Pharmaceuticals and Medical Devices Safety Information

No. 290 April 2012

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

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Pharmaceuticals and Medical Devices Safety Information
No. 290 April 2012

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

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BP	Blood pressure
bpm	beats per minute
BT	Body temperature
BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal dialysis
CF	Complement-fixation
CHDF	Continuous hemodiafiltration
CHF	Continuous hemofiltration
CRP	C-reactive protein
Cr	Creatinine
CT	Computed tomography
DDD	Dual chamber
DLST	Drug lymphocyte stimulation test
ECG	Electrocardiography
eGFR	estimated glomerular filtration rate
EF	Ejection fraction
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
Ga	Gallium
GVHD	Graft-versus-host disease
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HCV-Ab	Hepatitis C virus antibody
HCV-RNA	Hepatitis C virus ribonucleic acid
HLA-B*5801	Human leukocyte antigens-B*5801
HR	Heart rate
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IU	International unit
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
NAG	N-acetylglucosaminidase
NAT	Nucleic acid amplification test
OTC	Over-the-counter
PA	Particle agglutination
PLT	Platelet
PSL	Prednisolone
RA	Room air
RBC	Red blood cell count
RR	Respiratory rate
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
S.I.	Stimulation Index
SJS	Stevens-Johnson syndrome

SpO_2	Oxygen saturation
TEN	Toxic epidermal necrolysis
VVI	Ventricular inhibited
WBC	White blood cell count
Xp	X-ray photograph
γ-GTP	gamma-glutamyl transpeptidase

1

Lookback Study on Blood Products for Transfusion

1. Introduction

The risk of hepatitis virus infection from blood transfusion has been significantly reduced due to the introduction of highly sensitive laboratory screening tests. Since some blood donors are in the window period,* however, the infection risk cannot be eliminated completely.[1,2,3)] Pre- and post-transfusion infection tests therefore need to be given to patients who have received blood transfusions (blood recipients) in accordance with the "Guidelines for Blood Transfusion Therapy" (revised edition)[4)] to ensure early detection and treatment of transfusion-associated infections.

This section describes the overview of the lookback study on blood products for transfusion which is conducted to minimize health hazards when a hepatitis virus infection from a blood transfusion occurs. If hepatitis virus infections are suspected in blood recipients, it is important to promptly report the cases from medical institutions to the Japanese Red Cross Society. In addition, if the Japanese Red Cross Society gives notice of a lookback study, which means that a blood product possibly contaminated with a pathogen has been used, medical institutions are required to check the patient's condition and immediately perform a blood test. These are presented with specific cases (Case 1 to 3).

* Window period: In the very early stage of infection with hepatitis virus, even the nucleic acid amplification test (NAT) cannot detect the virus because there is only a trace of it (the NAT window period). The blood donated while the donor is in the window period may become a source of infection. Currently, one session of blood donor screening with NAT can test blood samples of 20 donors together at the same time. But even a NAT in 1 donor (individual NAT) cannot detect the trace virus below the detection limit if the blood has been donated during the window period.

2. Lookback study on blood products for transfusion and its necessity

Lookback study on blood products for transfusion by the Japanese Red Cross Society is a retrospective investigation of products manufactured from blood of the same donors when a blood product is suspected of being contaminated by a pathogen, and a scientific analysis and evaluation of the causality between the reported infection case and the product. The study is categorized into 2 types according to the trigger information.[5)]

(i) A report from the medical institution
A suspected infection occurs in a medical institution. Viral contamination of products manufactured from the blood of a specific donor is suspected.

(ii) A positive conversion of screening test if identified in a repeat donor
A pre-donation test shows that a donor is infected, and he/she has donated blood in the past. Viral contamination of products manufactured from the blood of the donor is suspected.

Lookback studies can prevent the spread of infection from blood transfusion. If infection from blood transfusion is suspected, medical institutions are required to promptly report the cases to the Japanese Red Cross Society. In addition, if the Japanese Red Cross Society gives notice, conditions of the relevant blood recipients should be immediately checked. Cooperation by healthcare professionals for lookback studies is important to prevent infection from spreading.

3. Importance of prompt study and past case examples

When hepatitis virus infection from blood transfusion is suspected in a blood recipient based on pre- and post-transfusion tests, the medical institution is required to provide appropriate treatment to the patient, promptly report the case to the Japanese Red Cross Society, and provide the test results, information of recipients' conditions, and pre- and post-transfusion stored blood specimens (serum or plasma).[5)]

Once a case of hepatitis virus infection from blood transfusion is reported by a medical institution, the Japanese Red Cross Society performs an individual NAT of stored samples of donated blood to evaluate the causality. The blood products manufactured at the same time using the same donor's blood will be identified without waiting for the NAT result to turn out. The supply of the products will be discontinued if they have not been supplied to medical institutions (Case 1). If the products have been supplied but have not been used, unused products will be recalled. If the NAT is positive and the donor has provided multiple blood donations, the supply of the products manufactured at the same time as well as other blood products containing the donor's blood will be discontinued (Case 2).

Prompt reporting from the medical institution can prevent other patients from becoming infected. Even if the product manufactured at the same time has been used in other patients, early detection and treatment of infection will be possible based on a post-transfusion hepatitis virus survey (recipient investigation).

Infection of other patients may not be prevented if a report of suspected infection to the Japanese Red Cross Society is delayed.[6)]

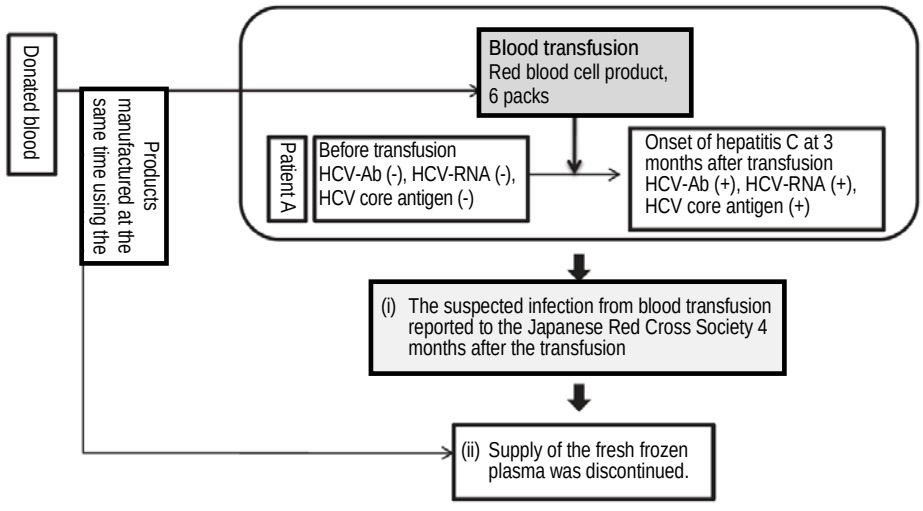
Lookback studies triggered by information from medical institutions are very important in terms of prevention of infection spread.

<Case 1>

A case of Patient A who developed post-transfusion hepatitis C was reported to the Japanese Red Cross Society. The supply of fresh frozen plasma manufactured at the same time as the product used in Patient A was discontinued, and it was successfully prevented from further use of products with possible pathogen contamination.

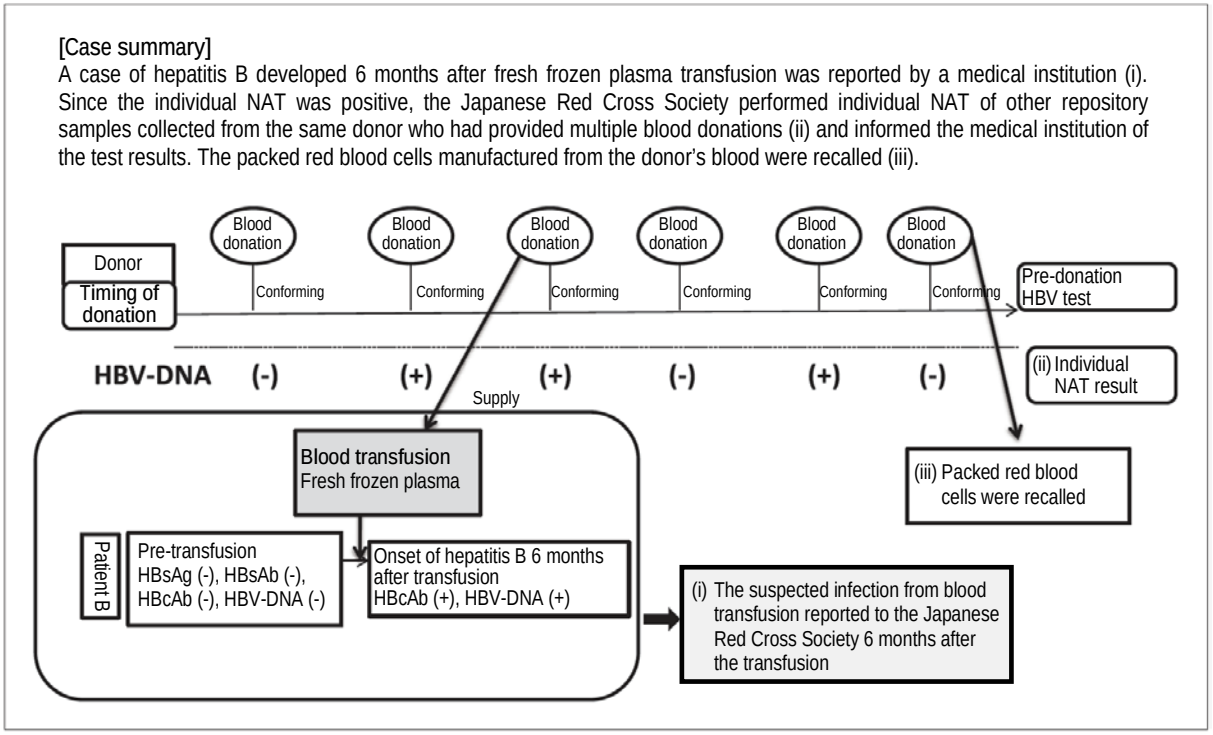
[Case summary]

A patient who was not infected with HCV developed hepatitis C 3 months after receiving red blood cell transfusion. Suspecting the infection was associated with the blood transfusion, the medical institution reported the case to the Japanese Red Cross Society (i), which discontinued the supply of products manufactured at the same time using the same donor's blood (ii). The individual NAT of the repository samples was all negative.



<Case 2>

A case of Patient B who developed post-transfusion hepatitis B was reported to the Japanese Red Cross Society. The packed red blood cells manufactured from the blood of the same donor were recalled, and it was successfully prevented from further use of products with possible pathogen contamination.



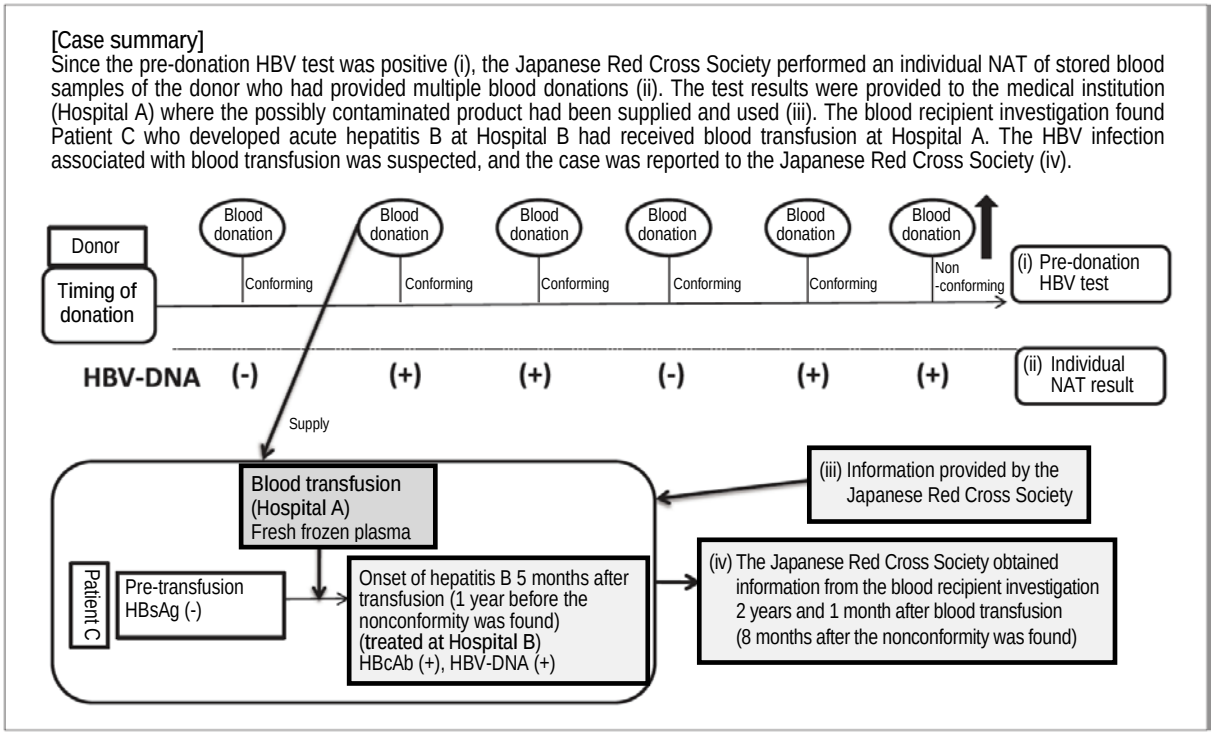
According to the Guidelines for Lookback Study on Blood Products revised in March 2012, the donor is asked to receive a test again to identify the causality between the blood transfusion and the hepatitis B virus (HBV) or hepatitis C virus (HCV) infection reported by a medical institution if he/she has not donated blood since. Possible non-transfusion infection routes should also be considered because, in some cases, the test ruled out the causality between the infection and the blood transfusion.

A lookback study is also required other than when triggered by the medical institutes (cases 1 and 2). This is for cases in which hepatitis is found at pre-donation screenings of hepatitis infections in donors who have donated blood before. Blood products for transfusion manufactured from the donor's blood may have been determined conforming since the results were lower than the detection limit because the donor was in the window period. If the test of a donor who has provided multiple blood donations is positive, the supply of the donor's blood will be discontinued, and a blood recipient investigation will be conducted in patients who have received products manufactured from the donor's blood. (Case 3)

<Case 3: Lookback study based on a suspected pathogen contamination identified by the donor's test result>

This case is one in which a donor's blood was determined non-conforming to the use as a material of blood product. Since the donor had provided multiple blood donations, supply of the products with possible pathogen contamination was discontinued, and the spread of infection was prevented.

After receiving blood transfusion at Hospital A, Patient C was treated for acute hepatitis at another institution (Hospital B). The lookback studies found the hepatitis B infection was probably from the blood transfusion. If the hepatitis virus infection had been reported to the Japanese Red Cross Society immediately after the suspected infection was identified (5 months after the blood transfusion), the product supply could have been discontinued earlier. Active cooperation and coordination of medical institutions can lead to earlier discontinuation of supply of possibly contaminated products, although patient follow-up may be difficult in some cases.



4. Request for cooperation in lookback studies

As shown in the previous section, it is very important that a medical institution promptly report hepatitis virus infection possibly from blood transfusion to the Japanese Red Cross Society. Medical institutions are required to check the patient's condition and immediately perform a blood test when the Japanese Red Cross Society gives notice of a lookback study, which means a blood product possibly contaminated with a pathogen has been used.

However, blood recipient investigations often fail to provide the Japanese Red Cross Society with information as to whether the recipients were infected or not.

Although post-transfusion follow-up may be difficult in some cases due to moving or transferring of the patient, medical institutions are requested to carefully monitor for post-transfusion hepatitis virus infection and promptly report suspected infection cases to the Japanese Red Cross Society.

If the Japanese Red Cross Society gives notice of a lookback study, please check and evaluate the pre- and post-transfusion tests of the blood recipient, contact him/her if necessary and advise him/her to seek medical consultation.

<References> (including provisionally translated titles)

1) Hepatitis B (General Q&As); revised in April 2008 (version 3)
http://www.vhfj.or.jp/06.qanda/about_btype.html
2) Hepatitis C (General Q&As); revised in April 2008 (version 7)
http://www.vhfj.or.jp/06.qanda/about_ctype.html
3) Chapter 3: Safety measures of blood products <infection tests>; 2010 Blood Project Report
http://www.mhlw.go.jp/new-info/kobetu/iyaku/kenketsugo/2i/dl/index-z.pdf
4) Partial revision of the "Guidelines for Blood Transfusion Therapy" and the "Guidelines for Blood Product Use" (PFSB Notification No. 0306-4, by the Secretary-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 6, 2012)
http://www.mhlw.go.jp/new-info/kobetu/iyaku/kenketsugo/5.html
5) Partial revision of the "Guidelines for Lookback Study on Blood Product" (PFSB Notification No. 0306-3, by the Secretary-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 6, 2012)
http://www.mhlw.go.jp/new-info/kobetu/iyaku/kenketsugo/5.html
6) Actions to be taken when hepatitis virus infection is suspected to be associated with blood transfusion (PFSB/SD Notification No. 0302-1 and PFSB/BBPD Notification No. 0302-1, by the Directors of Safety Division and Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 2, 2011)
http://www.mhlw.go.jp/new-info/kobetu/iyaku/kenketsugo/5anzen7.html

2

Drug-induced Serious Skin Disorders

1. Introduction

It has been well known that skin disorders occur as adverse drug reactions. Serious skin disorders include Stevens-Johnson syndrome (oculomucocutaneous syndrome; SJS) and toxic epidermal necrolysis (TEN).

The pathologies of SJS and TEN and relevant adverse reactions reported to the MHLW between April 1, 1997 and July 31, 2009 have been described in the Pharmaceuticals and Medical Devices Safety Information No. 163 (November 2000), No. 177 (May 2002), No. 203 (July 2004), No. 218 (October 2005), and No. 261 (September 2009).

Since adverse reaction reports have been collected for approximately 2 and half years from the article in September 2009, overview of the cases of SJS and TEN reported up to January 31, 2012 are presented.

2. Stevens-Johnson syndrome (oculomucocutaneous syndrome) and toxic epidermal necrolysis

SJS is characterized by severe enanthema and skin erythema in the mucocutaneous junctions such as lips, conjunctiva of eyes, and vulva, accompanied with pyrexia (≥ 38°C). Necrotic epidermal disorders, such as blisters and epidermolysis, are often noted. SJS is considered to be induced mainly by drugs. TEN is characterized by extensive erythema, marked necrotic epidermal disorders such as blisters, epidermolysis and erosion of more than 10% of the entire body surface, accompanied with pyrexia (≥ 38°C) and enanthema. Among the skin disorders, TEN is regarded as the most serious drug-induced skin disorder. [1)] While the incidence rates of SJS and TEN are extremely low (1 to 6 and 0.4 to 1.2 per 1 million person-years, respectively),[2,3)] once they occur, the prognosis may be quite poor. Sequelae of the eyes and the respiratory system may persist even after the skin symptoms resolve.

SJS and TEN can be caused by a wide range of drugs including antibiotics, antipyretics/ analgesics/anti-inflammatory agents, antiepileptics, gout preparations, sulfonamides, peptic ulcer agents, hypnotics, anxiolytics, psychoneurotics, therapeutic drugs for glaucoma, muscle relaxants, and antihypertensives. Some researches reported that SJS and TEN was caused by other drugs.[2,4-7)]

See Pharmaceuticals and Medical Devices Safety Information No. 285 (November 2011) for carbamazepine-induced serious drug eruption and genetic polymorphism.

3. Adverse reactions reported between August 1, 2009 and January 31, 2012

The MAHs reported 1505 cases of SJS or TEN as adverse reactions (1.8% of 82261 all reported adverse reaction cases) between August 1, 2009 and January 31, 2012. Suspected drugs were ethical drugs in 1410 cases (93.7% of SJS and TEN cases reported for this period) and over-the-counter (OTC) drugs in 95 cases (6.3% of SJS and TEN cases reported for this period).

The outcomes of the events were “recovered” or ”remitted” in 857 cases (56.9%), “not recovered” at the time of the report in 48 cases (3.2%), “with sequela" in 31 cases (2.1%), “death” in 131 cases (8.7%),, and “unknown” in 438 cases (29.1%).

The number of reports presented in this issue (in 2 and a half years) was compared with that in 4 years between October 1, 2005 and July 31, 2009 presented in the PMDSI No. 261, and no remarkable difference of the number of reports was observed on an annual basis (Table 1)

The suspected drugs of SJS or TEN reported include 265 active ingredients. The most frequently reported drugs are shown by active ingredient and therapeutic category in Table 2 and 3, respectively. The number of reports cannot be compared simply head to head due to different sales volume and varying usage, frequency of use, concomitant drugs, underlying diseases, and complications among the patients.

Table 1 Number of adverse reactions reported as SJS and TEN and event outcomes (including events for which a causality to the drugs was ruled out by experts)

Reporting period	Category	Number of adverse reaction reported as SJS or TEN (proportion of reported overall adverse reactions) [Annual average number of reports]	Number of adverse reaction reported as SJS or TEN by outcome (Proportion of SJS or TEN) [Annual average number of reports]				
			Recovered/ remitted	Not recovered	With sequelae	Death	Unknown
August 1, 2009 to January 31, 2012 (2 years and 6 months)	Overall	1505 (1.8%)	857 (56.9%)	48 (3.2%)	31 (2.1%)	131 (8.7%)	438 (29.1%)
		[602/year]	[342.8/year]	[19.2/year]	[12.4/year]	[52.4/year]	[175.2/year]
	OTC drugs	95	52 (54.7%)	4 (4.2%)	2 (2.1%)	3 (3.2%)	34 (35.8%)
October 1, 2005 to July 31, 2009 (3 years and 10 months)	Overall	2370 (2.2%)	1373 (57.9%)	85 (3.6%)	84 (3.5%)	239 (10.1%)	589 (24.9%)
		[618.3/year]	[358.2/year]	[22.2/year]	[22.0/year]	[62.3/year]	[153.7/year]
	OTC drugs	146	90 (61.6%)	5 (3.4%)	11 (7.5%)	3 (2.1%)	37 (25.3%)

Table 2 Frequently reported drugs (by active ingredient)

Name of drug	Number of reports
Allopurinol	107
Lamotrigine	101
Carbamazepine	86
Acetaminophen	54
Loxoprophen sodium hydrate	49
Garenoxacin mesilate hydrate	32
Levofloxacin hydrate	29
Salicylamide/acetaminophen/ anhydrous caffeine/promethazine methylenedisalicylate	29
Diclofenac sodium	29
Celecoxib	28

Table 3 Frequently reported drugs (by therapeutic category)

	Therapeutic category	Number of reports
Overall	Antiepileptics	257
	Antipyretics/analgesics/ anti-inflammatory agents	235
	Antibiotics	229
	Gout preparations	108
	Antineoplastics	105
	Common cold drugs	83
	Synthetic antibacterials	81
	Peptic ulcer agents	67
OTC drugs out of the above	Common cold drugs	54
	Antipyretics/analgesics/ anti-inflammatory agents	35
	Gastrointestinal agents and combinations	1
	Kampo product	1
	Vitamin B_1 preparations	1
	Nutrients, tonics-Miscellaneous	1
	Stomachics and digestives	1
	Antitussives	1

4. Major cases

Serious skin disorders such as SJS and TEN may induce severe sequelae in the cornea, etc. if the symptoms become prolonged or become aggravated. Early detection and treatment is therefore crucial. However, there were some cases for which it took a long time between the initial symptoms onset and the hospital visit (Case 1) or it took a long time until the disorder was diagnosed (Case 2). Delay in treatment led to aggravation of symptoms in some patients.

Case 1) A case for which there was a long time between the initial symptoms onset and the hospital visit (diclofenac sodium)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Back pain (none)	50 mg for unknown duration	**Stevens-Johnson syndrome** Day 1 of administration: The patient started using diclofenac sodium (suppository) 50 mg/day (treatment duration unknown). Day of onset: Oral erosion, genital erosion, and generalised erythema occurred. Pyrexia of 39°C developed. The patient could not take meals due to oral pain and lower back pain. 1 day after onset: Pyrexia occurred. Skin eruption occurred on the trunk. Pain and skin eruption occurred in the genital area. 7 days after onset: The patient visited the emergency outpatient department with a chief complaint of dyslalia. The patient was diagnosed with brain stem infarction (caused by ingestion disorder) and was admitted to the emergency department. 8 days after onset: The patient was referred to the dermatology department. The patient was diagnosed with drug eruption (Stevens-Johnson syndrome), and a topical corticosteroid was prescribed. Skin eruption gradually improved. 22 days after onset: Outcome (oral erosion, genital erosion, and generalised erythema): recovered. Outcome (brain stem infarction and dyslalia): sequelae 29 days after onset: Drug lymphocyte stimulation test (DLST) was performed, which suggested that diclofenac sodium was the causative drug.
	Concomitant medications: oxazolam, lansoprazole, oseltamivir phosphate, oxatomide			

Case 2) A case for which there was a long time until the disorder was diagnosed (allopurinol)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Hyperuricaemia, increased blood uric acid (mitral valve stenosis, tricuspid valve	100 mg for 15 days	**Stevens-Johnson syndrome** Day 1 of administration: The patient was prescribed allopurinol at a department of thoracic cardiovascular surgery. Day 10 of administration: Redness of pharynx, pyrexia of 38°C range, ocular

		incompetence, mitral valve replacement)		hyperaemia, eye discharge, lip swelling occurred. Day 11 of administration: The patient visited the department of general medicine. She was diagnosed with pharyngitis and was prescribed a non-pyrine common cold drug, ascorbic acid/calcium pantothenate, loxoprofen sodium hydrate, and povidone-iodine. Day 12 of administration: Face oedema developed. Day 13 of administration: Eyelid oedema and skin eruption on the trunk and palm developed. The patient was admitted to a department of otorhinolaryngology for pharyngitis. Administration of antibiotics and hydrocortisone sodium succinate were started. Day 15 of administration (day of discontinuation): Skin eruption, enanthema, and pharyngeal oedema progressed. Allopurinol was found to be the suspected drug, and then administration of allopurinol was discontinued. The patient was transferred to a department of dermatology and started receiving steroid pulse therapy (for 3 days). 1 day after discontinuation: Herpes simplex virus immunoglobulin G (IgG): 61.3 (+), Herpes simplex virus immunoglobulin M (IgM): 0.41 (-). 3 days after discontinuation: Allopurinol was switched to oral administration of prednisolone 30 mg. Neogenesis of skin eruption stopped. Due to oral administration of anticoagulant agent, haemorrhage from enanthema persisted. Mycoplasma pneumoniae complement-fixation (CF) (upper limit 4) (-) Mycoplasma pneumoniae particle agglutination (PA) (upper limit 40) (-) 13 days after discontinuation: The patient was discharged from the hospital. Slight shallow erosion on the oral mucosa was noted. 26 days after discontinuation: Last visit to a hospital; Epithelialization was noted. Specific symptoms of skin lesion: erythema multiforme, blister, enanthema Areas in which skin lesion occurred: face, trunk, and upper/lower limbs Desquamation (skin loss): observed Percentage of lesion area to body surface area: approximately 10% Mucosal lesion: observed (conjunctival hyperaemia, eye discharge, epistaxis, lip/oral mucosa erosion, pharyngitis, pharyngeal oedema, genital erosion) No systemic abnormalities or abnormal findings associated with skin lesion. Diagnosing doctor: dermatologist Important laboratory test results: DLST test was positive (allopurinol). HLA-B *5801 was negative. Biopsy skin: a skin biopsy suggested SJS. Liquefaction degeneration (necrotic keratinocyte) etc. were observed. History of drug allergy: none Recent history of infection: none
	Concomitant medications: aspirin, warfarin potassium			

5. Summary

Although the incidence of SJS and TEN is rare, once they occur, they may lead to fatal outcomes resulting from complications such as multi-organ failure. SJS and TEN are serious adverse drug reactions, which may induce sequelae of the eyes and the respiratory system even after the skin symptoms resolve.

If SJS or TEN is suspected in a patient who develops a rash accompanied with hyperthermia after being treated with a drug, administration of the suspected drug should be discontinued, and the patient should be referred to a dermatologist immediately. If the patient was diagnosed with SJS or TEN, the patient should be admitted to a hospital and treated by a team of ophthalmologists, pulmonologists and other specialists.

When administrating or selling drugs commonly reported for adverse reactions such as antiepileptics, antipyretics/analgesics/anti-inflammatory agents, antibiotics, gout preparations, antineoplastics, common cold drugs, synthetic antibacterials or peptic ulcer agents, patients should be informed of initial symptoms of SJS and TEN and be advised to seek medical consultation immediately if any symptoms are observed. Note that other drugs may, although rarely, cause SJS and TEN.

Details of initial symptoms, clinical course, and treatment of SJS and TEN are summarized in Manuals for Management of Individual Serious Adverse Drug Reactions "Stevens-Johnson Syndrome,"[8] and "Toxic Epidermal Nephrolysis"[9] on the PMDA website (http://www.info.pmda.go.jp/) as well as in "PMDA Alert for Proper Drug Use."

- Manuals for Management of Individual Serious Adverse Drug Reactions
  http://www.info.pmda.go.jp/juutoku/juutoku_index.html
- PMDA Alert for Proper Use of Drugs
  http://www.info.pmda.go.jp/iyaku_info/tekisei_pmda.html

<References> (including provisionally translated titles)

1) Assier H et al.: Erythema Multiforme With Mucous Membrane Involvement and Stevens-Johnson Syndrome Are Clinically Different Disorders With Distinct Causes. Arch. Dermatol. 131: 539-543 (1995)
2) Roujeau J-C et al.: Medication Use and The Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis. N. Engl. J. Med. 333: 1600-1607 (1995)
3) Rzany B et al.: Epidemiology of Erythema Exsudativum Multiforme Majus, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Germany (1990-1992): Structure and Results of a Population Based Registry. J. Clin. Epidemiol. 49: 769-773 (1996)
4) Aihara M, Ikezawa Y: Clinical Study of Decreased Cases of Toxic Epidermal Necrolysis (TEN) in Japan; Comparative Study with Surviving Cases of TEN and with Decreased Cases of Stevens-Johnson syndrome (SJS). Japanese Journal of Dermatology 109 (11): 1581-1590 (1999)
5) Nanko H: A Clinical Study of 126 Cases of Toxic Epidermal Necrolysis (TEN) in Japan; Is it Possible to Distinguish between Drug-induces TEN and Post-transfusion Graft-vs-Host Disease? 45: 571-578 (1991)
6) Takahashi R ed.: Book for easy understanding of clinically significant adverse drug reactions as written by a clinician: Adverse drug reactions seen by the patient (only available in Japanese language). Elsevier Japan (1998)
7) Izaki S: Toxic epidermal necrolysis (TEN). Kawagoe Clinical Conference, KCC Series, No. 39 (1998)
8) MHLW: Manuals for Management of Individual Serious Adverse Drug Reactions; "Stevens-Johnson syndrome" (2006)
9) MHLW: Manuals for Management of Individual Serious Adverse Drug Reactions; "Toxic epidermal necrolysis" (2006)

3

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated March 19, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Products Containing Acetaminophen

(1) Acetaminophen, Tramadol Hydrochloride/Acetaminophen

Brand Name (name of company)	**Acetaminophen** CALONAL Tab. 200, 300 (Showa Yakuhin Kako Co., Ltd.) ALPINY SUPPOSITORIES 50, 100, 200 (Hisamitsu Pharmaceutical Co., Inc.) ANHIBA Suppositories for Pediatric Use 50 mg, 100 mg, 200 mg (Abbott Japan Co., Ltd.) and the others. **Tramadol Hydrochloride/Acetaminophen** TRAMCET Combination Tablets (Janssen Pharmaceutical K.K.)
Therapeutic Category	Antipyretics and analgesics, anti-inflammatory agents
Indications	**Acetaminophen** (oral dosage form) 1. Relief of pain for the following diseases and symptoms Headache, ear pain, symptomatic neuralgia, lumbago, myalgia, bruising pain, sprain pain, painful menses, postpartum pain, pain due to cancer, toothache, pain after dental treatment, osteoarthritis 2. Antipyresis and relief of pain for the following diseases: Acute upper respiratory inflammation (including acute upper respiratory inflammation associated with acute bronchitis) 3. Antipyresis and relief of pain in the field of pediatrics (suppository) Antipyresis and relief of pain in the field of pediatrics **Tramadol Hydrochloride/Acetaminophen** Relief of pain for the following diseases which cannot be managed by treatments with non-opioid analgesics: Non-cancerous chronic pain Pain after tooth extraction

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored. If cough, dyspnoea, pyrexia or abnormal chest sound, etc. are

observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

Interstitial nephritis, acute renal failure: Interstitial nephritis or acute renal failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

(2) Isopropylantipyrine/Acetaminophen/Allylisopropylacetylurea/Anhydrous Caffeine

Brand Name (name of company)	SG Combination Granule (Shionogi & Co., Ltd.)
Therapeutic Category	Antipyretics and analgesics, anti-inflammatory agents
Indications	Antipyresis for common cold, ear pain, sore throat, painful menses, headache, toothache, symptomatic neuralgia, traumatic pain

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis:
Toxic epidermal necrolysis, oculomucocutaneous syndrome or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored. If cough, dyspnoea, pyrexia or abnormal chest sound, etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

Interstitial nephritis, acute renal failure: Interstitial nephritis or acute renal failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

(3) Salicylamide/Acetaminophen/Anhydrous Caffeine/Chlorpheniramine Maleate

Brand Name (name of company)	Pelex combination granule, Pediatric Pelex combination granule (Taiho Pharmaceutical Co, Ltd.) LL COMBINATION SYRUP FOR PEDIATRIC (Daiichi Sankyo Company, Limited) NEO-AMUNOLL COMBINATION POWDER (Sanwa Kagaku Kenkyusho Co., Ltd.)
Therapeutic Category	Common cold drugs
Indications	Improvement and alleviation of the following symptoms associated with common cold or upper respiratory inflammation: Nasal discharge, nasal congestion, pharyngeal/laryngeal pain, cough, sputum, headache, arthralgia, myalgia, pyrexia

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, exfoliative dermatitis:** Toxic epidermal necrolysis, oculomucocutaneous syndrome, acute generalised exanthematous pustulosis or exfoliative dermatitis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. **Interstitial nephritis, acute renal failure**: Interstitial nephritis or acute renal failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

(4) Salicynamide/Acetaminophen/Anhydrous Caffeine/Promethazine Methylenedisalicylate

Brand Name (name of company)	PL Combination Granule, PL Combination Granules for Infant (Shionogi & Co., Ltd) SALAZAC Combination Granule (Teva Pharma Japan Inc.) SELAPINA combination granulated (Shiono Chemical Co., Ltd.) TOWATHIEM COMBINATION GRANULES (Towa Pharmaceutical Co., Ltd.) PA TABLETS (Zensei Pharmaceutical Industries Co., Ltd.) MARIKINA Granules (Tsuruhara pharmaceutical Co., Ltd.)
Therapeutic Category	Common cold drugs
Indications	Improvement and alleviation of the following symptoms associated with common cold or upper respiratory inflammation: Nasal discharge, nasal congestion, pharyngeal/laryngeal pain, headache, arthralgia, myalgia, pyrexia

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, exfoliative dermatitis**: These adverse reactions may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

(5) Diprophylline/Dihydrocodeine Phosphate/dl-Methylephedrine Hydrochloride/Diphenhydramine Salicylate/Acetaminophen/ Bromovalerylurea

Brand Name (name of company)	Coughcode-N Combination Tablets (Mylan Seiyaku Ltd.)
Therapeutic Category	Antitussives
Indications	Cough suppression, relief of pain, and antipyresis in common cold syndrome Cough suppression in bronchitis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis**: Toxic epidermal necrolysis, oculomucocutaneous syndrome or acute generalised

exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored. If cough, dyspnoea, pyrexia or abnormal chest sound, etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

Interstitial nephritis, acute renal failure: Interstitial nephritis or acute renal failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to November 25, 2011)

- Acute generalized exanthematous pustulosis: 4 cases (no fatal cases)
- Interstitial pneumonia: 2 cases (no fatal cases)
- Interstitial nephritis-associated cases: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs (total): A total of approximately 62,300,000 (January to December 2011)

Launched in Japan:

(1) January 1958 (acetaminophen)
July 2011 (tramadol hydrochloride/acetaminophen)
(2) July 2003
(3) September 1967
(4) February 1962
(5) August 2002

Case Summary

Acetaminophen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Painful menses, pyrexia (none)	200 mg (as needed) (day of administration - 4 days after onset)	**Acute generalized exanthematous pustulosis** Day of administration: The patient received oral acetaminophen 200 mg for painful menses. Day 4 of administration (day of onset): Papule associated with itching developed in the popliteal fossa and was expanded. 2 days after onset: Erythema developed throughout the body. The patient visited a nearby dermatology clinic. She had oral acetaminophen 200 mg for pyrexia of 37.8°C. Betamethasone was topically used. 3 days after onset: Pyrexia of 40°C occurred. The patient had oral acetaminophen 200 mg twice. She visited a nearby hospital due to urticaria, acute pharyngitis, and hyperthermia (40°C). She experienced disturbed consciousness and visited another hospital. 4 days after onset: Pustules occurred on the neck. The patient had oral acetaminophen. Vesicles occurred on the neck and the

				thighs from the evening. As the symptoms did not remit, the patient visited this hospital. 5 days after onset: Pustules expanded to the intertriginous area, and pyrexia also persisted. 6 days after onset: The patient was admitted to the hospital for a detailed examination and treatment. Oral administration of prednisolone (PSL) 40 mg/day and topical administration of clobetasol were started. 10 days after onset: The dose of PSL was reduced to 35 mg/day. DLST: positive (Stimulation Index [SI], 322%) 13 days after onset: The dose of PSL was reduced to 30 mg/day. Erythema became severe desquamation. 15 days after onset: The dose of PSL was reduced to 25 mg/day. 17 days after onset: The dose of PSL was reduced to 20 mg/day. The skin eruption did not relapse. 18 days after onset: The patient was discharged from the hospital. After that, topical petrolatum only was used. 19 - 20 days after onset: PSL 15 mg/day was administered. 21 - 22 days after onset: PSL 10 mg/day was administered. 23 - 24 days after onset: PSL 5 mg/day was administered. The skin eruption did not relapse.
	Concomitant medications: none			

Laboratory Examination

	6 days after onset	9 days after onset	17 days after onset
WBC (/μL)	14660	11720	12660
Neutrophils (%)	78.5	58.5	66.5
CRP (mg/dL)	13.63	4.92	0.21

Acetaminophen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male Under age of 10	Pharyngitis (none)	200 mg twice (day of administration)	**Acute generalized exanthematous pustulosis** 1 day before administration: The patient had a skin eruption like mosquito bites at multiple sites on the abdomen. He visited a nearby dermatology clinic and was prescribed betamethasone/d-chlorpheniramine maleate. Pyrexia of 38.9°C occurred in the night of the same day.
			140 mg once (3 days after onset)	Day of administration: The rash expanded and pyrexia also persisted. The patient visited a nearby pediatric clinic. He was diagnosed with pharyngitis and viral rash. Acetaminophen was

				administered twice. He had oral betamethasone/d-chlorpheniramine maleate and cefteram pivoxil. Test results showed WBC 12900/μL, CRP 0.4 mg/dL, and rapid detection for hemolytic streptococci was negative. Rash was associated with pruritus. Pyrexia persisted. Day 2 of administration (day of onset): The patient visited the nearby pediatric clinic again. A transfusion was given due to impaired appetite. Rash and pyrexia persisted. 1 day after onset: Rash and pyrexia persisted, but the patient ate a small amount. The patient had an oral over-the-counter (OTC) common cold drug (acetaminophen). 2 days after onset: The patient visited the nearby pediatric clinic again. Hepatic dysfunction was noted with AST 113 IU/L and ALT 151 IU/L. The patient was referred and admitted to this department to have a detailed examination and treatment on this day. Sulbactam sodium/ampicillin sodium was intravenously administered. Fever was dealt with by cooling alone. <Findings at admission> Body temperature (BT): 38.7°C, Heart rate (HR): 120 bpm, SpO_2: 97% (Room air [RA]), Respiratory rate (RR): 32/min, being in a bad mood but having energy. Skin: Redness was noted on the neck, shoulders, forearms, and lower limbs. Desquamation was present predominantly on the neck. Countless small pustules measuring several mm not consistent with follicles were seen on the elbows and knees. Erosion and blister were not observed. Neck: Swollen lymph nodes were not found. Lips: Redness was noted. Pharynx: Mild redness was noted. Tonsilla: Tonsillitis was noted with no enlargement. Tongue: Redness and tongue papillae were noticeable. Respiration: Breath sounds were normal with no noises. Heat sounds: Heart sounds were normal with no noises. Abdomen: Flat/soft, with no increased Intestinal peristalsis sound <Medical history> Due to cretinism, the patient received thyroid hormone replacement therapy soon after birth (Hospital A). Oral administration was discontinued 10 days before administration of acetaminophen. <Course of treatment during hospitalisation> Drug eruption: At admission, redness was noted on the neck, shoulders, and lower limbs. Desquamation was present predominantly on the neck. Countless small pustules measuring several mm not consistent with follicles were showed on the elbows and knees, and redness was noted on the tongue and pharynx. The result of rapid detection for group A hemolytic streptococci was negative, but based on the possibility of scarlet fever associated with skin eruption, treatment was performed with intravenous administration of sulbactam sodium/ampicillin sodium 150 mg/kg/day and transfusion. Main symptoms of Kawasaki's disease were 3/6 (pyrexia, lip redness, rash). Echocardiography showed no coronary lesion. 3 days after onset:

				Pyrexia between 38 and 39°C persisted, and no improvement was seen in the range/degree of eruption. After the patient had orally acetaminophen 140 mg before noon, pyrexia of 38.9°C developed and elevated to 40°C after lunch. Bad mood and itching were severe, and redness of eruption also increased. Small pustules increased and their range expanded. When the patient consulted with a dermatologist, he/she expressed an opinion that the condition might be acute generalised exanthematous pustulosis. Test results showed WBC 11300/μL (Neu 68.2%, Eo 9.9%), CRP 0.5 mg/dL. Samples for blood culture and DLST (acetaminophen) were collected, drip infusion of sulbactam sodium/ampicillin sodium was discontinued, and intravenous administration of PSL 1 mg/kg/day 3 × was started from the evening. Blood test for DLST was performed based on the possibility of drug eruption. Administration of drugs including sulbactam sodium/ampicillin sodium other than transfusion was discontinued. 4 days after onset: Pyrexia between 39 and 40°C persisted. 5 days after onset: Pyrexia decreased to the level of 37°C, and small pustules began to disappear and were replaced by pigmentation. The range of redness tended to become reduced. On the same day, the findings of inflammation disappeared with WBC 8100/μL (Neu 52.5%, Eo 2.5%), and CRP 0.2 mg/dL. 7 days after onset: Small pustules resolved. 8 days after onset: Epidermolysis on the distal portions of limbs progressed (did not become erosion). 9 days after onset: No active skin eruption was observed, a gradual dose reduction of PSL was started. Pyrexia of 38°C due to suspected mental delay was noted, but skin eruption by gradual dose reduction of PSL was not aggravated. 10 days after onset: Administration of PSL was discontinued. Skin eruption did not appear again. 12 days after onset: The patient's general condition was good and the patient was discharged from the hospital. On the same day, DLST was positive for acetaminophen.
	Concomitant medications: betamethasone/d-chlorpheniramine maleate, cefteram pivoxil, common cold drug (OTC drug), sulbactam sodium/ampicillin sodium			

Laboratory Examination

	Day of administration	2 days after onset	3 days after onset	5 days after onset	9 days after onset	12 days after onset
WBC (/μL)	12900	13400	11300	8100	22600	13200
Neutrophils (%)	—	72.6	68.2	52.5	80.2	52.8
CRP (mg/dL)	0.4	1.1	0.5	0.2	0.0	0.0

Acetaminophen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 50s	Pyrexia, pharyngitis (none)	600 mg 3 times a day (Day 1 of administration - 1 day after onset)	**Interstitial pneumonia** Day 1 of administration: The patient developed pyrexia and pharyngitis and visited a nearby hospital. Acetaminophen and cefdinir were prescribed. Day 4 of administration: Symptoms did not remit, the patient visited the nearby hospital again, and administration of cefdinir was discontinued. Administration of ceftriaxone sodium hydrate was started, and acetaminophen continued to be prescribed. Day 7 of administration (day of onset): The patient visited the nearby hospital again due to aggravated cough and persisting pyrexia. X−ray photograph (Xp) showed pneumonia. The patient was referred to this hospital. 1 day after onset (day of discontinuation): The patient visited this department for the first time. The chest computed tomography (CT) showed bilateral multiple ground-glass opacities and infiltrative opacities, atypical pneumonia and drug-induced pneumonia were suspected. Blood test of markers for atypical pneumonia was performed. Concomitant medications were changed, and administration of acetaminophen was discontinued. Administration of cefepime dihydrochloride hydrate and clarithromycin was started. No respiratory failure was noted. 8 days after onset: The CT showed improvement of pneumonia. 9 days after onset: Administration of clarithromycin was continued. The patient was discharged from the hospital. Regarding atypical pneumonia, Chlamydia pneumoniae IgM was 2.00 and IgG was 2.4 (1 day after onset, probable diagnosis). 15 days after onset: The patient visited an outpatient department. Paired serum sample was collected for chlamydial pneumonia. IgM 2.06, IgG 2.6. No significant elevation was observed and chlamydial pneumonia was ruled out. 22 days after onset: The CT showed improvement of pneumonia (shadows almost disappeared), and medical care was terminated.
	Concomitant medications: cefdinir, ceftriaxone sodium hydrate, methyl L-cysteine hydrochloride, bifidobacterium preparation, trastuzumab (genetical recombination)			

Acetaminophen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Female Under age of 10	Pyrexia (upper respiratory tract inflammation)	100 mg for 1 day	**Tubulointerstitial nephritis, acute renal failure** 16 days before administration: The patient developed cough, nasal discharge, etc. from 16 days before administration, antibiotics, etc. were prescribed at a nearby hospital. Day of administration: Acetaminophen was administered. (only once). 4 days after administration (day of onset): Pyrexia persisted, and the patient was admitted to the previous hospital. Test results at admission: WBC 22300/mm^3, CRP 7.09 mg/dL, BUN 30.9mg/dL, Cr 1.7mg/dL, urine output decreased. Decreased urine output and decreased kidney function were noted from the time of hospital admission, and subsequently, renal function aggravation was noted, and consequently the patient was referred to this hospital. 5 days after administration: Anuria developed, kidney function decreased with BUN 30.9 mg/dL and Cr 3.1mg/dL, and then the patient was transferred to this hospital. On Day 1 of hospitalisation, continuous hemofiltration (CHF) was started. Antibiotic ceftriaxone sodium, panipenem/betamipron, and dopamine hydrochloride/dobutamine hydrochloride 3γ administration were also used concomitantly, but urination was still absent after that. Time unknown: Transfusion of packed red blood cell preparation was performed. Time unknown: 5% human serum albumin was administered. 7 days after administration: Continuous ambulatory peritoneal dialysis (CAPD) was started. 8 days after administration: Spontaneous urination occurred gradually. 9 days after administration: CAPD was discontinued. After that, the general conditions and urination were gradually improved, and administration of dopamine hydrochloride/dobutamine hydrochloride was discontinued with dose reduction. 14 days after administration: Administration of antibiotics was discontinued. 18 days after administration: Ultrasound percutaneous kidney biopsy was performed for definite diagnosis. The patient was diagnosed with acute tubulointerstitial nephritis based on the renal histopathological findings. In addition, renal echography showed kidney enlargement, urine eosinophil count increased, DLST was positive for only acetaminophen, and therefore the patient was diagnosed with interstitial nephritis associated with acetaminophen. DLST was positive for acetaminophen. The patient was definitely diagnosed with drug-induced tubulointerstitial nephritis associated with acetaminophen. After that, symptomatic therapies such as CHF and CAPD were performed, and then urine output gradually increased and

				the renal function and renal tubular function gradually improved. The condition had improved without using steroids, etc. 24 days after administration: CAPD tube removal was performed. 53 days after administration: The patient was discharged from the hospital.
	Concomitant medications: clarithromycin (suspected drug), amoxicillin hydrate (suspected drug), cefditoren pivoxil (suspected drug), cyproheptadine hydrochloride hydrate, mequitazine, antibiotics-resistant lactic acid bacteriae combination drug			

Acetaminophen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Male Under age of 10	Pyrexia of unknown origin (none)	200 mg for 1 day (as needed) ↓ 6 day drug withdrawal ↓ 200 mg for 1 day (as needed) ↓ 7 day drug withdrawal ↓ 200 mg for 1 day (as needed)	**Nephritis interstitial** 11 days before administration: The patient had pyrexia between 37°C and 38°C. 8 days before administration: The patient visited a nearby hospital. Pranoprofen, levofloxacin hydrate, etc. were administered based on the diagnosis of upper respiratory inflammation. After that, antibiotics were switched to several kinds and follow-up observation was performed, but pyrexia persisted intermittently. Day of administration: Acetaminophen (as needed), pranoprofen, etc. were administered. 1 day after administration: The patient was referred and admitted to this hospital. After hospital admission, antibiotics were switched to some different kinds for the treatment, but pyrexia did not resolve. Day of readministration: Acetaminophen was administered (as needed). 3 days after readministration: Gallium (Ga) scintillation showed diffuse accumulation. 5 days after readministration: CT image showed enlargement of both kidneys and multiple and bilaterally symmetric poorly-perfused areas inside the kidneys. 7 days after readministration: Magnetic resonance imaging (MRI) showed mild enlargement of both kidneys and the stains were also uniform. Day of re-readministration: Acetaminophen was administered (as needed). 12 days after re-readministration: Renal biopsy showed cellular infiltration mainly of mononuclear cells into the renal tubular interstitium, and the patient was diagnosed with acute interstitial nephritis. 26 days after re-readministration: Administration of prednisolone tablets 40 mg/day was started (28 days). 50 days after re-readministration: Renal function test values such as Cr became normal, and interstitial nephritis was remitted. 54 days after re-readministration:

				The dose of prednisolone tablet was reduced to 30 mg/day (14 days). 68 days after re-readministration: The dose of prednisolone tablet was reduced to 20 mg/day (25 days). 70 days after re-readministration: The patient was discharged from the hospital. 93 days after re-readministration: After that, the dose of prednisolone tablet was reduced in a step-by-step manner. Prednisolone tablet was administered at 15 mg/day (14 days), 10 mg/day (13 days), 7.5 mg/days (14 days), 5 mg/day (13 days), and 2.5 mg/day (16 days). <DLST test> positive for acetaminophen and pranoprofen, negative for azithromycin hydrate and meropenem hydrate
	Concomitant medications: pranoprofen (suspected concomitant drug), dimeticone, domperidone, levofloxacin hydrate, antibiotics-resistant lactic acid bacteriae preparation, famotidine, azithromycin hydrate, maintenance solution, meropenem hydrate, doxycycline hydrochloride hydrate, cefcapene pivoxil hydrochloride hydrate, glucose, fosfomycin sodium, flomoxef sodium, sulbactam sodium/ampicillin sodium, teicoplanin, minocycline hydrochloride, cefazolin sodium, carbazochrome sodium sulfonate, tranexamic acid			

Laboratory Examination

	5 days before administ-ration	1 day after administ-ration (hospital admission)	2 days after administ-ration	5 days after administ-ration	4 days after re-readmini stration	8 days after re-readmini stration	21 days after re-readmini stration	43 days after re-readmini stration	69 days after re-readmini stration
RBC ($\times 10^4/mm^3$)	447	-	-	426	414	371	324	390	445
Hemoglobin (g/dL)	12.8	-	-	12.4	12.1	10.9	9.3	11.7	14.3
Hematocrit (%)	36.5	-	-	35.5	33.9	30.4	26.8	33.9	40.2
WBC ($/mm^3$)	11900	11420	-	13350	11230	10190	6180	11970	10550
Neutrophils (%)	75	-	-	76.6	73.1	74.4	68.6	82.9	78.6
Eosinophils (%)	2	-	-	2.5	2.5	3.5	5.0	0.2	0.2
Basophils (%)	0	-	-	0.4	0.4	0.3	0.2	0.1	0.1
Monocytes (%)	7	-	-	5.8	7.4	8.2	6.5	4.4	8.6
Lymphocytes (%)	16	-	-	13.7	15.4	12.4	18.4	11.4	10.7
PLT ($\times 10^4/mm^3$)	49.4	-	-	71.1	52.1	43.2	43.0	39.4	37.0
CRP (mg/dL)	7.85	5.62	-	4.18	3.23	3.92	1.35	-	-
BUN (mg/dL)	-	-	-	13	10	12	6	14	18
Serum creatinine (mg/dL)	-	-	-	0.97	1.07	1.55	0.81	0.47	0.43
Uric acid (mg/dL)	-	-	-	4.2	3.4	2.9	2.4	2.2	2.9
K (mEq/L)	-	-	-	4.7	3.8	4.4	3.4	3.5	4.3
Na (mEq/L)	-	-	-	135	137	137	138	140	103
Cl (mEq/L)	-	-	-	97	101	101	103	102	138
Body temperature (°C)	-	-	-	37.6	36.3	36.6	36.4	36.2	36.2
Urinary β_2MG (μg/L)	-	-	145	-	7108	21730	-	-	-

Acetaminophen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
6	Male Under age of 10	Pyrexia (dehydration)	100 mg for 3 days	**Acute renal failure** Day 1 of administration: The patient was prescribed acetaminophen suppository, cefdinir, and alimemazine tartrate for acute pharyngitis at a nearby hospital. Day 2 of administration: The patient was prescribed tranexamic acid and another acetaminophen suppository at a pediatrics department of anther hospital. Day 3 of administration (day of completion): Test results showed increased inflammation with WBC 27700 cells/mm^3 and CRP 17.4 mg/dL, and the patient was admitted to the hospital. Treatment with cefotaxime sodium was started based on the diagnosis of pharyngitis and dehydration. 3 days after completion (day of onset): Pyrexia resolved, but oedema on the face and both lower legs and vomiting occurred from the night of the same day. 1 day after onset: Oliguria was noted and blood test results showed BUN 45.6 mg/dL, Cre 3.2 mg/dL, Na 111mEq/L, K 7.7 mEq/L, Cl 75 mEq/L, and CRP 10mg/dL, and consequently, the patient was diagnosed with hyperkalaemia and acute renal failure and was transported to a pediatric clinic. Continuous hemodiafiltration (CHDF) was performed. 2 days after onset: Hyperkalaemia improved and electrolytes also became stable, and therefore CHDF was discontinued. The patient entered into the diuretic phase and took a course without recurrence. 4 days after onset: Drug-induced acute tubulointerstitial nephritis was suspected based on an acute and transient course. When DLST test was performed, the test result was positive for acetaminophen. Both antibiotics (cefdinir and cefotaxime sodium) had a negative result. 19 days after onset: As the general conditions became stable, the patient was discharged from the hospital.
	Concomitant medications: alimemazine tartrate, tranexamic acid, cefdinir, cefotaxime sodium			

Acetaminophen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
7	Male Under age of 10	Pyrexia, optic neuritis (none)	300 mg 3 times (as needed) (day of administration - Day 5 of administration	**Acute renal disorder** 8 days before administration: The patient had pyrexia between 37°C and 38°C. 7 days before administration: Rash appeared on the knees and legs. 6 days before administration: Rash on the knees and legs resolved. 5 days before administration: Pyrexia repeated.

				3 days before administration: The patient felt poorly. 2 days before administration: The patient visited the previous hospital. Medications such as cefcapene pivoxil hydrochloride hydrate were prescribed. Day of administration: Pyrexia persisted. Influenza negative was found at the previous hospital. As high levels of WBC and CRP were found, the medications were switched to levofloxacin hydrate. Day 4 of administration: Pyrexia resolved but vomiting and general malaise had not improved. Day 5 of administration (day of onset): After visiting this department, the patient was admitted to the hospital. Blood test showed increased inflammatory reaction. BUN and Cr had increased, and the patient was admitted to the hospital for acute renal failure. After admission, sodium chloride/glucose product 500 mL + 50% glucose solution 3A was administered at 20 mL/h. For severe inflammatory reaction, administration of cefotaxime sodium 0.5 g + physiological saline 50 mL in one dose was started in the evening. After that, pyrexia was not noted, and urine output also gradually increased. 1 day after onset: While checking blood test and urine test, the volume of transfusion increased to 40 mL/h of sodium chloride/glucose product 500 mL + 50% glucose solution 3A. 2 days after onset: With increasing urine output, the volume of sodium chloride/glucose product 500 mL + 50% glucose solution 3A increased to 60 mL/h. 5 days after onset: The drip infusion route was removed and the patient was able to freely drink water. 12 days after onset: Normalization in blood/urine test results was confirmed. 13 days after onset: The patient was discharged from the hospital and started to be followed up on an outpatient basis.
	Concomitant medications: cefcapene pivoxil hydrochloride hydrate, non-pyrine common cold drug, ambroxol hydrochloride, levofloxacin hydrate, domperidone, antibiotics-resistant lactic acid bacteriae preparation			

Laboratory Examination

	Day 5 of administration	1 day after onset	9 days after onset	12 days after onset
BUN (mg/dL)	54	47	14	14
Cr (mg/dL)	2.53	2.58	0.64	0.64
Urine sugar (-, +)	(±)	(++)	(++)	(-)
NAG (U/g·Cr)	16.2	—	—	8.0

2 Cibenzoline Succinate

(1) Cibenzoline succinate (oral dosage form)

Brand Name (name of company)	Cibenol Tablets 50 mg, 100 mg (Astellas Pharma Inc.) CINOBEZILE TABLETS 50 mg, 100 mg (Towa Pharmaceutical Co., Ltd.) CIBENZOLINE SUCCINATE Tablet 50 mg "Sawai," 100 mg "Sawai" (Sawai Pharmaceutical Co., Ltd.) CIBENZOLINE SUCCINATE Tablets 50 mg "Tanabe," 100 mg "Tanabe" (Mitsubishi Tanabe Pharma Corporation)
Therapeutic Category	Antiarrhythmic agents
Indications	Patients with the following disease who cannot use or does not respond to other antiarrhythmic agents: Tachyarrhythmia

PRECAUTIONS (underlined parts are revised)

Precautions of Dosage and Administration

Since elderly patients often have poor liver and kidney functions and their body weights are likely to below, adverse reactions occur more readily. Careful attention should be exercised to the dosage such as initiating administration with a low dose (e.g. 150 mg/day), and this drug should be carefully administered by monitoring the patient's condition.

Important Precautions

Periodic laboratory tests (blood test, hepatic/renal function tests, blood glucose test, etc.) should be performed during administration of this drug, and the blood concentration of this drug should be measured as necessary. If any abnormalities are observed, appropriate measures such as dose reduction or drug suspension should be taken.

Hypoglycaemia due to increased blood concentration may occur especially in elderly patients and patients with renal impairment, and hepatic/renal impairment associated with circulatory failure due to heart function-suppressive action and arrhythmogenic effect may occur in patients with any underlying heart disorder. In these cases, administration of the drug should be discontinued.

This drug may elevate the heart pacing threshold. This drug should be carefully administered to patients using a permanent pacemaker or who are on temporary pacing. If this drug is administered to patients using a pacemaker, the pacing threshold should be measured at appropriate intervals. If any abnormalities are observed, the dose of this drug should be reduced, or administration of this drug should be discontinued immediately.

(2) Cibenzoline succinate (injectable dosage form)

Brand Name (name of company)	Cibenol Intravenous Injection 70 mg (Astellas Pharma Inc.)
Therapeutic Category	Antiarrhythmic agents
Indications	Tachyarrhythmia

PRECAUTIONS (underlined parts are revised)

Important Precautions

This drug may elevate the heart pacing threshold. This drug should be carefully administered to patients using a permanent pacemaker or who are on temporary pacing. If any abnormalities are observed, administration of the drug should be discontinued immediately.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to February 14, 2012)

- Elevated pacing threshold-associated cases: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:

(1) Approximately 100,000 (FY 2011)

(2) Approximately 10,000 (FY 2011)

Launched in Japan:

(1) January 1991

(2) September 1993

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Paroxysmal atrial fibrillation (cerebral infarction)	200 mg for about 7 years ↓ 300 mg for 8 days ↓ 100 mg for 7 days	**Elevated pacing threshold** Approximately 7 years before onset (Day 1 of administration): The patient underwent ventricular inhibited (VVI) pacemaker implantation for sick sinus syndrome. Oral administration of cibenzoline succinate 200 mg was started for atrial fibrillation. Approximately 1 year before onset: Pacing threshold 1.25 V/0.73 ms 6 days before onset: The patient was transferred to Hospital A for rehabilitation due to cerebral infarction that occurred 1 month ago. The patient orally took cibenzoline succinate 300 mg at the time of hospital transfer. 4 days before onset: Thirst, queasy feeling, and anorexia occurred. Day of onset: Wheezing developed. Electrocardiography (ECG) showed pacing failure, widened QRS, and prolonged QT, and echocardiography showed diffuse wall hypokinesia. 1 day after onset (day of discontinuation): The patient was admitted to the department of cardiovascular medicine at Hospital B for the detailed examination of cause and treatment. Pacing threshold was elevated to 3.25 V/0.73 ms, and echocardiography showed diffuse wall hypokinesia. Blood concentration of cibenzoline succinate: 2120 ng/mL Poisoning due to cibenzoline succinate was suspected, and administration of cibenzoline succinate was discontinued. Wash-out was performed with fluid replacement and diuresis. 6 days after discontinuation: QRS width was 0.16 seconds, showing improvement. 7 days after discontinuation (Day 1 of readministration): Administration of cibenzoline succinate was resumed at 100 mg, and follow-up observation was performed. Day 7 of readministration (day of discontinuation of readministration): The patient recovered from elevated pacing threshold, thirst, queasy feeling, anorexia, widened QRS, failed cardiac function, and prolonged QT. Threshold improved to 1.25 V/0.85 ms. QRS width was further shortened to 0.12 seconds, but atrial

				flutter developed, and therefore administration of cibenzoline succinate was discontinued. Rate control and anticoagulant therapy were performed, and then the patient was transferred to Hospital A. 15 days after discontinuation (Day 1 of re-readministration): Administration of cibenzoline succinate was resumed at 100 mg at Hospital A. 1 month after re-readministration: Blood concentration of cibenzoline succinate was 129 ng/mL within the normal range. Approximately 2 months after re-readministration: The patient visited Hospital B. Wall-motion further improved, atrial flutter disappeared, sinus rhythm was maintained, and QRS width did not increase. Pacing threshold was 1.25 V/0.85 ms with no change, showing a good clinical course.
	Concomitant medications: unknown			

Laboratory Examination

	Approximately 1 year before onset	1 day after onset (day of discontinuation)	Day 7 of readministration (day of discontinuation of readministration)	1 month after re-readministration	2 months after re-administration
Pacing threshold	1.25V/0.73ms	3.25V/0.73ms	1.25V/0.85ms	—	1.25V/0.85ms
EF (%)	—	33	47	—	50
QT (ms)	—	600	420	—	—
Blood concentration of cibenzoline succinate (ng/mL)	—	2120	—	129	—

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 90s	Sick sinus syndrome (none)	200 mg, unknown	**Elevated pacing threshold** Date unknown: The patient underwent dual chamber (DDD) pacemaker implantation for sick sinus syndrome. Day 1 of administration: Administration of cibenzoline succinate 200 mg/day was started for sick sinus syndrome. Date unknown (day of discontinuation): Cardiac failure due to pacing failure occurred. Administration of cibenzoline succinate was discontinued. 1 day after discontinuation: The patient was admitted to the hospital. Symptoms of bradycardia, anasarca, and circulatory failure were noted. ECG showed heart rate 40/min, and widened QRS and pacing wave were not observed. Pacing threshold was markedly elevated in both atrial and ventricular leads, and lead resistance was not noted. Ventricular capture became possible with the maximum output of ventricular pacing, and then VVI pacing and fluid replacement were performed. 4 days after discontinuation:

				Spontaneous beats appeared, and pacing threshold also decreased. Date unknown: Blood concentration of cibenzoline succinate: 2708 ng/mL. 31 days after discontinuation: The patient recovered from cardiac failure due to pacing failure.
	Concomitant medications: aspirin, amlodipine besilate, solifenacin succinate, carvedilol, famotidine			

3 Triclofos Sodium, Chloral Hydrate

(1) Triclofos Sodium

Brand Name (name of company)	TRICLORYL Syrup 10% (Alfresa Pharma Corporation)
Therapeutic Category	Hypnotics and sedatives, anxiolytics
Indications	Insomnia Sleep in electroencephalography, electrocardiography, etc.

PRECAUTIONS (underlined parts are revised)

Important Precautions	Respiratory depression, etc. may occur. Patients should be carefully monitored. In particular, careful attention should be paid to children by monitoring of respiratory rate, heart rate, percutaneous arterial oxygen saturation, etc. Chloral hydrate, as well as the drug, changes into the active metabolite trichloroethanol in the body. Attention should be paid to an overdose which may occur in concomitant use of chloral hydrate.
Precautions of Dosage and Administration	**Apnoea, respiratory depression:** Apnoea or respiratory depression may occur, resulting in cardio-respiratory arrest in some cases. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.
Pediatric use	Some cases of apnoea or respiratory depression leading to cardio-respiratory arrest have been reported. This drug should be carefully administered, and patients should be monitored.

(2) Chloral Hydrate (oral dosage form, enema)

Brand Name (name of company)	Chloral Hydrate "Whey" (Mylan Seiyaku Ltd.)
Therapeutic Category	Hypnotics and sedatives, anxiolytics
Indications	<Oral dosage form> Insomnia <Enema> Convulsive status epilepticus for which intravenous injection is difficult

PRECAUTIONS (underlined parts are revised)

Important Precautions	Respiratory depression, etc. may occur. Patients should be carefully monitored. In particular, careful attention should be paid to children by monitoring of respiratory rate, heart rate, percutaneous arterial oxygen saturation, etc. Triclofos sodium , as well as the drug, changes the active metabolite trichloroethanol in the body. Attention should be paid to an overdose which may occur in concomitant use of triclofos sodium.
Precautions of Dosage and Administration	**Apnoea, respiratory depression**: Apnoea or respiratory depression may occur, resulting in cardio-respiratory arrest in some cases. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.
Pediatric use	Some cases of apnoea or respiratory depression leading to cardio-respiratory arrest have been reported. This drug should be carefully administered, and patients should be monitored.

(3) Chloral hydrate (suppository, kit preparation for enema)

Brand Name (name of company)	ESCRE SUPPOSITORIES "250," "500," ESCRE RECTAL KIT "500" (Hisamitsu Pharmaceutical Co., Inc.)
Therapeutic Category	Hypnotics and sedatives, anxiolytics
Indications	Sedation and hypnogenesis in physical examination Convulsive status epilepticus for which intravenous injection is difficult

PRECAUTIONS (underlined parts are revised)

Important Precautions	Respiratory depression, etc. may occur. Patients should be carefully monitored. In particular, careful attention should be paid to children by monitoring of respiratory rate, heart rate, percutaneous arterial oxygen saturation, etc. Triclofos sodium , as well as the drug, changes the active metabolite trichloroethanol in the body. Attention should be paid to an overdose which may occur in concomitant use of chloral hydrate.
Precautions of Dosage and Administration	**Apnoea, respiratory depression:** Apnoea or respiratory depression may occur, resulting in cardio-respiratory arrest in some cases. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.
Pediatric use	Some cases of apnoea or respiratory depression leading to cardio-respiratory arrest have been reported. This drug should be carefully administered and patients should be monitored.
Reference Information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to December 31, 2011) • Apnoea, respiratory depression: 3 cases (no fatal cases) The number of patients using this drug per year estimated by MAHs: (1) Approximately 250,000 (January to December 2011) (2) (3) Approximately 280,000 (January to December 2011) Launched in Japan: (1) November 1964 (2) December 1953 (3) February 1980 (suppository) August 2006 (kit preparation for enema)

Case Summary
Triclofos Sodium

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male Under age of 1	Premedication (none)	517.5 mg for 1 day	**Respiration stillness** 2 days before administration: The patient had pyrexia. 1 day before administration: Pyrexia, lip redness, palpable lymph node, and rash were observed, and therefore Kawasaki's disease was suspected. Day of administration: Echocardiography was performed. Left coronary artery φ3.6 mm, right coronary artery φ 2.4 mm, brightness increased (±). When echocardiography was performed, triclofos sodium 50 mg/kg was administered and 25 mg/kg was additionally administered, and then respiration became still. Respiratory support was given with a mask and bag, but spontaneous respiration was not observed. The patient was endotracheally intubated. As laryngeal oedema was noted, methylprednisolone sodium succinate for injection was intravenously administered. Tension was present in the upper limbs, and therefore convulsion could not be ruled out. Phenytoin sodium injection solution was intravenously administered at a low rate. Mechanical ventilation was used. Lymph node was palpable. Pyrexia, bulbar conjunctiva hyperaemia, lip redness, rash, and changes in the distal portions of the limbs occurred. Ulinastatin and meropenem hydrate for injection were administered. 1 day after completion: Administration of immunoglobulin G was started. Administration of meropenem hydrate for injection and ulinastatin was started. 2 days after completion: Echocardiography showed increased brightness and pericardial effusion. No coronary lesion was found. Administration of aspirin was started. 3 days after completion: Administration of immunoglobulin was started due to exacerbation of pyrexia, and continued for 3 days. 4 days after completion: Brain MRI showed a high area in the posterior horn of corpus callosum, and therefore encephalopathy was suspected. 5 days after completion: Echocardiography showed increased brightness, pericardial effusion, and mass forming. As spontaneous respiration was confirmed, extubation was performed. The patient recovered.
	Concomitant medications: none			

4 **Metformin Hydrochloride** (products with "Dosage and Administration" of maximum daily dosage of 2250mg)

Brand Name (name of company)	METGLUCO Tablets 250 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatment: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies

PRECAUTIONS (underlined parts are revised)

Warnings

WARNINGS

Serious lactic acidosis may occur, resulting in fatal outcomes in some cases. This drug should not be administered to patients who can easily develop lactic acidosis.

When this drug is administered to patients with renal impairment or hepatic dysfunction or elderly patients, this drug should be carefully administered by periodically checking the renal function or hepatic function. Especially for elderly patients aged 75 years or older, use of this drug should be carefully determined.

Important Precautions

Serious lactic acidosis may occur. Patients and their families should be given the following information.

1) Patients should avoid excessive alcohol consumption.
2) If there is concern about the state of dehydration due to pyrexia, diarrhoea, vomiting, poor meal ingestion, etc., patients should temporarily discontinue taking this drug and consult a physician.
3) If any initial symptoms of lactic acidosis are observed, patients should seek immediate care.

Hypoglycemic symptoms may occur. Attention should be paid when administering the drug to patients engaged in working at heights, driving, etc. Patients and their families should be informed of the precautions concerning hypoglycemic symptoms.

Patients should be carefully monitored for renal impairment, and use of this drug or dosing adjustment should be considered. Renal function should be determined by referring to eGFR, serum creatinine level, etc.

Adverse Reactions (clinically significant adverse reactions)

Lactic acidosis: Lactic acidosis (showing increased blood lactic acid, increased lactate pyruvate ratio, decreased blood pH, etc.) is frequently associated with a poor prognosis. There are a variety of clinical symptoms that generally occur, but symptoms such as gastrointestinal symptoms, malaise, myalgia, and hyperpnoea are frequently observed. If such symptoms are observed, administration of this drug should be discontinued immediately, and necessary examinations should be performed. If lactic acidosis is highly suspected, appropriate measures should be taken without waiting for data such as the results of measurement of lactic acid.

Use in the Elderly

Since elderly patients often have poor kidney and liver functions, etc. and are likely to develop the symptoms of dehydration. In these conditions, lactic acidosis may readily occur. Attention should be paid to the following points:

Patients should be carefully monitored for their conditions including renal impairment or symptoms of dehydration, and discontinuation of administration or dose reduction should be considered. Especially for elderly patients aged 75 years or older, many cases of lactic acidosis have been reported, and their prognosis is often poor. Use of this drug should be determined more carefully.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 9 months (May 10, 2010 to February 22, 2012)

- Lactic acidosis: 12 cases (5 fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 1,000,000 (March 2011 to February 2012) Launched in Japan: May 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Diabetes mellitus (hypertension)	500 mg for 61 days	**Lactic acidosis** The patient visited Hospital A due to diabetes mellitus, hypertension, etc. There is information that he took excessive alcohol. He took another metformin preparation (500 mg/day) from about 8 months before administration. Day 1 of administration: This metformin preparation was switched to metformin hydrochloride (500 mg/day). Day 62 of administration (day of discontinuation): The patient did not come at the time when he usually wakes up in the morning. His family went to his room and then found him lying down. He was conscious but was not able to walk, so he was brought to Hospital B by ambulance. Blood gas test showed pH 7.077 and lactic acid of 153.1 mg/dL. Marked lactic acidosis was noted. Lactic acidosis associated with metformin hydrochloride was suspected, and the patient was admitted to the hospital. Sodium bicarbonate was intravenously administered, and then pH recovered to 7.39. The patient and his family said that he started to take metformin hydrochloride recently. Administration of metformin hydrochloride was discontinued after hospital admission. After acidosis improved, the patient gained lucidity, and therefore dietary intake was started from the night of the day of hospital admission. He was able to take almost the whole amount. <Dehydration findings> Physical findings: No dry tongue, etc. were found. Serum creatinine level was 1.43 mg/dL and improved at the next blood sampling. 1 day after discontinuation: After that, blood gases were checked almost every day, but lactic acidosis did not occur. 5 days after discontinuation: His condition became stable and the course was favorable. The patient was discharged from the hospital. (Lactic acidosis resolved)
	Concomitant medications: pioglitazone hydrochloride, glimepiride, mosapride citrate hydrate, miglitol, terazosin hydrochloride hydrate, glibenclamide, trichlormethiazide, telmisartan/amlodipine besilate			

Laboratory Examination

Hospital A

	Approximately 1 year before administration	Approximately 8 months before administration	140 days before administration
BUN (mg/dL)	14.4	12.9	13.1
Serum creatinine (mg/dL)	0.78	0.78	0.77

Hospital B

	Day 62 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	4 days after discontinuation
BUN (mg/dL)	17	18	—	—
Serum creatinine (mg/dL)	1.43	0.87	—	—
eGFR (mL/min/1.73 m^2)	37.0	63.8	—	—
pH (arterial blood)	7.077	—	—	—
pH (venous blood)	—	7.500	7.444	7.412
Lactic acid (arterial blood) (mg/dL)	153.1	—	—	—
Lactic acid (venous blood) (mg/dL)	—	7.2	7.2	9.0
Blood ketone body (mmol/L)	1.3	—	—	—

4

Revision of Precautions (No. 235)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated March 19, 2012 (excluding those presented in "3. Important Safety Information" of this Bulletin).

1

Antidiabetic agents

Pioglitazone Hydrochloride/Metformin Hydrochloride
Metformin Hydrochloride (products with “Dosage and Administration” of maximum daily dosage of 750 mg)

Brand Name

METACT Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
Glycoran Tablets 250 mg (Nippon Shinyaku Co., Ltd.) and the others

Warnings

WARNINGS

Serious lactic acidosis may occur, resulting in fatal outcomes in some cases. This drug should not be administered to patients who can easily develop lactic acidosis. In addition, serious hypoglycaemia may occur. Careful attention should be paid to the Dosage and Administration and Precautions.

Contraindications

Patients with gastrointestinal disorders such as diarrhoea and vomiting for which there is concern about dehydration or a state of dehydration.

Important Precautions

Serious lactic acidosis may occur. Patients and their families should be adequately instructed regarding the following information.

1) Patients should avoid excessive alcohol consumption.
2) If there is concern about the state of dehydration due to pyrexia, diarrhoea, vomiting, poor meal ingestion, etc., patients should temporarily discontinue taking this drug and consult a physician.
3) If any initial symptoms of lactic acidosis are observed, patients should visit a hospital immediately.

Hypoglycemic symptoms may occur. Attention should be paid when administering the drug to patients engaged in working at heights, driving, etc. Patients and their families should be adequately instructed of the precautions concerning hypoglycemic symptoms.

Lactic acidosis may occur due to dehydration. If any symptoms of dehydration are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

In patients with renal impairment, the excretion of this drug in the kidneys decreases, leading to increased blood concentration. Before and during the administration of this drug, use of this drug should be considered based on careful monitoring of the renal function and condition of the patient. Renal function should be determined by referring to eGFR, serum creatinine level, etc.

Adverse Reactions (clinically significant adverse reactions)	**Lactic acidosis**: Lactic acidosis (showing increased blood lactic acid, increased lactate pyruvate ratio, decreased blood pH, etc.) is frequently associated with a poor prognosis. There are a variety of clinical symptoms that generally occur, but symptoms such as gastrointestinal symptoms, malaise, myalgia, and hyperpnoea are frequently observed. If such symptoms are observed, administration of this drug should be discontinued immediately, and necessary examinations should be performed. If lactic acidosis is highly suspected, appropriate measures should be taken without waiting for data such as the result of measurement of lactic acid.

2 **Antidiabetic agents**

Buformin Hydrochloride

Brand Name	DIBETOS Tablets 50 mg (Nichi-iko Pharmaceutical Co., Ltd.), DIBETON S ENTERIC COATED TAB. 50 mg (Kotobuki Pharmaceutical Co., Ltd.)
Warnings	**WARNINGS** Serious lactic acidosis may occur, resulting in fatal outcomes in some cases. This drug should not be administered to patients who can easily develop lactic acidosis. In addition, serious hypoglycaemia may occur. Careful attention should be paid to the Dosage and Administration and Precautions.
Contraindications	Dialysis patients (including peritoneal dialysis) Patients with gastrointestinal disorders such as diarrhoea and vomiting for which there is concern about dehydration or a state of dehydration.
Important Precautions	Serious lactic acidosis may occur. Patients and their families should be adequately instructed regarding the following information. 1) Patients should avoid excessive alcohol consumption. 2) If there is concern about the state of dehydration due to pyrexia, diarrhoea, vomiting, poor meal ingestion, etc., patients should temporarily discontinue taking this drug and consult a physician. 3) If any initial symptoms of lactic acidosis are observed, patients should visit a hospital immediately. Hypoglycemic symptoms may occur. Attention should be paid when administering the drug to patients engaged in working at heights, driving, etc. Patients and their families should be adequately instructed of the precautions concerning hypoglycemic symptoms. Lactic acidosis may occur due to dehydration. If any symptoms of dehydration are observed, administration of this drug should be discontinued, and appropriate measures should be taken. In patients with renal impairment, the excretion of this drug in the kidneys decreases, leading to increased blood concentration. Before and during the administration of this drug, use of this drug should be considered based on careful monitoring of the renal function and condition of the patient. Renal function should be determined by referring to eGFR, serum creatinine level, etc.
Adverse Reactions (clinically significant adverse reactions)	**Lactic acidosis**: Lactic acidosis (showing increased blood lactic acid, increased lactate pyruvate ratio, decreased blood pH, etc.) is frequently associated with a poor prognosis. There are a variety of clinical symptoms that generally occur, but symptoms such as gastrointestinal symptoms, malaise, myalgia, and hyperpnoea are frequently observed. If such symptoms are observed, administration of this drug should be discontinued immediately, and necessary examinations should be performed. If lactic acidosis is highly suspected, appropriate measures should be taken without waiting for data such as the result of measurement of lactic acid.

3

Miscellaneous metabolism agents-Miscellaneous

Fingolimod Hydrochloride

Brand Name

IMUSERA Capsules 0.5 mg (Mitsubishi Tanabe Pharma Corporation),
GILENYA Capsules 0.5 mg (Novartis Pharma K.K.)

Warnings

WARNINGS

After initiating the administration of this drug, a decreased heart rate may be observed for several days. In particular, heart rate may decrease substantially in the initial treatment stage. Administration of this drug should be started under management which enables appropriate measures, such as collaboration with a physician specializing in cardiology.

Important Precautions

Decreased heart rate or delayed atrioventricular conduction may occur at the beginning of administration of this drug. Before and during treatment, attention should be paid to the following points:
Vital signs should be monitored for at least 6 hours after the initial administration of this drug, and 12-lead ECG should be measured before and 6 hours after the initial administration of this drug. For 24 hours after the initial administration of this drug, it is preferable to monitor ECG continuously, in addition to measurement of heart rate and blood pressure.
If any signs or symptoms related to bradyarrhythmia are observed after administration of this drug, appropriate measures should be taken, and patients should be monitored at least until these signs/symptoms disappear and become stable.

4

Hypnotics and sedatives, anxiolytics

Triazolam

Brand Name

Halcion Tablets 0.125 mg, 0.25 mg (Pfizer Japan Inc.) and the others

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylactoid symptoms: Shock, anaphylactoid symptoms (rash, angioedema, dyspnoea, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of the drug should be discontinued and appropriate measures should be taken.

5

Antipyretics and analgesics, anti-inflammatory agents

Tramadol Hydrochloride
Tramadol Hydrochloride/Acetaminophen

Brand Name

Tramal Capsules 25 mg, 50 mg, Tramal Injection 100 (Nippon Shinyaku Co., Ltd.)
TRAMCET Combination Tablets (Janssen Pharmaceutical K.K.)

Important Precautions

Sleepiness, dizziness, or loss of consciousness may occur. Patients treated with this drug should be provided with precautions not to engage in potentially hazardous machine operations including driving. Some cases of loss of consciousness leading to automobile accident have been reported.

Adverse Reactions (clinically significant adverse reactions)

Loss of consciousness: Loss of consciousness may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of the drug should be discontinued, and appropriate measures should be taken.

6 Psychotropics

Paliperidone
Risperidone

Brand Name	Invega Tablets 3 mg, 6 mg, 9 mg (Janssen Pharmaceutical K.K.) and the others
Adverse Reactions (clinically significant adverse reactions)	RISPERDAL Tablets 1 mg, 2 mg, 3 mg, RISPERDAL Fine Granules 1%, RISPERDAL Oral Solution 1 mg/mL, RISPERDAL OD Tablets 0.5 mg, 1 mg, 2 mg, RISPERDAL Consta Intramuscular Injection 25 mg, 37.5 mg, 50 mg (Janssen Pharmaceutical K.K.) **Priapism**: Priapism based on the α sympatholytic effect may occur. In such cases, appropriate measures should be taken.

7 Psychotropics

Blonanserin

Brand Name	LONASEN 2 mg Tablets, LONASEN 4 mg Tablets, LONASEN 8 mg Tablets, LONASEN 2% Powder (Dainippon Sumitomo Pharma Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Syndrome of inappropriate antidiuretic hormone secretion (SIADH)**: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) accompanied by hyponatraemia, blood hyposmosis, increased urine sodium, hypersthenuria, convulsions, or disturbed consciousness may occur. In such cases, administration of this drug should be discontinued, and appropriate measures such as restricting fluid intake should be taken. **Hepatic dysfunction**: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), γ-GTP, Al-P, and bilirubin may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

8 Diuretics

Furosemide

Brand Name	Lasix 10 mg Tab., Lasix 20 mg Tab., Lasix 40 mg Tab., Lasix 4% Fine granule, Lasix 20 mg Injection, Lasix 100 mg Injection, Eutensin Capsule 40 mg (sanofi-aventis K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

9 Anabolic steroid preparations

Metenolone Enanthate
Metenolone Acetate

Brand Name	Primobolan-Depot intramuscular injection 100 mg (Fuji Pharma Co., Ltd.) Primobolan Tablet 5 mg (Bayer Yakuhin, Ltd.)
Important Precautions	Hepatic dysfunction or jaundice may occur. Particularly when this drug is administered long term, laboratory tests (liver function test, etc.) should be performed periodically.

Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), or γ-GTP, etc., or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of the drug should be discontinued, and appropriate measures should be taken.

10 Urogenital and anal organ agents-Miscellaneous

Mirabegron

Brand Name	Betanis Tablets 25 mg, 50 mg (Astellas Pharma Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Urinary retention**: Urinary retention may occur. Patients should be carefully monitored. If any symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

11 Vitamin B preparations

Pyridoxal Phosphate Hydrate (injection dosage form) (products containing benzyl alcohol as excipient)
Pyridoxine Hydrochloride (injectable dosage form)

Brand Name	PYDOXAL Injection 10 mg, 30 mg (Chugai Pharmaceutical Co., Ltd.) and the others B-Six Injection "Fuso" -10 mg, -30 mg (Fuso Pharmaceutical Industries, Ltd.), Vitamin B_6 Injection "Nichi-iko" 10 mg (Nichi-iko Pharmaceutical Co., Ltd.)
Precautions of Dosage and Administration	This drug contains benzyl alcohol as excipient. If a high dose of this drug is used in neonates (low birth weight babies), etc., the use of other products not containing benzyl alcohol should be considered.
Pediatric use	There have been reports of cases such as neonates (low birth weight babies) who developed toxic symptoms (gasping respiration, acidosis, convulsion, etc.) suspected to be caused by benzyl alcohol contained as an excipient in this drug.

12 Antivirals

Ribavirin (capsules)

Brand Name	REBETOL Capsules 200 mg (MSD K.K.)
Adverse Reactions (clinically significant adverse reactions)	**<Administration in combination with interferon beta>** **Diabetes mellitus (types 1 and 2)**: Diabetes mellitus may be aggravated or occur and some of the cases may result in coma. Tests (blood glucose, urinary sugar, etc.) should be performed periodically. If any abnormalities are observed, administration of the drug should be discontinued, and appropriate measures should be taken.

13 Biological preparations-Miscellaneous

Interferon Beta (products for administration in concomitant with ribavirin)

Brand Name	FERON for Injection (1×106 IU), (3×106 IU), (6×106 IU) (Toray Industries Inc.)
Adverse Reactions (clinically significant adverse reactions)	**<Administration in concomitant with ribavirin>** **Diabetes mellitus (types 1 and 2)**: Diabetes mellitus may be aggravated or occur and some of the cases may result in coma. Tests (blood glucose, urinary sugar, etc.) should be performed periodically. If any abnormalities are observed, administration of the drug should be discontinued, and appropriate measures should be taken.

14 X-ray contrast media

Iopamidol

Brand Name

Iopamiron Inj. 150, 300, 370, Iopamiron Inj. Syringe 300, 370 (Bayer Yakuhin, Ltd.) and the others

Adverse Reactions (clinically significant adverse reactions)

Acute respiratory distress syndrome, pulmonary oedema: Acute respiratory distress syndrome or pulmonary oedema may occur. Patients should be carefully monitored, and if rapidly progressing dyspnoea, hypoxaemia or chest X-ray abnormalities including diffuse infiltrative shadow in bilateral lung are observed, appropriate measures should be taken if necessary.

15 Over-the-counter drugs

Products containing acetaminophen

Brand Name

TYLENOL FD (Daito Pharmaceutical Co., Ltd.) and the others

Consultation

If the following symptoms are observed after taking this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician, pharmacist, or registered salesperson for a consultation.
The following serious symptoms occur in rare cases. In such a case, immediately seek medical aid.

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis, acute generalised exanthematous pustulosis: Hyperthermia, ocular hyperaemia, eye discharge, sore lips, pharynx pain, widespread skin rash/redness, small zits (small pustules) on reddened skin, general malaise, anorexia, etc. may persist or suddenly worsen.

Interstitial pneumonia: Shortness of breath or difficulty in breathing when climbing the stairs or during light exertion, dry cough, pyrexia, etc. may occur suddenly or persist.

Renal disorder: Pyrexia, rash, anasarca, general malaise, arthralgia (pain in joints), diarrhoea, etc. may occur.

5

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of the drug in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of April 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Crizotinib XALKORI Capsules 200 mg, 250 mg	Pfizer Japan Inc.	March 30, 2012
Duloxetine Hydrochloride Cymbalta Capsules 20 mg, 30 mg*[1]	Shionogi & Co., Ltd.	February 22, 2012
Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, 24 mg*[2]	Otsuka Pharmaceutical Co., Ltd.	January 18, 2012
Human Fibrinogen/Thrombin Fraction TachoSil Tissue Sealing sheet	CSL Behring K.K.	January 17, 2012
Fosphenytoin Sodium Hydrate Fostoin 750 mg for Injection	Nobelpharma Co., Ltd.	January 17, 2012
Rebamipide Mucosta ophthalmic suspension UD 2%	Otsuka Pharmaceutical Co., Ltd.	January 5, 2012
Everolimus AFINITOR tablets 5 mg*[3]	Novartis Pharma K.K.	December 22, 2011
Everolimus Certican Tablets 0.25 mg, 0.5 mg, 0.75 mg*[4]	Novartis Pharma K.K.	December 22, 2011
Pranlukast Hydrate ONON drysyrup 10%*[5]	Ono Pharmaceutical Co., Ltd.	December 22, 2011
Peginterferon Alfa-2b (Genetical Recombination) PEGINTRON Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL*[6]	MSD K.K.	December 22, 2011
Ribavirin REBETOL Capsules 200 mg*[7]	MSD K.K.	December 22, 2011
Fosaprepitant Meglumine PROEMEND for Intravenous Infusion 150 mg	Ono Pharmaceutical Co., Ltd.	December 9, 2011
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg	Pfizer Japan Inc.	December 7, 2011

Canakinumab (Genetical Recombination) ILARIS for s.c. injection 150 mg	Novartis Pharma K.K.	December 7, 2011
Telaprevir TELAVIC Tablets 250 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride IMUSERA Capsules 0.5 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride GILENYA Capsules 0.5 mg	Novartis Pharma K.K.	November 28, 2011
Imiquimod BESELNA CREAM 5%*[8]	Mochida Pharmaceutical Co., Ltd.	November 25, 2011
Teriparatide Acetate Teribone Inj. 56.5 μg	Asahi Kasei Pharma Corporation	November 25, 2011
Fulvestrant FASLODEX intramuscular injection 250 mg	AstraZeneca K.K.	November 25, 2011
Modafinil MODIODAL Tablets 100 mg*[9]	Alfresa Pharma Corporation	November 25, 2011
Live Attenuated Human Rotavirus Vaccine, Oral Rotarix Oral Solution	GlaxoSmithKline K.K.	November 21, 2011
Olopatadine Hydrochloride ALLELOCK Granules 0.5%*[10]	Kyowa Hakko Kirin Co., Ltd.	November 15, 2011

*1 An additional indication for “treatment of pain in patients with diabetic neuropathy”

*2 An additional indication for “improvement of manic symptoms in patients with bipolar disorder”

*3 An additional indication for “treatment of patients with pancreatic neuroendocrine tumour”

*4 An additional indication for “prophylaxis rejection in renal transplantation”

*5 An additional indication for “treatment of patients with allergic rhinitis”

*6 An additional indication for “improvement of viraemia in compensated cirrhosis C in combination therapy with ribavirin”

*7 An additional indication for “improvement of viraemia in compensated cirrhosis C in combination therapy with peginterferon alfa-2b (genetical recombination)”

*8 An additional indication for “treatment of patients with actinic keratosis (limited to face or baldness)”

*9 An additional indication for “treatment of excessive daytime sleepiness in patients with obstructive sleep apnoea syndrome who receive treatment for airway obstruction with continuous positive airway pressure (CPAP) therapy, etc.”

*10 An additional administration for “pediatrics (aged 2 to under age of 7)”

Increase of the Number of Cooperating Hospitals in the Project for "Japan Drug Information Institute in Pregnancy"

The project for Japan Drug Information Institute in Pregnancy (JDIIP) has been carried out with the cooperation of 20 hospitals nationwide. The system for consultation service and prompt information collection was strengthened in FY 2012, by getting the cooperation of 3 hospitals newly joined, in order to enhance the convenience. The contact information of JDIIP and the cooperating hospitals are listed below.

See Pharmaceuticals and Medical Devices Safety Information No. 235 (April 2008), No. 268 (April 2010), and No. 279 (May 2011) for details of the project for JDIIP.

	Name of medical institution	Contact information, reception hours, etc.
1	Japan Drug Information Institute in Pregnancy	2-10-1 Okura, Setagaya-ku, Tokyo 157-8535 in National Center for Child Health and Development (NCCHD) TEL: (+81)-3-5494-7845 FAX: (+81)-3-3415-0914 Reception hours: 10:00 –12:00, 13:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.ncchd.go.jp/kusuri
Cooperating hospitals (◎: Joined since 2012)		
2	Hokkaido University Hospital	Kita 14, Nishi 5, Kita-ku, Sapporo-city, Hokkaido 060-8648 TEL: (+81)-11-716-1161 (Extension 7723 or PHS 82943) FAX: (+81)-11-706-7616 Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
3	Iwate Medical University Hospital	19-1 Uchimaru, Morioka-city, Iwate 020-8505 TEL: (+81)-19-624-5263 (Pregnancy and drugs counseling desk: Direct call) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays) URL:http://www.iwate-med.ac.jp/hospital/ninsin/index.html
4	National Hospital Organization Sendai Medical Center	2-8-8 Miyagino, Miyagino-ku, Sendai-city, Miyagi 983-8520 TEL: (+81)-22−293−1111 (Please ask for "Outpatient office for pregnancy and drugs" in Pharmacy department) Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.snh.go.jp/Medicine/index.html

5	Tsukuba University Hospital	2-1-1 Amakubo, Tsukuba, Ibaraki 305-8576 TEL: (+81)-29-853-3630 FAX: (+81)-29-853-7025 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
6	Maebashi Red Cross Hospital	3-21-36 Asahi-cho, Maebashi, Gunma 371-0014 TEL: (+81)-27-224-4585 (Division of Pharmacy: Extension 7709) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.maebashi.jrc.or.jp/
7	Saitama Medical University Hospital	38 Morohongo Moroyama-machi, Iruma-gun, Saitama 350-0495 TEL: (+81)-49-276-1297 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours: 15:00 – 17:00 (Monday to Saturday, excluding national holidays)
8	Chiba University Hospital	1-8-1 Inohana, Chuo-ku, Chiba-city, Chiba 260-8677 TEL: (+81)-43-226-2628 (Drug Information, Division of Pharmacy) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
9	Toranomon Hospital	2-2-2 Toranomon, Minato-ku, Tokyo 105-8470 TEL: (+81)-3-3588-1111 (Extension 3410) FAX: (+81)-3-3505-1764 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
10	St. Luke's International Hospital	9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560 TEL: (+81)-3-5550-2412 FAX: (+81)-3-5550-2563 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
11	Yokohama City University Hospital	3-9 Fukuura, Kanazawa-ku, Yokohama-city, Kanagawa 236-0004 TEL: (+81)-45-787-2800 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.fukuhp.yokohama-cu.ac.jp/
◎ 12	Niigata University Medical & Dental Hospital	1-754 Asahimachi-dori, Chuo-ku, Niigata-city, Niigata 951-8520 TEL: (+81)-25-227-0352 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-25-227-0363 Reception hours: 9:00 – 13:30 (Tuesday and Friday, excluding national holidays)

13	Shinshu University Hospital	3-1-1 Asahi, Matsumoto-city, Nagano 390-8621 TEL: (+81)-263-37-3022 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-263-37-3072 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
14	National Hospital Organization Kanazawa Medical Center	1-1 Shimoishibiki-machi,Kanazawa-city, Ishikawa 920-8650 TEL: (+81)-76-262-4161 Reception hours: 9:00 – 16:30 (Monday to Friday, excluding national holidays) URL: http://www.kanazawa-hosp.jp/pv/preg.htm
15	National Hospital Organization Nagara Medical Center	1300-7 Nagara, Gifu-city, Gifu 502-8558 TEL: (+81)-58-232-7755 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-58-295-0077 Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays)
16	Japanese Red Cross Nagoya Daiichi Hospital	3-35 Michishita-cho, Nakamura-ku, Nagoya-city, Aichi 453-8511 TEL: (+81)-52-481-5111 (Division of Pharmacy: Extension 38376) FAX: (+81)-52-482-7733 Reception hours: 13:00 – 16:00 (Monday to Friday, excluding national holidays)
◎ 17	University Hospital, Kyoto Prefectural University of Medicine	465 Kajii-cho, Hirokoji agaru, Kawaramachi-dori, Kamigyo-ku, Kyoto-City, Kyoto 602-8566 TEL: (+81)-75-251-5862 (Drug Information, Division of Pharmacy) FAX: (+81)-75-251-5859 (same as above): Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
18	Osaka Medical Center and Research Institute for Maternal and Child Health	840 Murodo-cho, Izumi-city, Osaka 594-1101 TEL: (+81)-725-56-5537 (“Outpatient department for pregnancy and drugs”) Reception hours: 10:00 – 12:00, 14:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.mch.pref.osaka.jp/
◎ 19	Kobe University Hospital (to be opened in May 2012)	7-5-2 Kusunoki-cho, Chuo-ku, Kobe-city, Hyogo 650-0017 TEL: (+81)-78-382-5111 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours:13:00 – 17:00 (Monday to Friday, excluding national holidays)

20	Nara Medical University Hospital	840 Shijo-cho, Kashihara-city, Nara 634-8522 TEL: (+81)-744-22-3051 (Division of Pharmacy: Extension 3565) FAX: (+81)-744-29-8027 Reception hours: 8:30 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.naramed-u.ac.jp/~gyne/kusuri.html
21	Hiroshima University Hospital	1-2-3 Kasumi, Minami-ku, Hiroshima-city, Hiroshima 734-8551 TEL: (+81)-82-257-5079 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
22	National Hospital Organization Kagawa National Children's Hospital	2603 Zentsuji-cho, Zentsuji-city, Kagawa 765-8501 TEL: (+81)-877-62-0885 FAX: (+81)-877-62-5484 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
23	Kyushu University Hospital	3-1-1 Maidashi, Higashi-ku, Fukuoka-city, Fukuoka 812-8582 TEL: (+81)-92-642-5900 Reception hours: 14:00 – 17:00 (Monday to Friday, excluding national holidays)
24	Kagoshima City Hospital	20-17 Kajiya-cho, Kagoshima-city, Kagoshima 892-8580 TEL: (+81)-99-224-2101 (Pharmacy department: Extension 2603) (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-99-224-9916 Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays)