days after discontinuation: Urine volume was 2700 mL/day. 3 days after discontinuation: Urine volume was 3300 mL/day. 4 days after discontinuation: Urine volume was 1900 mL/day. 5 days after discontinuation: Urine volume was 1650 mL/day. 6 days after discontinuation: Urine volume was 1300 mL/day. 7 days after discontinuation: Serum creatinine recovered to 2.4 mg/dL, cardiac failure also disappeared.	
	Concomitant medications: nifedipine, temocapril hydrochloride, benzbromarone, allopurinol, isosorbide mononitrate, theophylline, furosemide, dilazep dihydrochloride, isosorbide dinitrate adhesive preparation, triazolam, cefoperazone sodium				

Clinical Laboratory Values

	7 days before administration	3 days before administration	On day 8 of administration	2 days after discontinuation	7 days after discontinuation
BUN (mg/dL)	41	—	53	84	26
Creatinine (mg/dL)	2.2	—	2.6	4.7	2.4
Serum sodium (mEq/L)	—	143	143	143	145
Serum potassium (mEq/L)	—	5.4	5	5 2	4
Serum chloride (mEq/L)	—	104	110	106	102
Urine volume (mL/day)	—	—	1250	2700	—

BUN: Blood Urea Nitrogen

3 Tegafur/Gimeracil/Oteracil Potassium

Brand Name (name of Company)	TS-1 Capsule 20 and 25 (Taiho Pharmaceutical Co., Ltd.)
Therapeutic Category	Antimetabolites
Indications	Gastric cancer, colon cancer/rectal cancer, head and neck cancer

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

[Adverse Reactions (clinically significant adverse reactions)]

Serious stomatitis, gastrointestinal ulceration, haemorrhage of digestive tract, gastrointestinal perforation: Serious stomatitis, gastrointestinal ulceration, haemorrhage of digestive tract, and gastrointestinal perforation may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued, necessary tests, such as abdominal X-rays, etc. should be performed, and appropriate measures 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	Male 60s	Advanced gastric cancer (Cerebral infarction, hypertension)	120 mg 9 days	**Gastric perforation** The patient visited neighborhood doctor due to stomach symptoms and weight decreased. Anaemia, CEA antigen increased, and gastric lesion based on contrast test of upper digestive tract were suggested. 23 days before administration: Type 2 gastric cancer in pylorus was suggested based on GIF. 15 days before administration: The patient was diagnosed with non-resectable advanced gastric cancer based on CT. On day 1 of administration: Administration of 120 mg of this drug + cisplatin treatment were initiated. On day 8 of administration: Cisplatin (110 mg) was administered. On day 9 of administration (day of discontinuation): Development of upper left abdominal pain starting in the morning. In physical findings, tenderness was confirmed in upper left abdomen, and emergency CT test was conducted. Free air confirmed in CT, and the patient was diagnosed with gastric perforation. Emergency operation was performed. Administration of this drug was discontinued. Perforation in lesion area (front wall side) of gastric cancer of vestibular part was confirmed during operation. 12 days after discontinuation: Improvement after operation was favorable, gastric perforation recovered.	Company report
	Concomitant medications: cisplatin, ifenprodil tartrate, benidipine hydrochloride, troxipide, trandolapril, triazolam, D-mannitol, ramosetron hydrochloride, etizolam, dexamethasone, metoclopramide				

Clinical Laboratory Values

	9 days before administration	6 days before administration	On day 1 of administration	On day 7 of administration	On day 9 of administration (day of discontinuation)	1 day after discontinuation	11 days after discontinuation
WBC (/mm^3)	5400	4400	5600	3200	8400	6200	3300
RBC ($\times10^4$/mm^3)	373	398	337	295	309	368	281
Haemoglobin (g/dL)	9.6	10.8	9.3	8.2	9.0	10.4	8.3
PLT ($\times10^4$/mm^3)	31.5	25.9	28.4	30.6	33.5	25.0	31.2
Total protein (g/dL)	6.2	—	5.7	5.4	5.4	4.2	5.0
Albumin (g/dL)	3.6	—	3.3	3.2	—	2.6	2.7
Total bilirubin (mg/dL)	0.6	—	0.5	0.6	1.0	1.3	—
Direct bilirubin (mg/dL)	0.1	—	0.1	0.1	—	0.4	—
AST (GOT) (IU/L)	14	—	12	12	16	17	35
ALT (GPT) (IU/L)	11	—	11	10	12	12	78
LDH (IU/L)	160	—	149	175	265	196	196
Al-P (IU/L)	218	—	198	168	168	132	532
γ-GTP (IU/L)	14	—	14	18	—	11	119
BUN (mg/dL)	11	—	11	8	17	12	9
Creatinine (mg/dL)	0.6	—	0.6	0.6	0.5	0.5	0.6
Blood uric acid (mg/dL)	3.5	—	3.5	2.4	—	1.8	1.6
Total cholesterol (mg/dL)	155	—	145	113	—	89	113
Neutral fat (mg/dL)	—	—	67	60	—	—	53
FBG (mg/dL)	87	—	86	119	251	149	136
Serum Na (mEq/L)	133	—	136	137	131	131	138
Serum K (mEq/L)	4.2	—	4.1	4.6	3.4	3.9	4.1
Serum Cl (mEq/L)	100	—	100	102	99	99	99
CRP (mg/dL)	0.3	—	—	—	—	7.3	3.1

WBC: White Blood Cell
RBC: Red Blood Cell
PLT: Platelet
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
BUN: Blood Urea Nitrogen
FBG: Fasting blood glucose
CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	Gastric cancer (none)	(1st course) 120 mg 14 days ↓ (2nd course) 120 mg 28 days ↓ (1st course of concomitant treatment) 120 mg 21 days ↓	**Gastric perforation** On day 1 of administration: Administration of 120 mg of this drug was initiated (1st course). 22 days after administration: Anaemia developed. Blood transfusion (2 days) of concentrated human red blood cells (1 unit) was conducted. The patient was recovered from anaemia on the same day. 28 days after administration: Administration of 120 mg of this drug was initiated (2nd course). 35 days after administration: Blood transfusion of concentrated human red blood cells was conducted. 70 days after administration: Concomitant administration of 120 mg of this drug was initiated (1st course of concomitant treatment).	Company report

			(2nd course of concomitant treatment) 120 mg 12 days	78 days after administration: Intravenous drip infusion of 100 mg of cisplatin was conducted. 112 days after administration: Concomitant administration of 120 mg of this drug was initiated (2nd course of concomitant treatment). 120 days after administration: Intravenous drip infusion of 100 mg of cisplatin was conducted during hospitalization. 124 days after administration: The patient was discharged from the hospital (no adverse reactions). 125 days after administration (day of discontinuation): Abdominal pain developed. The patient received diagnosis at another hospital, where he was received intramuscular administration of an analgesic drug, but pain did not improve and the patient was referred to this hospital. At the hospitalization, the patient had peritonitis symptoms, and after being diagnosed with peritonitis resulting from gastric cancer perforation, an emergency operation (lavage drainage, gastrostomy) was performed (the perforation area was consistent with the ulcer base of the stomach cancer). CT: Large amount of ascites. Administration of this drug was discontinued. 3 days after discontinuation: Blood transfusion of concentrated human red blood cells was conducted (2 days). 45 days after discontinuation: The patient was discharged from the hospital. 130 days after discontinuation: The patient died. Cause of death: gastric cancer, autopsy: not performed.	
	Concomitant medications: cisplatin				

Clinical Laboratory Values

	120 days after administration	123 days after administration	125 days after administration	3 day after discontinuation	17 days after discontinuation	38 days after discontinuation
WBC (/mm^3)	19200	26100	40300	31000	17400	17100
Basophils (%)	0.7	0.4	0.1	0.1	0.5	0.5
Eosinophils (%)	2.1	0.3	0.2	1.4	3.3	2.3
Neutrophils (%)	76.1	87.9	94.2	94.5	74.1	71.9
Lymphocytes (%)	17.3	10.3	4.7	3.3	16.9	22.4
Monocytes (%)	3.8	1.3	0.8	0.7	5.2	2.9
RBC ($\times10^4$/mm^3)	331	287	328	268	299	322
Haemoglobin (g/dL)	9.2	8.1	9.2	7.4	8.5	9.1
Haematocrit (%)	28.9	24.6	28.2	23.0	26.2	28.0
MCV (FL)	87.3	85.7	86.0	85.8	87.6	87.0
PLT ($\times10^4$/mm^3)	50.5	47.3	46.2	27.2	55.9	25.1
Total protein (g/dL)	6.5	—	4.8	4.5	5.9	6.6
Total bilirubin (mg/dL)	0.81	—	1.23	1.37	0.37	0.67
AST (GOT) (IU/L)	24	17	17	14	12	16
ALT (GPT) (IU/L)	10	10	8	7	5	4

LDH (IU/L)	447	420	365	285	235	281
Al-P (IU/L)	201	158	114	124	207	255
BUN (mg/dL)	9.0	16.6	36.9	21.7	15.4	13.5
Creatinine (mg/dL)	1.13	1.18	1.67	1.15	0.71	0.97
CRP (mg/dL)	≤0.5	—	1.9	18.7	—	1.2
Serum Na (mEq/L)	136	137	134	133	135	139
Serum K (mEq/L)	4.4	3.7	3.8	3.6	4.3	4.0
Serum Cl (mEq/L)	111	98	98	101	99	105

WBC: White Blood Cell
RBC: Red Blood Cell
MCV: Mean Corpuscular Volume
PLT: Platelet
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
Al-P: Alkaline Phosphatase
BUN: Blood Urea Nitrogen
CRP: C-Reactive Protein

4 Melphalan (injectable dosage form)

Brand Name (name of Company)	Alkeran for Injection 50 mg (GlaxoSmithKline K.K.)
Therapeutic Category	Alkylating agent
Indications	Pretreatment for the following diseases during hematopoietic stem cell transplantation Leukemia, malignant lymphoma, multiple myeloma, solid tumors in children

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

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur, and cardiac arrest associated with such symptoms may occur in rare instances. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Serious hepatic function disorder, jaundice: Hepatic function disorder with an increase in AST (GOT), ALT (GPT), bilirubin values, Al-P, and LDH, and jaundice, as well as hepatic veno occlusive (disease) associated with jaundice, rapid weight increased, and painful hepatomegaly may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures 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 40s	Pretreatment for sibling peripheral blood stem cell transplantation /multiple myeloma (nephrotic syndrome, chronic renal failure)	70 mg/m^2 2 days	**Hepatic veno-occlusive disease (VOD), aggravation of chronic renal failure, nausea, vomiting, mucositis, skin eruption** The patient to undergo second transplantation. 3 days before administration: Administration of fludarabine phosphate was initiated as pretreatment for sibling peripheral blood stem cell transplantation (4 days). On day 1 of administration: Administration of this drug was started. Nausea and vomiting developed. As treatment, metoclopramide, hydroxyzine pamoate, granisetron hydrochloride, and antiulcer drug were administered. 1 day after completion: Sibling peripheral blood stem cell transplantation was performed. 6 days after completion: Mucositis developed. As treatment, antiulcer drug and lidocaine hydrochloride (external gargling solution) were administered. 7 days after completion: Skin eruption developed. As treatment, steroid ointment and zinc oxide ointment were administered. 10 days after completion: Hepatic veno-occlusive disease (ascites, weight increased, hepatic failure) developed. Liver supporting therapy using ursodeoxycholic acid, ethyl icosapentate, and glycyrrhizin/glycine/cysteine was conducted. 11 days after completion: Nausea and vomiting improved. 15 days after completion: Secondary cardiac failure resulting from hepatic veno-occulsive disease manifested. As treatment, vapopressors and diuretics were administered. 19 days after completion: Aggravation of chronic renal failure occurred. As treatment, vapopressors and diuretics were administered. 21 days after completion: The patient died from hepatic veno-occulsive disease. Autopsy: not performed	Company report
	Concomitant medications: fludarabine phosphate, famotidine, sulfamethoxazole/trimethoprim, fluconazole, levofloxacin, polymixin B sulfate, dalteparin sodium, dopamine hydrochloride, furosemide, glycyrrhizin/glycine/cysteine, granisetron hydrochloride, allopurinol, aciclovir, deproteinized calf blood extract, menatetrenone, trandolapril, ciclosporin, potassium canrenoate, methotrexate, cefozopran hydrochloride, filgrastim (Genetical recombination), human serum albumine, omeprazole sodium, prednisolone, ursodeoxycholic acid, ethyl icosapentate, meropenem trihydrate, antiulcer drug, ranitidine hydrochloride				

Clinical Laboratory Values

	4 days before administration	On day 1 of administration	2 days after completion	7 days after completion	12 days after completion	16 days after completion	21 days after completion
AST (GOT) (IU/L)	24	96	84	60	17	6	156
ALT (GPT) (IU/L)	54	140	143	108	54	25	197
LDH (IU/L)	299	342	340	239	164	119	70
Al-P (IU/L)	534	591	587	634	563	293	428
BUN (mg/dL)	21	17	23	36	83	108	203
Serum creatinine (mg/dL)	1.7	2.0	2.1	2.5	3.4	2.9	4.9
Total bilirubin (mg/dL)	0.5	0.6	0.5	0.9	4.8	6.5	17.6
CRP (mg/dL)	0.1	0.1	0.1	0.7	7.5	11.7	18.7

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
Al-P: Alkaline Phosphatase
BUN: Blood Urea Nitrogen
CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male Under age of 10	Pretreatment for autologous peripheral blood stem cell transplantation/ neuroblastoma (drug-induced hepatic function disorder)	35 mg 1 day ↓ 30 mg 2 days	**Hepatic veno-occlusive disease (VOD), fever infectious, stomatitis** Height: 80 cm, weight: 9.2 kg 14 days before administration: Hepatic function disorder was confirmed [AST (GOT) 70 IU/L, ALT (GPT) 43 IU/L.]. On day 1 of administration: Administration of this drug was initiated as pretreatment for transplantation. On day 3 of administration: Total-body irradiation (3 Gy × 2) was performed (2 days) as pretreatment for transplantation. 2 days after completion: Autologous peripheral blood stem cell transplantation was performed. 5 days after completion: Onset of fever infectious. Although administration of ampicillin was carried out since before the treatment, medication was changed to meropenem trihydrate and fluconazole due to pyrexia of 38.9°C. 7 days after completion: Since pyrexia was not alleviated (40.4°C), administration of vancomycin hydrochloride was initiated. 10 days after completion: Stomatitis developed. The inside of the patient's mouth became very rough, and oral mucosal sloughing was also confirmed. Treatment for stomatitis was not implemented. 11 days after completion: CRP 15.2 mg/dL. 12 days after completion: Oral erosion and oral haemorrhage were confirmed. In a test conducted on the same day, total bilirubin was increased to 1.3 mg/dL. Starting around this time, a weight increased of approximately 100 g/day was started to observe.	Company report

				14 days after completion: White blood cell count recovered and pyrexia alleviated (infectious pyrexia improved). The pathogenic bacteria and infection focus were not clear. In addition, improving trends in stomatitis were found on the same day. Liver was palpated 3 fingerbreadths. 15 days after completion: Hepatic veno-occlusive disease developed. 17 days after completion: Although there was a white portion on the tongue, the patient's lips were clean. 18 days after completion: Stomatitis recovered. Abdominal distension due to ascites, weight increased, and painful hepatomegaly (3 fingerbreadths) were confirmed. Since hepatic veno-occlusive disease was suspected, administration of alprostadil alfadex was started. 19 days after completion: Weight increased, intensified abdominal distension, and urine output decreased were confirmed. The patient was diagnosed with aggravation of hepatic veno-occlusive disease, administration of alteplase (Genetical recombination) was initiated. 20 days after completion: Abdominal distension and dyspnoea due to accumulation of pleural effusion developed. Administration of prednisolone sodium succinate and freeze-dried concentrated human antithrombin III was also initiated. 21 days after completion: Administration of fresh frozen plasma for the purpose of replenishing protein C was conducted. 23 days after completion: Since efficacy could not be confirmed with alteplase (Genetical recombination) and freeze-dried concentrated human antithrombin III, administration was discontinued. Since dyspnoea progressed, an abdominal drainage was placed to improve symptoms. 24 days after completion: Liver was hard, palpated 4 fingerbreadths. 25 days after completion: Amount of abdominal drainage and body weight decreased. Administration of prednisolone was discontinued. Hepatomegaly was persisted afterwards, and although the liver was found to be hard upon palpation, improvements were observed, and a liver biopsy was forgone. 36 days after completion: Hepatic veno-occlusive disease improved (total bilirubin: 1.2 mg/dL). 44 days after completion: Total bilirubin was 0.8 mg/dL.	

	Concomitant medications: Polymixin B sulfate, sulfamethoxazole/trimethoprim, amphotericin B, ursodeoxycholic acid, tocopherol acetate, aciclovir, granisetron hydrochloride, ampicillin sodium/cloxacillin sodium, dalteparin sodium, dexamethasone sodium phosphate, pentazocine, diazepam, thiamylal sodium, sodium bicarbonate, freeze-dried sulfonated human normal immunoglobulin, chlorpheniramine maleate, hydrocortisone sodium succinate, human haptoglobin, meropenem trihydrate, fluconazole, nartograstim (Genetical recombination), vancomycin hydrochloride, nafamostat mesilate, potassium canrenoate, acetazolamide sodium, alprostadil alfadex, alteplase (Genetical recombination), freeze-dried concentrated human antithrombin III, prednisolone, panipenem/betamipron, famotidine, amantadine hydrochloride, fosfomycin sodium, imipenem/cilastatin sodium, antibiotics-resistant lactic acid bacteriae, heparin sodium, glutathione, mefenamic acid, furosemide, midazolam, hydroxyzine hydrochloride, human serum albumine

4

Revision of PRECAUTIONS

(No. 157)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 202) (excluding those presented in "3. Important Safety Information" of this Bulletin), together with reference materials.

1 <Psychotropics> Milnacipran Hydrochloride

[Brand Name]	Toledomin Tablets 15 and 25 (Asahi Kasei Pharma Corporation)
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder with an increase in AST (GOT), ALT (GPT), and γ-GTP levels, and jaundice 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

2 <Psychotropics> Olanzapine

[Brand Name]	Zyprexa Fine Granules 1%, Zyprexa Tablets 2.5 mg, 5 mg, and 10 mg (Eli Lilly Japan K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Convulsions:** Convulsions (tonicoclonic, partial seizures, myoclonus seizures) may occur. If any abnormalities are observed, appropriate measures, such as discontinuation of the administration, should be taken. **Rhabdomyolysis:** Rhabdomyolysis may occur. If symptoms such as myalgia, feelings of weakness, increased CK (CPK), increased myoglobin blood , and increased urine myoglobin are observed, administration should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for the onset of acute renal failure due to rhabdomyolysis.
<Reference Information>	Company report

6 <Antivirals> Lamivudine (100 mg)

[Brand Name]	Zefix Tablets 100 (GlaxoSmithKline K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Platelets decreased** may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.
<Reference Information>	Company report

7 <Opium alkaloids> Oxycodone Hydrochloride

[Brand Name]	OxyContin Tablets 5 mg, 10 mg, 20 mg, and 40 mg (Shionogi & Co., Ltd.)
[Careful Administration]	Patients with cardiac function disturbance or hypotension Patients with drug/alcohol dependence or a history of such dependence Patients with mental disorder caused by drugs, alcohol, etc.
<Reference Information>	Company report

3 <Skeletal muscle relaxants>
Dantrolene Sodium (oral dosage form)

[Brand Name]
Dantrium 25 and 50
(Yamanouchi Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]
Pleurisy: Pleurisy may occur. Patients should be carefully monitored. If symptoms such as chest pain and pleural effusion are observed, appropriate measures should be taken.

<Reference Information>
Company report

4 <Autonomic nervous system agents>
Distigmine Bromide (oral dosage form)

[Brand Name]
Ubretid Tab.
(Torii Pharmaceutical Co., Ltd.), and others

[Precautions of Dosage and Administration]
To prevent **cholinergic crisis**, treatment should be normally initiated at 5 mg per day for adults under close supervision by a physician, and dosage should be adjusted depending on the symptoms while monitoring patient (there have been many reports of cholinergic crisis developed within 2 weeks after initiating administration).
If efficacy is not observed, this drug should not be administered chronically, and other methods of treatment should be considered.

[Important Precautions]
Cholinergic crisis with consciousness disturbed may occur as symptoms of acute intoxication caused by this drug, pay attention to the following points.
1) As there have been many reports of cholinergic crisis develops within 2 weeks after initiating administration, caution should be exercised for initial symptoms (bradycardia, abdominal pain, diarrhoea, sweaty, saliva secretion excessive, miosis, dyspnoea, serum cholinesterase decreased, fasciculation, etc.) for especially 2 weeks after initiating administration.
2) Treatment should be normally initiated at 5 mg per day for adults. Dosage should be adjusted depending on the symptoms while monitoring patient.
3) Patient should be instructed to stop taking this drug and contact a physician etc. immediately, if abnormalities such as abdominal pain, diarrhoea, sweaty, and saliva secretion excessive are observed.

Serious aggravation of myasthenia, dyspnoea, and dysphagia (crisis) may occur in patients with myasthenia gravis. In such cases, crisis should be differentiated based on clinical symptoms, and if it is difficult to do so, intravenously administer 2 mg of edrophonium chloride, differentiate the crisis, and conduct the following treatment.
1) Cholinergic crisis: If symptoms such as bradycardia, abdominal pain, diarrhoea, sweaty, saliva secretion excessive, miosis, dyspnoea, serum cholinesterase decreased, and fasciculation are observed, or if aggravation/unchange of symptoms is confirmed after edrophonium chloride is administered, administration should be immediately discontinued and intravenous administration of 0.5 to 1 mg of atropine sulfate (dosage should be adjusted depending on the symptoms) should be conducted. In addition, secure an air passage as necessary, such as through artificial respiration or tracheostomy.
2) Myasthenic crisis: If symptoms such as dyspnoea, difficulty in ejecting saliva, cyanosis, or weakness generalised are confirmed, or if improvement in symptoms is confirmed after the administration of edrophonium chloride, the dosage of this drug should be increased.

In patients with dysuria due to hypotonic urinary bladder, such as after an operation or a neurogenic bladder, **cholinergic crisis** (initial symptoms: bradycardia, abdominal pain, diarrhoea, sweaty, saliva secretion excessive,

	miosis, dyspnoea, serum cholinesterase decreased, fasciculation, etc.) with consciousness disturbed may occur as acute intoxication caused by this drug. In such cases, administration should be immediately discontinued and intravenous administration of 0.5 to 1 mg of atropine sulfate (dosage should be adjusted depending on the symptoms) should be conducted. In addition, secure an air passage as necessary, such as through artificial respiration or tracheostomy.
[Adverse Reactions (clinically significant adverse reactions)]	**Cholinergic crisis:** Cholinergic crisis (initial symptoms: bradycardia, abdominal pain, diarrhoea, sweaty, saliva secretion excessive, miosis, dyspnoea, serum cholinesterase decreased, fasciculation, etc.) with consciousness disturbed may occur as symptoms of acute intoxication caused by this drug. In such cases, administration should be immediately discontinued and intravenous administration of 0.5 to 1 mg of atropine sulfate (dosage should be adjusted depending on the symptoms) should be conducted. In addition, secure an air passage as necessary, such as through artificial respiration or tracheostomy (there have been many reports of cholinergic crisis developed within 2 weeks after initiating administration).
[Use in the Elderly]	Since the elderly often have a decrease in hepatic/kidney functions and a tendency towards low body weight, adverse reactions develop easily. Treatment should be normally initiated at 5 mg per day. This drug should be administered cautiously for initial symptoms of cholinergic crisis for especially 2 weeks after initiating administration.
[Overdosage]	Signs and symptoms: Cholinergic crisis (initial symptoms: bradycardia, abdominal pain, diarrhoea, sweaty, saliva secretion excessive, miosis, dyspnoea, serum cholinesterase decreased, fasciculation, etc.) with consciousness disturbed may occur as a result of overdosage of this drug. Treatment: Administration should be immediately discontinued and intravenous administration of 0.5 to 1 mg of atropine sulfate (dosage should be adjusted depending on the symptoms) should be conducted. In addition, secure an air passage as necessary, such as through artificial respiration or tracheostomy.
<Reference Information>	Company report

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5 **<Alkylating agents>**

Melphalan (oral dosage form)

[Brand Name]	Alkeran Tablets (GlaxoSmithKline K.K.)
[Contraindications]	Patients with a history of hypersensitivity to ingredients of this drug
[PRECAUTIONS of Indications]	Since clearance of this drug decreases and adverse reactions caused by this drug are intensified in patients with renal disorder, considerations should be made to prevent overdose.
[Careful Administration]	Patients with renal impairment
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur, and in rare instances, cardiac arrest may occur associated with such symptoms. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Haemolytic anaemia:** Haemolytic anaemia 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