Pharmaceuticals and Medical Devices Safety Information

No. 296 November 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).

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

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

Pharmaceuticals and Medical Devices Safety Information
No. 296 November 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
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
ALP	Alkaline phosphatase
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CD	Cluster of differentiation
Cr	Creatinine
CPR	C-peptide reactivity
CRP	C-reactive protein
CT	Computed tomography
DIHS	Drug-induced hypersensitivity syndrome
DLST	Drug lymphocyte stimulation test
ECG	Electrocardiogram
EEG	Electroencephalogram
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
FIP1L 1-PDGFRa	Fip-1-like 1-platelet-derived growth factor receptor alpha
FT3	Free triiodothyronine
FT4	Free thyroxine
FY	Fiscal year
GAD	Glutamic acid decarboxylase
HbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
HPV-IgG	Human papilloma virus-Immunoglobulin G
I-131	Iodine 131
IA-2	Insulinoma antigen 2
ICA	Islet cell antibody
ICD	Implantable cardioverter defibrillator
IU	International unit
JCS	Japan Coma Scale
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
NGSP	National glycohemoglobin standardization program
PLT	Platelet
RBC	Red blood cell count
S.I.	Stimulation index
SpO_2	Oxygen saturation
SS-A	Sjögren's syndrome A
Tc-99m	Technetium 99m
TEN	Toxic epidermal necrolysis
TgAb	Thyroglobulin antibody
TP	Total protein
TPOAb	Thyroid peroxidase antibody
TRAb	Thyroid-stimulating hormone receptor antibody
TSH	Thyroid-stimulating hormone
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

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Summary of Payment/Non-payment of Adverse Drug Reaction Relief Benefits and Drugs with Many Cases of Improper Use

1. Introduction

The Relief System for Sufferers from Adverse Drug Reactions was established in 1980 to bring prompt relief to people who suffer from adverse health effects such as disorders or disabilities caused by adverse reactions to drugs (including over-the-counter drugs), despite using them properly. This is a public service funded by contributions from marketing authorization holders of drugs as a way to fulfill some of their social responsibilities. As shown in **Table 1**, the number of applications for the Relief System for Sufferers and payments of relief benefits has been increasing in recent years.

In 2004, the Relief System for Sufferers from Diseases Infected from Biological Products, which is also a public service, was established to bring prompt relief to people who suffered from adverse health effects such as disorders or disabilities caused by infections from viruses, etc., despite using biological products properly.

People who have suffered from adverse health effects are encouraged to use this system as much as possible; however, some cases of adverse health effects were not approved for relief benefits due to improper use of drugs. Thus, MHLW/PMDA presents here drugs with many such cases and encourages proper use of drugs.

Table 1 Number of relief benefits from the Relief Systems

Fiscal year	Number of applications	Number of payments	Number of non-payments
1980-1997	3064 (2506)	2370 (1971)	471 (345)
1998	361 (300)	306 (261)	49 (40)
1999	389 (318)	289 (238)	46 (41)
2000	480 (414)	343 (293)	61 (54)
2001	483 (411)	352 (294)	64 (54)
2002	629 (531)	352 (288)	79 (66)
2003	593 (702)	465 (407)	99 (82)
2004	769 (675)	513 (460)	119 (101)
2005	760 (643)	836 (745)	195 (157)
2006	788 (679)	676 (599)	169 (133)
2007	908 (785)	718 (617)	135 (107)
2008	926 (811)	782 (690)	136 (111)
2009	1052 (947)	861 (776)	127 (96)
2010	1018 (906)	897 (813)	122 (97)
2011	1075 (951)	959 (861)	143 (122)
Total	13495 (11579)	10719 (9313)	2015 (1606)

* The numbers of claimants (actual number)

- Number of claimants: a second claim for the same cause was counted.
- Actual number: a second claim for the same cause was not counted.
- The number of applications and the total number of payment and non-payment are not consistent since approximately 8 to 10 months are required from the receipt of the application to the decision of benefit payment.

2. Information on the Relief Systems

For details of both Relief Systems, please refer to the PMDA website (http://www.pmda.go.jp/kenkouhigai.html [only available in Japanese language]) or the PMDSI No. 273 (October 2010) for outline of these services. The following materials are also available on the PMDA website (only available in Japanese language). Promotion of the Relief Systems using these materials is encouraged.

- Relief System information booklet
  http://www.pmda.go.jp/kenkouhigai/file/higaikyusai.pdf
- Relief System information leaflet
  http://www.pmda.go.jp/kenkouhigai/ldp/file/fukusayo_leaflet.pdf
  http://www.pmda.go.jp/kenkouhigai/ldp/file/seibutuyurai.pdf
- Poster
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_keiji.pdf
- Materials for medication bag
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_kusuri.pdf

If adverse health effects including disorders leading to hospital admission or disabilities that results in significant limitation during his/her daily life performance that are considered to be associated with drugs, healthcare professionals should provide information regarding the Relief Systems to patients or their family and help them file a benefit claim.

Consultation service is available:

- Relief System Consultation Service
  0120−149−931 (toll-free)
  Monday to Friday 9:00-17:00 (excluding national holidays and New Year holidays)

Caution should be paid to the cases not applicable for relief benefits as shown in **Table 2**.

Table 2 Examples of cases not applicable for relief benefits

a. Cases of adverse health effects resulting from statutory vaccination practice (Relief System for Injury to Health with Vaccination is applicable in accordance with the Preventive Vaccination Law). However, cases of adverse health effects resulting from voluntary vaccinations are applicable for relief benefits under the Relief System for Sufferers.
b. Cases where it is clear who is responsible for adverse health effects, including the product liability of the marketing authorization holders of the drugs or biological products.
c. Cases where it is necessary to use the pharmaceutical or biological product in an amount exceeding the approved dosage for the purpose of saving the patient's life, even if it was recognized beforehand that adverse health effects may occur.
d. Cases where it is not confirmed that the drugs or biological products are used for a proper purpose and with a proper method.
   (e.g. cases where the drugs or biological products have been used in ways other than indications approved by the Minister of Health, Labour and Welfare, or cases where the drugs or biological products have not been used in accordance with the Precautions section in the package inserts)
e. Cases of adverse health effects caused by drugs inapplicable for the relief benefits[Note)].
   Note) Drugs inapplicable for the relief benefits:
   (1) Drugs used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
   (2) Drugs that do not have the possibility to cause adverse reactions, including drugs not used directly on human bodies or drugs without pharmacological effects (insecticides, disinfectant

agents, and in vitro diagnostics, etc.)

f. Cases of mild adverse health effects (including a hospital or treatment equivalent to inpatient care is not required) or cases where disabilities caused by drugs fail to meet the disability criteria under the Relief Systems[Note)].

Note) Degree of disability does not meet the criteria of "Disability that prevents a person from performing daily life activities by himself/herself (Grade 1)" or "Disability that results in significant limitation during his/her daily life performance (Grade 2)"

g. Cases where the deadline of claiming the relief benefits has passed.

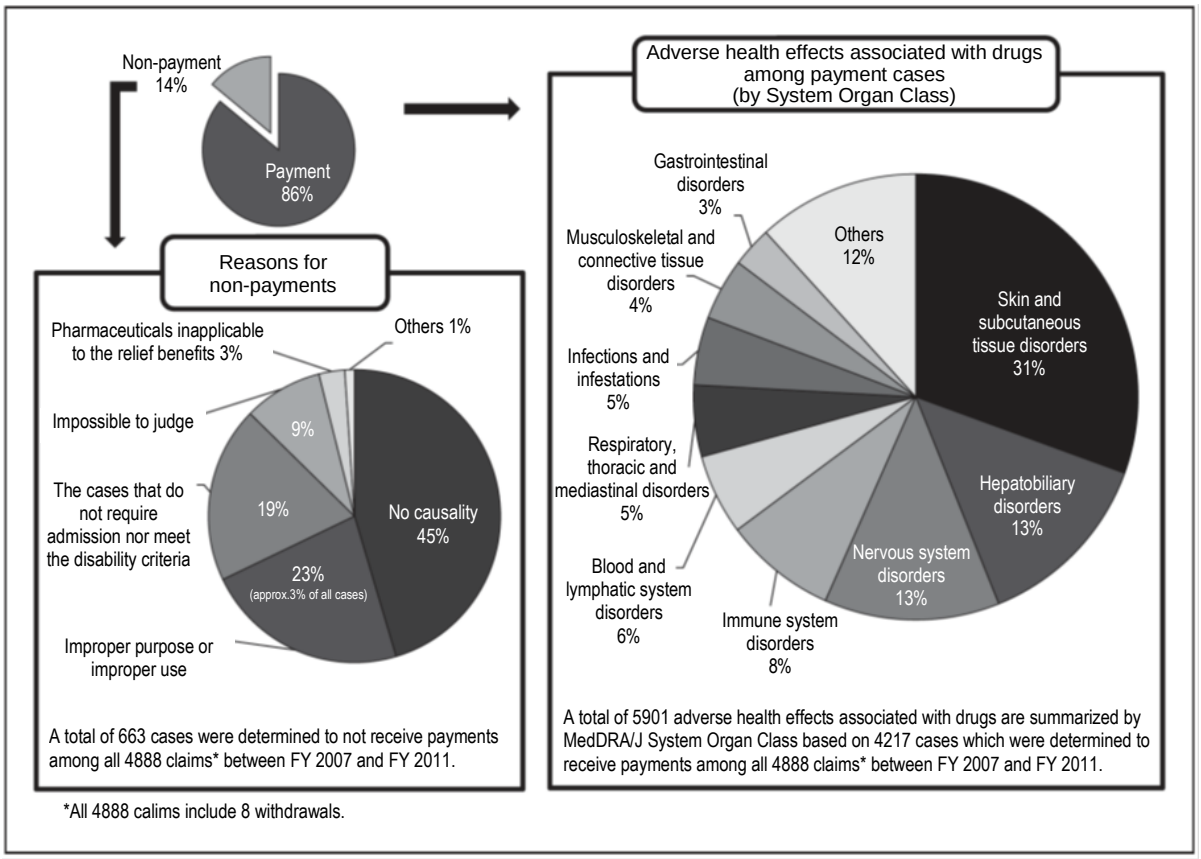
h. Other cases that have not been approved by the Pharmaceutical Affairs and Food Sanitation Council of MHLW based on medical and pharmaceutical judgment.

- Cases where the disorders or disabilities are considered to be unlikely caused by adverse drug reactions (those are not considered to be associated with drugs).
- Cases where it cannot be judged whether there are causalities or whether drugs are used for proper purpose and with the proper method, because of insufficient documentation (impossible to judge).

3. Summary of Payment/Non-payment cases

Between FY 2007 and FY 2011, the percentage of payments and non-payments was 86% and 14%, respectively. **Figure 1** shows details of adverse health effects associated with drugs among cases receiving payments and reasons for non-payments.

Figure 1 Percentage for payments and non-payments with details of adverse health effects and reasons for non-payments between FY 2007 and FY 2011



4. Drugs with Many Cases of Improper Use

During one and a half years between April 2011 to September 2012, the following drugs were involved in many cases not receiving payments due to improper use: lamotrigine (Lamictal), 15 cases; thiamazole (MERCAZOLE), 6 cases; and benzbromarone (URINORM and others) 5 cases.

(1) Cases of improper use of lamotrigine (Lamictal)

Severe drug eruption occurred during treatment with lamotrigine for epilepsy. Lamotrigine was used in concomitant with sodium valproate and administered at 25 mg daily everyday for the first week and at 75 mg daily everyday from the second week. This case was deemed improper use because the doctor did not prescribe the drug every other day in the beginning and the dose was increased too fast and too much.
(The “Dosage and Administration” and “Precautions” sections of the package insert specify that, when sodium valproate is concomitantly used, "The usual dose of lamotrigine is 25 mg given orally once every other day for the first two weeks and 25 mg/day once daily for the next two weeks. The dose should be gradually increased by 25 to 50 mg every 1 to 2 weeks thereafter.")

Severe drug eruption occurred during treatment with lamotrigine for bipolar affective disorder. Treatment with lamotrigine was started at 50 mg daily everyday without concomitant use of sodium valproate or any drug that induces glucuronidation. This case was deemed improper use because the initial dose was too high.
(The “Dosage and Administration” and “Precautions” sections of the package insert specify that, when lamotrigine is used alone, "The usual adult dose of lamotrigine is 25 mg/day given orally once daily for the first two weeks and 50 mg/day once daily or twice daily in divided doses for the next two weeks. During the fifth week, 100 mg/day of lamotrigine should be given orally once daily or twice daily in divided doses.")

(2) Cases of improper use of thiamazole (MERCAZOLE)

Agranulocytosis occurred during treatment with thiamazole for hyperthyroidism. This case was deemed improper use because no blood tests were performed for approximately 7 weeks between the start of treatment and the onset of agranulocytosis.
(The “Warnings” section of the package insert specifies that, Serious agranulocytosis has been reported especially within the first 2 months after administration, leading to fatal outcome in some cases. Blood tests including differential leukocyte count should be performed once every 2 weeks in principle for at least 2 months after administration, and periodically after that. If any abnormalities such as decreasing tendency of granulocytes are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. Similarly, caution should be exercised when resuming treatment after temporary discontinuation.")

(3) Cases of improper use of benzbromarone (URINORM and others)

Drug-induced liver injury occurred during treatment with benzbromarone for hyperuricaemia. This case was deemed improper use because no liver function tests had been performed for approximately 10 months between the start of treatment and the onset of liver disorder.
(The Warnings section of the package insert specifies that, "Serious hepatic disorders such as fulminant hepatitis have been reported especially within the first 6 months after administration, leading to serious outcomes such as death in some cases. Liver function tests should be periodically performed for at least the first 6 months after administration. Patients should be carefully monitored, and if any abnormal liver function test results or jaundice are observed, administration of this drug should be discontinued, and appropriate measures should be taken.")

The above-mentioned drugs are known to cause serious adverse reactions and "PMDA Request for Proper Use of Drugs" has been prepared to encourage healthcare professionals to use drugs properly.

- Compliance with Dosage and Administration and Ensuring Early Detection for Lamictal Tablets (lamotrigine)-induced Serious Skin Disorders
  http://www.pmda.go.jp/english/service/pdf/request/No6.pdf
  A high incidence of skin disorders has been reported in cases where administration of Lamictal Tablets was not in compliance with the "Dosage and Administration" section.

- Prevention and early detection of thiamazole-induced agranulocytosis
  http://www.pmda.go.jp/english/service/pdf/request/No5.pdf
  For prevention and early detection of agranulocytosis associated with the antithyroid drug thiamazole, periodic blood tests and symptom check are required.

- Recommendation of periodic liver function tests and monitoring of signs/symptoms for patients treated with the gout/hyperuricaemia treatment benzbromarone
  http://www.pmda.go.jp/english/service/pdf/request/No4.pdf
  Hepatic disorder may occur as an adverse reaction associated with benzbromarone for gout/hyperuricaemia treatment. Continuous treatment despite signs of hepatic disorder has resulted in aggravation of symptom in some cases. Periodic liver function tests are required when using benzbromarone.

5. Closing comments

Healthcare professionals are encouraged to thoroughly read the "Precautions" section of the package insert before using drugs (not only the above-mentioned 3 drugs) and to use them properly. Please note that the cases where drugs are not used properly are not applicable for the relief benefits under public relief systems, even though the adverse health effects are suspected to have been caused by adverse drug reactions.

As mentioned in Section 2, when adverse reactions occur and healthcare professionals are consulted by their patient about the reactions, the healthcare professionals should provide information regarding the Relief Systems to the patient, if the reactions are possibly applicable for the relief benefits. MHLW/PMDA hopes for your particular cooperation in preparing the documents required to claim these relief benefits.

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Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated October 30, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Imatinib Mesilate

Brand Name (name of company)	Glivec Tablets 100 mg (Novartis Pharma K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	1. Chronic myeloid leukaemia 2. KIT (CD117)-positive gastrointestinal stromal tumors 3. Philadelphia chromosome positive acute lymphocytic leukaemia 4. Following FIP1L1-PDGFRα-positive diseases: Hypereosinophilic syndrome, chronic eosinophilic leukaemia

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Pulmonary hypertension: Pulmonary hypertension may occur. Patients should be carefully monitored, and if any symptoms such as dyspnoea and chest pain are observed, administration of this drug should be discontinued and appropriate measures should be taken after making a differential diagnosis versus other causes of disease (e.g. pleural effusion, pulmonary oedema).

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, 2009 to July 26, 2012)

- Pulmonary hypertension-associated cases: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 13,000 (June 1, 2011 to May 31, 2012)

Launched in Japan: July 2005

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Chronic myeloid leukaemia (hypertension, depression, chronic gastritis)	400 mg for 16 days ↓ (administration suspended for 13 days) ↓ 200 mg for approx. 2 months ↓	**Pulmonary arterial hypertension, toxicoderma, reflux oesophagitis, increased weight** Approximately 1 month before administration: The patient developed chronic myeloid leukaemia. Day 1 of administration: Administration of imatinib mesilate 400 mg/day was started. Day 13 of administration: Skin eruption (toxicoderma) appeared. Day 16 of administration (day of discontinuation): Administration of imatinib mesilate was temporarily discontinued.

			400 mg for approx. 4 years and 2 months ↓ (administration suspended for 12 days) ↓ 200 mg continued	14 days after discontinuation (day of readministration): The patient recovered from toxicoderma under the treatment with oral administration of betamethasone. Administration of imatinib mesilate was resumed at a dose of 200 mg/day. Approximately 2 months of readministration: The dose of imatinib mesilate was increased to 400 mg/day. Approximately 4 months of readministration: Reflux oesophagitis appeared. Administration of lansoprazole 15 mg/day was started as a therapeutic drug. Approximately 4 years and 4 months of readministration (day of onset): Pulmonary hypertension, oedema of lower leg, and increased weight appeared. The patient was admitted to the hospital (weight, 45.8 kg). The pulmonary artery pressure on echocardiography was 62 mmHg, and this finding showed pulmonary arterial hypertension. The oedema was seemed to be caused by pulmonary arterial hypertension. Laboratory findings included fatigueability and echocardiography showed a tricuspid valve systolic pressure gradient of 62 mmHg. Chest X-ray showed expansion of the trunk of pulmonary arteries and miniaturization of shadows in peripheral pulmonary vessels. Electrocardiogram (ECG) showed the finding of right ventricular hypertrophy. The clinical classification is pulmonary arterial hypertension associated with drugs/poisonous substances. Several days after the onset (day of discontinuation of readministration): Administration of imatinib mesilate was discontinued. The patient was kept at rest and followed up. 11 days after discontinuation of readministration: Echocardiography showed improvement of pulmonary arterial pressure with 35 mmHg. 13 days after discontinuation of readministration (day of re-readministration): Administration of imatinib mesilate was resumed at 200 mg/day. Day 11 of re-readministration: Symptoms remitted and the patient was discharged from the hospital. The patient's weight was 40 to 41 kg. The patient recovered from pulmonary hypertension and reflux oesophagitis. Oedema was not found. Administration of imatinib mesilate was continued at 200 mg/day. Day 30 of re-readministration: Oedema was not found.
	Concomitant medications: valsartan, furosemide, metoprolol tartrate, rebamipide			

2 Ceftriaxone Sodium Hydrate

Brand Name (name of company)	ROCEPHIN Intravenous 0.5 g, 1 g, ROCEPHIN Infusion Bag 1 g (Chugai Pharmaceutical Co., Ltd.)

	SEFIROM for Intravenous Injection 0.5 g, 1 g (Nichi-Iko Pharmaceutical Co., Ltd.) CEFXONE for Intravenous Injection 0.5 g, 1 g (Shiono Chemical Co., Ltd.) CEFTRIAXONE Na for Intravenous Injection 0.5 g "Sawai," 1 g "Sawai" (Sawai Pharmaceutical Co., Ltd.) Ceftriaxone Na for Intravenous Injection 0.5 g "SANDOZ," 1 g "SANDOZ" (Sandoz K.K.) Ceftriaxone Na for Intravenous Injection 0.5 g "Mylan," 1 g "Mylan" (Mylan Seiyaku Ltd.) CEFTRIAXONE SODIUM FOR INTRAVENOUS 0.5 g "NP," 1 g "NP," CEFTRIAXONE SODIUM FOR INFUSION 1 g "NP" (Nipro Pharma Corporation) CEFTRIAXONE Na for Intravenous Injection 0.5 g "Taiyo" (Teva Pharma Japan Inc.) Ceftriaxone for Intravenous Injection 1 g "TX" (Try-X Co., Ltd.) CEFTRIAXONE Sodium Hydrate for Injection Bag 1 g [Pfizer] (Pfizer Japan Inc.) CERONEED for Intravenous Injection 0.5 g, 1 g (Sawai Pharmaceutical Co., Ltd.) LIASOPHIN for Intravenous Injection 0.5 g, 1 g (Chemix Inc.) ROZECLART for Intravenous Injection 1g, ROZECLART Kit for Infusion 1 g (Teva Pharma Japan Inc.)
Therapeutic Category	Acting mainly on gram-positive and gram-negative bacteria
Indications	Applicable microorganisms: Strains of Staphylococcus, Streptococcus, Pneumococcus, Neisseria gonorrhoeae, Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Serratia, Proteus, Morganella morganii, Providencia, Haemophilus influenzae, Peptostreptococcus, Bacteroides, and Prevotella species those are susceptible to ceftriaxone (except Prevotella bivia) Applicable conditions: Sepsis, pharyngitis/laryngitis, tonsillitis, acute bonchitis, pneumonia, lung abscess, pyothorax, infection secondary to chronic respiratory disease, cystitis, pyelonephritis, epididymitis, urethritis, cervicitis, pelvic inflammatory disease, proctitis, peritonitis, intra-abdominal abscess, cholecystitis, cholangitis, bartholinitis, intrauterine infection, adnexitis, parametritis, suppurative meningitis, keratitis (including corneal ulcer), otitis media, sinusitis, cellulitis around jawbone and jaw inflammation

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Pancytopenia, agranulocytosis, decreased platelets, haemolytic anaemia: Pancytopenia, agranulocytosis, decreased platelets, or haemolytic anaemia may occur. Patients should be carefully monitored through periodic tests, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Acute renal failure, interstitial nephritis: Acute renal failure or interstitial nephritis may occur. Patients should be carefully monitored through period tests, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Disturbed consciousness: Disturbed consciousness including loss of consciousness and decreased level of consciousness may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken. These cases of disturbed consciousness have been reported in many patients with severe renal disorder.

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 and 6 months (April 1, 2009 to September 18, 2012)

- Pancytopenia-associated cases: 2 cases (no fatal cases)
- Interstitial nephritis-associated cases: 3 cases (no fatal cases)
- Disturbed consciousness-associated cases: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 2,170,000 (2011)

Launched in Japan: June 1986

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Pneumonia (none)	2.0 g for 8 days ↓ 1.0 g for 4 days	**Pancytopenia** Day 1 of administration: The patient started receiving ceftriaxone sodium hydrate 2.0 g/day for pneumonia. Day 8 of administration: Pancytopenia was noted. Day 9 of administration: The dose of ceftriaxone sodium hydrate was reduced to 1.0 g/day. Day 12 of administration (day of discontinuation): Administration of ceftriaxone sodium hydrate was discontinued. 3 days after discontinuation: White blood cell (WBC) count 990/mm^3, hemoglobin 8.8 g/dL, platelet count $4.7 \times 10^4/mm^3$, showing marked pancytopenia. Administration of lenograstim (genetical recombination) 100 μg and meropenem hydrate 1.5 g/day was started. Approximately 6 days after discontinuation: WBC count improved to 11690/mm^3, hemoglobin to 9.7 g/dL, platelet count to $16.4 \times 10^4/mm^3$. Administration of lenograstim (genetical recombination) 100 μg was discontinued. Administration of meropenem hydrate was continued.
	Concomitant medications: prednisolone, limaprost alfadex, lansoprazole, alfacalcidol, furosemide, spironolactone, celecoxib, methotrexate			

Laboratory Examination

	Day 1 of administration	Day 5 of administration	Day 8 of administration	Day 11 of administration	3 days after discontinuation	6 days after discontinuation
RBC ($\times 10^4/mm^3$)	348	391	382	310	304	288
Hemoglobin (g/dL)	10.6	11.6	11.4	9.0	8.8	8.4
Hematocrit (%)	32.3	35.2	34.6	28.3	28.2	26.7
PLT ($\times 10^4/mm^3$)	12.5	11.1	10.6	7.4	4.7	4.0
WBC ($/mm^3$)	31000	11930	2750	3070	990	950
Basophils (%)	0.2	0.0	0.0	0.3	0.0	0.02
Eosinophils (%)	0.0	0.0	0.4	0.7	2.0	3.2
Neutrophils (%)	96.6	96.9	87.6	80.4	35.4	36.8
Lymphocytes (%)	0.7	2.8	11.3	17.9	58.6	46.3
CRP (mg/dL)	21.56	10.82	4.67	2.07	0.56	0.64

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 10s	Suspected appendicitis, bacterial enterocolitis	2 g for 3 days	**Interstitial nephritis** Body height: 136 cm Body weight: 45.2 kg History of adverse drug reaction: Unknown History of administration of Rocephin: Initial administration; history of administration of cephems: yes Unknown: The patient developed pyrexia in the 39°C range and cold symptoms, and visited a nearby hospital. Abdominal pain occurred 2 days later, the patient was admitted to the surgical department of the nearby hospital for suspected acute appendicitis. 3 days before administration: Pyrexia occurred. Clarithromycin and cefcapene pivoxil hydrochloride hydrate were prescribed. 1 day before administration: Abdominal pain, pyrexia, and an elevation in inflammatory response in tests at hospital admission were observed. Administration of cefotiam hydrochloride was started at the another hospital. Day 1 of administration: Cefotiam hydrochloride was switched to ceftriaxone sodium hydrate 2 g/day. Day 3 of administration (day of discontinuation) (day of onset): As a diagnosis of appendicitis was ruled out, the patient was transferred to the pediatrics department. Blood urea nitrogen (BUN) and creatinine (Cr) were elevated and C-reactive protein (CRP) and WBC increased. Fosfomycin sodium was added. Acute renal failure developed. 2 days after discontinuation: Treatment with antibiotics was continued, but worsening of renal function was noted in tests and oliguria developed. The patient was transferred to another hospital. (At the time of hospital transfer) Oedema and electrolyte abnormality were noted, and administration of all antibiotics were discontinued. Conservative treatment with transfusion and systemic management was performed. [Physical findings at hospital transfer] Chest: clear Heart sounds: pure Abdomen: swollen, soft Liver/spleen: non-palpable (-) Abdominal pain: (+) Oedema of lower leg: (-) Diarrhoea: (+) 8 days after discontinuation: Urine output increased, but the renal function did not improve. 10 days after discontinuation: Renal biopsy was conducted to identify the cause. Histological findings for renal showed no abnormalities of the glomerulus, but showed sever inflammatory cell infiltration into the tubulointerstitium. 16 days after discontinuation: Outcome of acute renal failure :recovery Renal function and oedema gradually improved, the patient was discharged from the hospital. After that, renal function was not aggravated. Drug lymphocyte stimulation test (DLST) was performed to identify the cause of interstitial nephritis. Since

				the DLST was positive for ceftriaxone sodium hydrate,the patient was diagnosed with acute renal disorder due to ceftriaxone sodium hydrate. The symptoms improved through only discontinuation of antibiotics and using transfusion.
	Concomitant medications: cefotiam hydrochloride, clarithromycin, cefcapene pivoxil hydrochloride hydrate			

Laboratory Examination

	Day 1 of administration	Day 3 of administration	2 days after discontinuation	4 days after discontinuation	6 days after discontinuation	9 days after discontinuation
RBC ($\times 10^4$/mm^3)	378	363	372	355	345	341
Hemoglobin (g/dL)	11.2	10.6	10.7	10.3	9.9	9.9
WBC (/mm^3)	20160	27250	9980	12050	10310	7890
PLT ($\times 10^4$/mm^3)	36.8	39.7	39.4	40.1	53.9	55.9
AST (GOT) (IU)	19	17	10	19	19	19
ALT (GPT) (IU)	50	20	16	16	18	22
TP (g/dL)	6.6	6.0	5.7	6.0	6.7	7.0
BUN (mg/dL)	13.7	44.6	81.7	78	32	12
Cr (mg/dL)	0.61	3.34	5.86	6.6	2.11	0.67
Urine protein	-	2(+)	-	-	(-)	(-)
Urinary occult blood	-	(-)	(-)	-	(-)	(-)
Urine output (mL/day)	-	-	438/half day	145	5820	2235
CRP (mg/dL)	11.06	22.14	8.93	4.6	2.1	0.5

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female Under age of 10	Upper respiratory tract inflammation	500 mg for 5 days	**Interstitial nephritis** Body height: 71 cm Body weight: 10 kg History of administration of ceftriaxone sodium hydrate: Initial 5 days before administration: The patient had pyrexia. Cefcapene pivoxil hydrochloride hydrate and an expectorant drug were prescribed at a nearby hospital. 3 days before administration: Pyrexia resolved. 2 days before administration: Pyrexia occurred again. Day 1 of administration: Body temperature was 40°C. CRP was 9.9 mg/dL and WBC was 26700/mm^3, ceftriaxone sodium hydrate was intravenously administered. Day 3 of administration (day of onset): CRP increased to 18 mg/dL, WBC to 24700/mm^3, BUN to 20.5 mg/dL, and serum Cr to 0.81 mg/dL. Oedema and oliguria were found. The patient was admitted to the previous hospital. Massive transfusion, diuretic, albumin, and ceftriaxone sodium hydrate were administered. Acute renal failure developed. Day 4 of administration: Urine output slightly increased. Day 5 of administration (day of discontinuation): Serum Cr was elevated to 3.74 mg/dL. Considering the possible necessity of dialysis, the patient was transferred to another hospital. Ceftriaxone sodium hydrate was not administered after hospital transfer. Unknown

				After that, fluid restriction, diuretic administration, and sodium bicarbonate correction were carried out, serum Cr reached a peak of 4.15 mg/dL 1 day after discontinuation and then decreased. Urine output also increased, and oedema improved. On abdominal contrast-enhanced computed tomography (CT), a diagnosis of focal bacterial nephritis,.was ruled out, and vesicoureteric reflux was also not observed. In the pathological findings of kidney biopsy, oedema, fibrosis, cellular infiltration mainly of lymphocytes, and dropout of renal tubule were observed in the tubulointerstitium. To differentiate tubulointerstitial renal disorder, Yersinia antibodies were searched for, but the results were negative. 257 days after discontinuation: Although the symptoms had not resolved, but serum Cr, etc. gradually stabilized toward recovery. The patient was required to be admitted to the hospital for about 1 to 1.5 months. DLST showed a stimulation Index (S.I.) of 330% for ceftriaxone sodium hydrate.
	Concomitant medications: panipenem/betamipron, human serum albumin, acetaminophen, cefcapene pivoxil hydrochloride hydrate			

Laboratory Examination

	192 days before administration	Day 1 of administration	Day 3 of administration	Day of discontinuation	1 day after discontinuation	10 days after discontinuation	66 days after discontinuation
RBC ($\times 10^4$/mm^3)	395	-	376	392	377	345	425
Hemoglobin (g/dL)	9.8	-	7.5	7.9	7.1	7.0	11.4
WBC (/mm^3)	8000	26700	24700/ 19000	16000	11200	6500	11800
PLT ($\times 10^4$/mm^3)	42.7	-	44.6	46.9	48.2	30.4	26.2
AST (GOT) (IU)	39	-	14	14	9	22	27
ALT (GPT) (IU)	17	-	3	2	<1	4	9
TP (g/dL)	5.3	-	4.6	4.8	4.7	6.8	7.1
Alb (g/dL)	3.6	-	3.0	3.0	2.7	4.1	4.6
BUN (mg/dL)	1.5	-	20.5/44.7	49.4	50.1	19.3	24.7
Serum Cr (mg/dL)	0.19	-	0.81/2.73	3.74	4.15	0.78	0.32
Urine protein	20	-	100	(-)	-	(+-)	(-)
Urinary occult blood	(-)	-	(+-)	(+)	-	(1+)	(1+)
CRP (mg/dL)	1.02	9.9	18.7/9.8	6.9	4.59	4.58	0.93

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Female 60s	Diabetic gangrene (chronic renal failure, type 2 diabetes mellitus, diabetic retinopathy)	2 g (alternate-day) for 7 days 2 g (alternate-day) for 5 days	**Disturbed consciousness** Haemodialysis, non-smoker History of adverse drug reaction: Minocycline hydrochloride (vomiting), nitroglycerin (contact dermatitis) Day 1 of administration: The patient started receiving ceftriaxone sodium hydrate (2 g × 1, alternate-days administration) for diabetic foot ulcer infection. 5 days after administration: Her response became slow.

				7 days after administration (day of discontinuation): Utterance disappeared. Blood concentration of ceftriaxone sodium hydrate was 56.3 μg/mL. Administration of ceftriaxone sodium hydrate was discontinued. 3 days after discontinuation: The patient was able to speak from this day. 315 days after discontinuation (day of readministration): Administration of ceftriaxone sodium hydrate was started (2 g × 1, alternate-days administration) for diabetic foot ulcer infection. Ceftriaxone sodium hydrate was administered after haemodialysis. 4 days after readministration (day of discontinuation of readministration): Blood concentration of ceftriaxone sodium hydrate was approximately 200 μg/mL. 1 day after discontinuation of readministration (day of onset): The patient had nonsensical utterance, poor response, inability to meet eyes. (Disturbed consciousness occurred.) 2 days after discontinuation of readministration: The patient could not recognize her husband, and could not say his name. She was transported to hospital by ambulance and admitted. Electroencephalogram (EEG) triphasic waves were observed slightly. Blood concentration of ceftriaxone sodium hydrate was 30.6 μg/mL. Consciousness improved after administration of ceftriaxone sodium hydrate was discontinued. 7 days after discontinuation of readministration: Blood concentration of ceftriaxone sodium hydrate was 0.7 μg/mL. 8 days after discontinuation of readministration: Disturbed consciousness improved, and the patient was discharged from the hospital. Outcome of disturbed consciousness: Remission
	Concomitant medications: human insulin (genetical recombination), clopidogrel sulfate, aspirin, lansoprazole, bisoprolol fumarate, nicorandil, enalapril maleate, alfacalcidol, pancol/B_2/B_6/nicotinamide, folic acid			

Laboratory Examination

	2 days after discontinuation of readministration	3 days after discontinuation of readministration	4 days after discontinuation of readministration	8 days after discontinuation of readministration
RBC (× 10^4/mm^3)	318	277	-	-
Hemoglobin (g/dL)	10.8	9.4	-	-
WBC (/mm^3)	7800	7000	-	-
PLT (× 10^4/mm^3)	26.1	24.8	-	-
AST (GOT) (IU)	18	15	16	-
ALT (GPT) (IU)	6	4	5	-
T-Bil (mg/dL)	0.3	0.4	0.4	-
BUN (mg/dL)	22.4	26.2	15.0	-
Cr (mg/dL)	5.7	7.1	4.1	-
CRP (mg/dL)	2.2	1.4	-	-

Systolic blood pressure (mmHg)	132	-	-	90
Diastolic blood pressure (mmHg)	60	-	-	48

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Male 70s	Common bile duct stone (diabetes mellitus, severe infection, introduction to dialysis)	1 g-4 g for 22 days	**Disturbed consciousness** The patient developed diabetes mellitus in his 40s. He started on dialysis 3 years ago. Body height 169 cm, body weight 59 kg. 19 days before administration: The patient developed common bile duct stone. Day 1 of administration: Drain was removed. Administration of cetriaxone sodium hydrate 1 g/day was started due to severe infection. 2 days after administration: The dose of cetriaxone sodium hydrate was increased to 2 g/day. 3 days after administration: The dose of cetriaxone sodium hydrate was increased to 4 g/day. Single administration of amikacin sulfate injection was additionally performed at a dose of 200 mg/day. Haemodialysis was performed. 6 days after administration: Haemodialysis was performed. Biliary enzyme and inflammatory marker were improving. The patient was fuzzy headed from the morning, showing a depressed level of consciousness. Head computerized tomography (CT) showed no apparent abnormalities. The dose of ceftriaxone sodium hydrate was reduced to 2 g/day. 7 days after administration: Level of consciousness had improved since the previous day. The dose of ceftriaxone sodium hydrate was reduced to 1 g/day. 9 days after administration: Level of consciousness remitted. 21 days after administration: Administration of ceftriaxone sodium hydrate was discontinued. Outcome: Remission
	Concomitant medications: omeprazole, alfacalcidol, aspirin, nifedipine, precipitated calcium carbonate, losartan potassium, doxazosin mesilate, epinastine hydrochloride, sennoside, glucose-electrolyte solution (starting solution), ursodeoxycholic acid, thiamine/ascorbic acid, amikacin sulfate			

Laboratory Examination

	15 days before administration	14 days before administration	11 days before administration	6 days before administration	4 days before administration	1 day before administration	1 day after administration	3 days after administration	6 days after administration	7 days after administration	10 days after administration	18 days after administration	20 days after administration	1 day after discontinuation	6 days after discontinuation
RBC ($\times 10^4$/mm^3)	245	255	219	283	232	238	236	232	245	247	248	213	241	242	229
Hemoglobin (g/dL)	8.2	8.5	7.2	9.5	7.5	7.7	8.0	7.5	8.2	8.2	8.3	6.5	7.4	7.5	7.2
Hematocrit (%)	24.8	25.9	22.5	28.7	23.5	24.3	23.6	23.5	25.1	25.7	25.8	20.3	22.1	22.6	21.9
WBC (/mm^3)	6740	8930	7400	7400	7440	10200	15210	12570	11640	9170	9990	13690	10500	10200	10200
PLT ($\times 10^4$/mm^3)	11.8	12.5	11.6	13.1	18.6	18.9	18.0	16.9	19.6	19.6	18.4	18.7	18.0	19.8	20.6
AST (GOT)	43	-	23	83	48	26	51	23	19	17	13	-	16	14	-

(IU/L)															
ALT (GPT) (IU/L)	2	-	1	4	0	0	1	1	2	2	3	-	9	6	-
Al-P (IU/L)	946	-	933	1264	-	736	865	593	441	404	375	-	414	447	390
γ-GTP (IU/L)	284	-	199	260	-	163	222	136	87	76	61	-	42	37	-
Total bilirubin (mg/dL)	1.86	-	1.10	2.05	2.12	1.25	3.13	1.77	1.05	0.95	0.90	2.44	2.23	1.80	-
BUN (mg/dL)	50.5	-	22.9	34.1	26.9	35.6	26.8	32.2	37.3	20.6	7.4	29.4	25.8	21.2	15.4
Creatinine (mg/dL)	9.34	-	7.76	8.16	6.48	8.50	7.38	7.72	7.21	4.96	4.22	6.31	6.16	5.63	6.89
Blood glucose (mg/dL)	102	-	180	259	72	53	180	125	147	206	193	-	336	273	333
Serum potassium (mEq/L)	4.1	-	3.5	4.2	3.7	3.6	3.3	3.4	3.3	3.5	3.6	3.7	3.2	3.1	3.3
Serum sodium (mEq/L)	134	-	138	134	134	136	135	131	134	139	139	144	142	145	141
Total serum protein (g/dL)	5.8	-	5.6	6.7	5.6	5.6	5.4	4.7	4.8	4.6	4.9	-	4.6	4.5	4.5
CRP (mg/dL)	2.24	-	1.39	3.18	2.43	2.99	5.66	15.25	9.05	7.62	4.29	10.28	11.85	11.37	2.63

3 Mexiletine Hydrochloride

(1) Mexiletine Hydrochloride (oral dosage form)

Brand Name (name of company)	Mexitil Capsules 50 mg, 100 mg (Nippon Boehringer Ingelheim Co., Ltd.) CIRUMIMERU Capsules 50 mg, 100 mg (Tsuruhara pharmaceutical Co., Ltd.) TOY Tablets 50, 100 (KYORIN Rimedio Co., Ltd.) POERUTEN CAPSULES 50 mg, 100 mg (Yoshindo Inc.) Mexibal Capsule 50, 100 (Nichi-iko Pharmaceutical Co., Ltd.) Mexirate tab. 50, 100 (I'rom Co., Ltd.) MEXILETINE HYDROCHLORIDE Capsules 50 mg "Tanabe," 100 mg "Tanabe" (Mitsubishi Tanabe Pharma Corporation) MEQUITOLIDE CAPSULES 50, 100 (Towa Pharmaceutical Co., Ltd.) MELDEST Capsule 50 mg, 100 mg (Teva Pharma Japan Inc.) MELATE Capsule 50, 100 (Sawai Pharmaceutical Co., Ltd.) MOBALEN Capsules 50 mg, 100 mg (Tatsumi Kagaku Co., Ltd.)
Therapeutic Category	Antiarrhythmic agents
Indications	Improvement of tachyarrhythmia (ventricular) or symptoms (spontaneous pain, numbness) associated with diabetic neuropathy

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 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.

This drug may elevate the defibrillation threshold for implantable cardioverter defibrillators (ICDs). If this drug is additionally administered to patients using an ICD or if the dose of this drug is changed, patients should be carefully followed up.

Adverse Reactions (clinically significant adverse reactions)

Hypersensitivity syndrome: Rash or pyrexia may occur as the initial symptom followed by serious late-onset hypersensitive symptoms with swollen lymph nodes, hepatic dysfunction, increased white blood cell, increased eosinophil, atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged, and thus, caution should be exercised.
In addition, type 1 diabetes mellitus associated with hypersensitivity syndrome, resulting in ketoacidosis in some cases. In such cases, appropriate measures should be taken.

Ventricular tachycardia, atrioventricular block: Ventricular tachycardia (including torsades de pointes) or atrioventricular block may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

(2) Mexiletine Hydrochloride (injectable dosage form)

Brand Name (name of company)	Mexitil Injection 125 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic Category	Antiarrhythmic agents
Indications	Tachyarrhythmia (ventricular)

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, the dose of this drug should be reduced or administration of this drug should be discontinued.
This drug may elevate the defibrillation threshold for implantable cardioverter defibrillators (ICDs). If this drug is additionally administered to patients using an ICD, patients should be carefully followed up.

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 and 6 months (April 1, 2009 to September 20, 2012)

- Cases related to diabetes mellitus associated with hypersensitivity syndrome: 7 cases (no fatal cases)

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

1. Approximately 177,000 (2011)
2. Approximately 180 (2011)

Launched in Japan: 1. July 1985
2. September 1987

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Ventricular extrasystoles (hypertension) (autoimmune thyroid disease) (Sjogren's syndrome) (hyperlipidaemia) (insomnia)	300 mg/day for approx. 2 years	Drug-induced hypersensitivity syndrome, fulminant type 1 diabetes mellitus associated with drug eruption, and autoimmune thyroid disease (worsening of Hashimoto's disease, Basedow's disease) Day 1 of administration: The patient started receiving mexiletine hydrochloride. Approximately 2 years after administration (day of onset): Pyrexia and body trunk redness developed. Approximately 2 weeks after the onset (day of discontinuation):

				Symptoms did not remit, the patient was admitted to the hospital. Prodromes and accompanying symptoms: Upper airway symptom: Non, pyrexia 38ºC Digestive symptom: Nausea Swollen lymph nodes: Neck, axilla, and inguina Ketoacidosis: Non Disturbed consciousness: Non Administration of mexiletine hydrochloride was discontinued. Blood glucose level was 310 mg/dL, hyperglycaemia was observed, and the subcutaneous administration of insulin was started. Administration of prednisolone (60 mg/day) was started. Human papilloma virus-Immunoglobulin G (HHV-6 IgG) was elevated, the patient was diagnosed with drug-induced hypersensitivity syndrome (DIHS). 8 days after discontinuation: Insulin secretion was depleted. The patient was diagnosed with fulminant type 1 diabetes. One week after hospital admission, pyrexia and rash remitted gradually. HbA1c (NGSP) 6.4%, amylase 29 IU/L, serum CPR < 0.05 ng/mL, urinary CPR 0.1 μg/day, anti-GAD antibody/anti-IA-2 antibody/ICA Negative, HLA: DRB1* 0405, DQB1* 0401, DRB1* 0901, DQB1* 0303. Date unknown after discontinuation: FT4 l.06 ng/mL, TSH 0.6 μU/mL, TgAb 5.1 U/mL, TPOAb 44.3 U/mL, TRAb 5.8%. Concomitant Hashimoto's disease occurred. Approximately 30 days after discontinuation: Decreased thyroid function was observed. Concomitant Sjogren's syndrome was suspected (antinuclear antibody positive, SS-A antibody positive). Approximately 37 days after discontinuation: Administration of prednisolone was discontinued, but rash did not relapse. Administration of insulin was continued. 39 days after discontinuation: The patient was discharged from the hospital. 60 days after discontinuation: Thyroglobulin antibody (TgAb) and Thyroid peroxidase antibody (TPOAb) decreased transiently. After that, TgAb increased to > 100 U/mL, TPOAb to > 60 U/mL. Approximately 220 days after discontinuation: Rash did not relapse, but insulin secretion did not return to normal. Administration of insulin was continued. 450 days after discontinuation: TRAb was 24.2% (positive conversion). 540 days after discontinuation: The patient developed Basedow's disease. FT4 3.53 ng/mL, FT3 10.9 pg/mL, TSH < 0.01 μU/mL, TRAb 56.9%, Tc-99m uptake 2.40%. Treatment was started with Iodine 131 (I-131) 370 MBq.

	Concomitant medications: atorvastatin calcium hydrate, atenolol, olmesartan medoxomil, amlodipine besilate, ethyl loflazepate

Laboratory Examination

	Day of discontinu-ation	5 days after discontinu-ation	15 days after discontinu-ation	21 days after discontinu-ation	28 days after discontinu-ation	35 days after discontinu-ation	54 days after discontinu-ation
WBC (/mm^3)	4200	-	6500	-	4500	-	5600
Eosinophils (%)	17	-	1	-	0	-	3
Blood glucose (mg/dL)	310	-	150	-	242	-	121
HHV-6 (IgG)	-	20	-	10	-	10	160

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Diabetic neuropathy (type 2 diabetes mellitus)	Unknown for 24 days	Diabetic ketoacidosis, drug rash with eosinophilia and systemic symptoms, type 1 diabetes mellitus The patient had been found to have type 2 diabetes mellitus since 2000. Blood glucose has been well-controlled with administration of oral hyperglycemic agent (mitiglinide) by a nearby hospital (HbA1c: 5.8%). HbA1c level remained at 5.5%-5.9%. Day 1 of administration: The patient started receiving mexiletine hydrochloride for diabetic neuropathy. Day 22 of administration: Erythema appeared predominantly on both lower legs with pyrexia of 39°C, and spread systemically. Day 24 of administration (day of discontinuation): Administration of mexiletine hydrochloride was discontinued. Date unknown after discontinuation: Thirst, malaise, and depressed level of consciousness were observed. 17 days after discontinuation: The patient visited the endocrinology department. Depressed level of consciousness associated with hyperglycaemia (824 mg/dL) was noted. Based on the symptoms and blood test at hospital admission, the patient was diagnosed with diabetic ketoacidosis. Continuous infusion of insulin was started. DIHS due to mexiletine was suspected from the characteristic of skin eruption. Drip infusion of prednisolone was started at 30 mg/day. <At hospital admission> Consciousness level JCS 10, blood pressure 100/60 mmHg, heart rate 126/min, Spo2 94% (O2, 3L), body temperature 36.3ºC. Bulbar conjunctiva: Hyperaemia was not found. Palpebral conjunctiva: Mild hyperaemia was found. Face: Marked oedema was found wholly. Erythema with 5 mm or less in diameter was noted densely.

				Femoral region: Light red erythema and red papules with 5 mm or less in diameter were found, and some erythema were fused. Whole body: Disseminated and poorly-demarcated erythema with several millimeters or less in diameter were found. Swollen lymph nodes were not found in the bilateral neck. <Histopathological findings> Horny layer and epidermis at sites of erythema on the left thigh: No significant change was noted. Dermis: Mild perivascular lymphocytic infiltrates with oedema were found (some eosinophilic infiltration was found). <Tests related to diagnosis and drugs> Human herpes virus 6 (HHV-6) IgG antibody titer: 160-fold higher. Blood insulin 0.5 μU/mL (normal range, 1.5-17.1), blood C peptide 0.2 ng/mL (normal range, 0.94-2.8), urinary C peptide < 1.6 ng/mL (normal range, 29.2-167), suggesting depletion of insulin secretory capacity. Anti-GAD antibody < 0.4 U/mL (normal range, < 1.5), anti-IA 2 antibody 1.6 U/mL (normal range, < 0.4), HbA1c 9.3% (normal range, 4.3-5.8), total ketone body 14600 μmol/L. Arterial blood gas: pH 7.143. DLST (mexiletine): positive rate was 115% (acceptance criteria: negative, ≤ 179%; false-positive, 180%-199%; positive, ≥ 200%). Blood concentration of mexiletine: < 0.10 μg/mL (normal range). Date unknown after discontinuation: After the start of insulin treatment, ketoacidosis promptly improved. 30 days after discontinuation: After drip infusion of prednisolone, WBC gradually decreased and skin eruption improved. The dose was gradually reduced to 25 mg/day. 32 days after discontinuation: On Day 16 of hospitalization, the patient was discharged from the hospital (insulin self-injection). HHV6 IgG antibody titer: 2560-fold higher, showing reactivation. 72 days after discontinuation: The dose of prednisolone was gradually reduced to 10 mg/day. 78 days after discontinuation: C peptide: Glucagon tolerance test showed no response. 163 days after discontinuation: HHV6 IgG antibody titer: Improved to 160-fold higher. Insulin therapy was continued for type 1 diabetes mellitus. Relapses of skin eruption, pyrexia, renal impairment, etc. were not found
	Concomitant medications: betamethasone/d-chlorpheniramine maleate, betamethasone			

3

Revision of Precautions (No. 241)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated October 23 and October 30, 2012 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1

Vaccines

Inactivated Poliomyelitis Vaccine

Brand Name

IMOVAX POLIO subcutaneous (Sanofi Pasteur K.K.)

Precautions of Dosage and Administration

This drug should be usually administered to individuals aged 3 months to 90 months after birth. The initial immunization should be performed 3 times at intervals of 3 to 8 weeks in individuals aged 3 months to 12 months after birth as standard. Booster immunization should be performed once after an interval of 6 months or more after the initial immunization (12 to 18 months after the end of the initial immunization as standard).

2

Antipyretics and analgesics, anti-inflammatory agents, Common cold drugs, Antitussives

Acetaminophen

Isopropylantipyrine/Acetaminophen/Allylisopropylacetylurea/ Anhydrous Caffeine

Tramadol Hydrochloride/Acetaminophen

Salicylamide/Acetaminophen/Anhydrous Caffeine/ Chlorpheniramine Maleate

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

Brand Name

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

SG Combination Granules (Shionogi & Co., Ltd.)

TRAMCET Combination Tablets (Janssen Pharmaceutical K.K.)

LL COMBINATION SYRUP FOR PEDIATRIC (Daiichi Sankyo Company, Limited), NEO-AMUNOLL COMBINATION POWDER (Sanwa Kagaku Kenkyusho Co., Ltd.), Pelex combination granule, Pediatric Pelex combination granule (Taiho Pharmaceutical Co, Ltd.)

Coughcode-N Combination Tablets (Mylan Seiyaku Ltd.)

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

3 Diuretics

Spironolactone

Brand Name	Aldactone-A Fine Granules 10%, Aldactone-A Tablets 25 mg, 50 mg (Pfizer Japan Inc.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome)**: Toxic epidermal necrolysis or oculomucocutaneous syndrome 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 Anticoagulants

Dabigatran Etexilate Methanesulfonate

Brand Name	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Anaphylaxis**: Anaphylaxis (urticaria, face swelling, dyspnoea, etc.) 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 Vaccines

Rotavirus Vaccine, Live, Oral, Pentavalent

Brand Name	RotaTeq Oral Solution (MSD K.K)
Adverse Reactions (clinically significant adverse reactions)	**Anaphylaxis**: Anaphylaxis (rash, swollen tongue, etc.) may occur. Patients should be carefully monitored after vaccination, if any abnormalities are observed, appropriate measures should be taken.

4

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 new drugs. 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 drugs 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 November 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine TETRABIK Subcutaneous Injection Syringe	The Research Foundation for Microbial Diseases of Osaka University	October 31, 2012
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine Quattrovac Subcutaneous Injection Syringe	The Chemo-Sero-Therapeutic Research Institute	October 31, 2012
Degarelix Acetate Gonax 80 mg for Subcutaneous Injection, Gonax 120 mg for Subcutaneous Injection	Astellas Pharma. Inc.	October 23, 2012
Clopidogrel Sulfate PLAVIX 25 mg Tablets, 75 mg Tablets*1	Sanofi-aventis K.K.	September 28, 2012
Tazobactam Sodium/Piperacillin Sodium ZOSYN for Intravenous Injection 2.25, 4.5*2	Taiho Pharmaceutical Co., Ltd.	September 28, 2012
Pazopanib Hydrochloride Votrient Tablets 200 mg	GlaxoSmithKline K.K.	September 28, 2012
Iguratimod KOLBET Tablets 25 mg	Toyama Chemical Co., Ltd.	September 12, 2012
Iguratimod Careram Tablets 25 mg	Eisai Co., Ltd.	September 12, 2012
Teneligliptin Hydrobromide Hydrate TENELIA Tablets 20 mg	Mitsubishi Tanabe Pharma Corporation	September 10, 2012
Formoterol Fumarate Hydrate Oxis 9 μg Turbuhaler 28 doses, 60 doses*3	AstraZeneca K.K.	September 3, 2012
Inactivated Poliomyelitis Vaccine (Salk Vaccine) IMOVAX POLIO subcutaneous	Sanofi Pasteur K.K.	August 31, 2012
Axitinib Inlyta Tablets 1 mg, 5 mg	Pfizer Japan Inc.	August 30, 2012
Ropinirole Hydrochloride ReQuip CR Tablets 2 mg, 8 mg	GlaxoSmithKline K.K.	August 28, 2012
Atomoxetine Hydrochloride Strattera Capsule 5 mg, 10 mg, 25 mg, 40 mg*4	Eli Lilly Japan K.K.	August 24, 2012

Sulbactam Sodium/Ampicillin Sodium UNASYN-S for Intravenous Use 0.75 g, 1.5 g, UNASYN-S KIT for Intravenous Use 1.5 g, 3 g*[5, 6]	Pfizer Japan Inc.	August 10, 2012
Budesonide/Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses*[7]	AstraZeneca K.K.	August 10, 2012
Perflubutane SONAZOID FOR INJECTION 16 μL*[8]	Daiichi Sankyo Company, Limited	August 10, 2012
Sunitinib SUTENT Capsule 12.5 mg*[9]	Pfizer Japan Inc.	August 10, 2012
Apomorphine Hydrochloride Hydrate Apokyn subcutaneous injection 30 mg	Kyowa Hakko Kirin Co., Ltd.	July 27, 2012
Rotavirus Vaccine, Live, Oral, Pentavalent RotaTeq Oral Solution	MSD K.K.	July 20, 2012
Gabapentin Enacarbil Regnite Tablets 300 mg	Astellas Pharma. Inc.	July 10, 2012
Bixalomer Kiklin Capsules 250 mg	Astellas Pharma. Inc.	June 26, 2012
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg, ZITHROMAC Tablets 250 mg*[10]	Pfizer Japan Inc.	June 22, 2012
Aprepitant EMEND Capsules 125 mg, 80 mg, EMEND Capsules Set*[11]	Ono Pharmaceutical Co., Ltd.	June 22, 2012
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg*[12]	AstraZeneca K.K.	June 22, 2012
Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg*[13]	Pfizer Japan Inc.	June 22, 2012
Lidocaine Penles Tape 18 mg*[14]	Nitto Denko Corporation	June 22, 2012
Dornase Alfa (Genetical Recombination) PULMOZYME Inhalation Solution 2.5 mg	Chugai Pharmaceutical Co., Ltd.	June 8, 2012
Rilpivirine Hydrochloride EDURANT Tablets 25 mg	Janssen Pharmaceutical K.K.	June 8, 2012
Miglustat BRAZAVES Capsule 100 mg	Actelion Pharmaceuticals Japan Ltd.	May 30, 2012
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg	Ferring Pharmaceutical Co., Ltd.	May 29, 2012
Mogamulizumab (Genetical Recombination) POTELIGEO Injection 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 29, 2012
Azilsartan AZILVA Tablets 20 mg, 40 mg	Takeda Pharmaceutical Company Limited	May 28, 2012
Oxycodone Hydrochloride Hydrate OXIFAST Injection 10 mg, 50 mg	Shionogi & Co., Ltd.	May 28, 2012
Thalidomide THALED CAPSULE 50, 100*[15]	Fujimoto Pharmaceutical Corporation	May 25, 2012
Doripenem Hydrate FINIBAX for Intravenous Infusion 0.25 g, 0.5 g, FINIBAX Kit for Intravenous Infusion 0.25 g*[16, 17]	Shionogi & Co., Ltd.	May 25, 2012
Thyrotropin Human Alfa (Genetical Recombination) THYROGEN for Intramuscular Injection 0.9 mg*[18]	Sato Pharmaceutical Co., Ltd.	May 25, 2012

Mometasone Furoate Hydrate NASONEX Nasal 50 μg 56 sprays, NASONEX Nasal 50 μg 112 sprays*[17]	MSD K.K.	May 25, 2012
Lidocaine/Propitocaine EMLA CREAM	Sato Pharmaceutical Co., Ltd.	May 14, 2012
Brimonidine Tartrate AIPHAGAN OPHTHALMIC SOLUTION 0.1%	Senju Pharmaceutical Co., Ltd.	May 11, 2012
Alendronate Sodium Hydrate Bonalon Bag for I.V. Infusion 900 μg	Teijin Pharma Limited	May 10, 2012
Crizotinib XALKORI Capsules 200 mg, 250 mg	Pfizer Japan Inc.	March 30, 2012

*1 An additional indication for "prevention of thrombus and embolus formation in patients with peripheral arterial disease"

*2 An additional indication for "treatment of patients with peritonitis, intra-abdominal abscess, cholecystitis, or cholangitis"

*3 An additional indication for "remission of various symptoms associated with airway obstructive disorder in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)"

*4 An additional indication for "treatment of patients with attention deficit/hyperactivity disorder (AD/HD) in adulthood"

*5 An additional indication for "Streptococcus pneumonia, Moraxella (Branhamella) catarrhalis"

*6 An additional administration for "severe infections"

*7 An additional indication for "remission of various symptoms in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema) (for patients who require concomitant use of inhaled corticosteroids and long acting inhaled beta-2 agonist)"

*8 An additional indication for "contrast enhanced imaging for breast mass lesion in mammary ultrasonography"

*9 An additional indication for "treatment of patients with pancreatic neuroendocrine tumour"

*10 An additional indication for "treatment of patients with pelvic inflammatory disease"

*11 An additional administration for "pediatrics (aged 12 and older)"

*12 An additional indication for "treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low-doses aspirin"

*13 An additional indication for "treatment of pain in patients with fibromyalgia"

*14 An additional indication for "relief of pain at removal of molluscum contagiosum"

*15 An additional indication for "erythema nodosum leprosum"

*16 An additional indication for "pyogenic meningitis"

*17 An additional administration for "pediatrics"

*18 An additional indication for "adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of metastatic thyroid cancer"