Pharmaceuticals and Medical Devices Safety Information

No. 291 June 2012

Table of Contents

This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare (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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No. 291 June 2012

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Safety Measures for Cervical Cancer Prevention Vaccines**		Adverse reactions to cervical cancer prevention vaccines are reported to MHLW in accordance with the "Procedures for Urgent Vaccination Promotion," irrespective of causality. These reactions are then discussed by an expert panel and information about the incidence is released to the public. Although an alert against common adverse reactions to cervical cancer prevention vaccines, such as syncope and vasovagal reaction, has been included in package inserts since the launch of the vaccines, many cases of syncope or vasovagal reaction have been reported, some of which resulted in secondary damage. Accordingly, MHLW will describe the information about the adverse reaction cases and safety measures in this section. Healthcare professionals are requested to further exercise caution to prevent medication errors, because there have been reported cases where both 2-valent and 4-valent HPVs were used alternately by mistake.	5
2	**Important Safety Information**	*P* *C*	**Alogliptin Benzoate (and 3 others):** Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated April 24, 2012, the contents of important revisions and case summaries that served as the basis for these revisions will be provided in this section.	9
3	Revision of Precautions (No. 236)		**Ibuprofen (oral dosage form) (and 29 others)**	26
4	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of June 1, 2012.	37

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

ACIP	Advisory Committee on Immunization Practices
ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CK (CPK)	Creatine kinase (Creatine phosphokinase)
CMV-IgM	Cytomegalovirus immunoglobulin M
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
DPP-4	Dipeptidyl peptidase-4
EBV VCA-IgG	Epstein-Barr virus viral capsid antigen immunoglobulin G
EPPV	Early Post-marketing Phase Vigilance
EU	European Union-
FFP	Fresh frozen plasma
FY	Fiscal year
HA-IgM	Hepatitis A immunoglobulin M
HbA1c	Hemoglobin A1c
HBs	Hepatitis B surface
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV-RNA	Hepatitis E virus ribonucleic acid
HHV-6	Human herpesvirus 6
HPV	Human papilloma virus
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IU	International unit
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MMWR	Morbidity and Mortality Weekly Report
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
PFC	Persistent fetal circulation
PLT	Platelet
PT	Prothrombin Time
PT INR	Prothrombin time - international normalized ratio
RBC	Red blood cell count
SJS	Stevens-Johnson syndrome
SpO_2	Oxygen saturation
TEN	Toxic epidermal necrolysis
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Safety Measures for Cervical Cancer Prevention Vaccines

1. Introduction

In November 2010, the project for urgent vaccination promotion was started for human papillomavirus (HPV) vaccines for cervical cancer prevention as well as for a pediatric pneumococcal conjugate vaccine and Haemophilus influenzae type b (Hib) vaccines. Adverse events that are associated to a certain degree with cervical cancer prevention vaccines should be reported to MHLW in accordance with the "Procedures for Urgent Vaccination Promotion,"[1)] irrespective of causality.

Reported adverse reactions were discussed at a joint meeting of the Subcommittee on Drug Safety of Committee on Drug Safety and Vaccine Adverse Reaction Review Committee for Carcinoma of the Uterine Cervix (hereinafter referred to as the Joint Meeting), to evaluate the safety, etc. of vaccines. The review results have been released to the public. This section includes the reported adverse reaction cases of syncope, which led to secondary damage (e.g. injuries) due to falls, and an alert for medication errors, such as alternate vaccination of different HPV vaccines by mistake.

2. Syncope/vasovagal reaction and secondary damage due to fall

As of June 2012, there are 2 approved and marketed HPV vaccines: recombinant adsorbed 2-valent human papillomavirus-like particle vaccine Cervarix® (2-valent HPV vaccine) and recombinant adsorbed 4-valent human papillomavirus-like particle vaccine GARDASIL® (4-valent HPV vaccine). These two vaccines are covered under the project for urgent vaccination promotion.

Table 1 shows adverse reactions to the HPV vaccines which have been reported by the marketing authorization holders (MAHs) or medical institutions starting from the launch of each product until March 31, 2012.

Of these adverse reactions, Table 2 shows syncope-related adverse reactions [Note 1], some of which resulted in secondary damage due to falls. The secondary damage included bruises on the head, face, jaw, etc., leading to facial fractures or MRI confirmed mild brain contusions or haematoma formations in some cases. Such secondary damage occurred when the recipients were standing after the vaccination, stood up to move to another place, or were sitting on a chair without a backrest or armrests.

Note 1 Adverse reactions reported using the following Preferred Terms from MedDRA/J version 14.1 are included: "loss of consciousness," "syncope," "presyncope," "shock," "neurogenic shock," "depressed level of consciousness," and "altered state of consciousness."

Table 1 Reported number of adverse reactions to HPV vaccines (unit: case [person])[2,3)]

	Total number of recipients (No. of vaccinations)	Adverse reactions reported by MAHs [Note 2]	Adverse reactions reported by medical institution	
		Number of reported cases (reported deaths) Reporting frequency	Reporting frequency	Total number of reports: Serious cases[Note 3] (reported deaths)
2-valent HPV vaccine [Note 4] Launched in December 2009	6,338,709	597 (0) 0.009% (0%)	869 0.013%	75 (1 [Note 6]) 0.001% (0.00001%)
4-valent HPV vaccine [Note 5] Launched in August 2011	530,826	19 (0) 0.004% (0%)	69 0.013%	7 (0) 0.0013% (0%)

Table 2 Syncope-related adverse reactions in Japan[4)]

	Syncope-related cases (incidence per 100,000 vaccinations)	Loss of consciousness (incidence per 100,000 vaccinations)	Secondary damage (percentage)
2-valent HPV vaccine Launched in December 2009	683 (10.78)	476 (7.51)	38 (10%) [Note 7]
4-valent HPV vaccine Launched in August 2011	129 (24.3)	91 (17.1)	13 (14%)

The cause of syncope is not thought to be the HPV vaccines themselves but pain from injection and vasovagal reaction[5)], secondary to fear, excitement, etc. Approximately 90% of the reported cases, excluding those for which the onset time were unknown, occurred immediately or within 15 minutes after vaccination, while some occurred more than 15 minutes after vaccination.[4)] This indicates that the reported cases may include another cause of syncope such as orthostatic hypotension.

As a safety measure, an alert against syncope or vasovagal reaction has been included in the "Important Precautions" and "Other Adverse Reactions" of the "Precautions" section in package inserts of both HPV vaccines since the launch of the products. Since secondary damage occurred due to falls immediately after vaccination in some reported cases, the MAHs started to provide the following information in February 2012[6,7)]: (i) When a recipient moves to another place after vaccination, a healthcare professional, parent, etc. should accompany her to prevent syncope; and (ii) the recipient should be instructed to avoid standing up unnecessarily and rest for approximately 30 minutes after vaccination at a place where the recipient is able to place her body weight on something.

Note 2 The adverse reactions reported by MAHs were determined to be serious in accordance with the Pharmaceutical Affairs Law Article 77-4-2 and may overlap some other cases of adverse reaction reports by the medical institutions. Also, they may include cases that were found to be not reportable by a subsequent investigation, etc. and therefore were withdrawn.

Note 3 A "serious" adverse reaction is defined as death, disability, a reaction that may result in death or disability, and a reaction that needs hospitalization. However, an adverse reaction that is not serious may be reported as serious in some cases.

Note 4 The adverse reactions to 2-valent HPV vaccine reported by MAHs were those received from the launch of the product until March 31, 2012, and those reported by medical institutions were those received from November 26, 2010 until March 31, 2012.

Note 5 The adverse reactions to 4-valent HPV vaccine reported by MAHs were those received from the launch of the product until March 31, 2012, and those reported by medical institutions were those received from September 20, 2011 until March 31, 2012.

Note 6 The expert panel concluded that there was no direct or clear causal relationship with the vaccinations.

Note 7 Number of recipients who developed loss of consciousness within 30 minutes after vaccination.

In the Joint Meeting on May 25, 2012, it was reported that if the recipient developed vasovagal reaction, she may suddenly fall without any sign. Some reported cases resulted in secondary damage such as fracture, while others fell forward. This led to the conclusion that extended alerts should be issued against falls.

Healthcare professionals should inform recipients of HPV vaccines of possible syncope after vaccination and secondary damage due to falls and ensure the following measures to avoid falls due to syncope:

(i) When a recipient moves to another place after vaccination, a healthcare professional, parent, etc. should accompany her while holding her arm;

(ii) The recipient should avoid standing up unnecessarily for approximately 30 minutes after vaccination and rest at a place where the recipient is able to place her body weight on something (e.g., sitting on a chair with a backrest or armrests).

If syncope occurs, let the recipient lie down and slightly elevate her legs, and provide transfusion, oxygen or other treatments as necessary.[5)]

3. Incorrect alternate vaccination with 2-valent and 4-valent HPV vaccines

The 2-valent and 4-valent HPV vaccines should be given 3 times respectively, and the same HPV vaccine should be used for each of the 3 doses. Since these HPV vaccines partially differ in indications and the compatibility of their preventive effects and safety has not been demonstrated, alternate vaccination with different HPV vaccines is not recommended. The package inserts of these vaccines include an alert stating that "the safety, immunogenicity and efficacy of compatibility have not been demonstrated" in the "Important Precautions" section. Similar alerts have been issued by the CDC Advisory Committee on Immunization Practices (ACIP)[8)] in the U.S. and can be found in Summary of Product Characteristics of both HPV vaccines in the EU.

However, according to information received by the MAHs through their call center, etc., 27 cases of incorrect vaccination in which the vaccine used for the second or third dosing was different from that used for the first dosing have been reported for 2-valent HPV vaccine (as of April 30, 2012) and 34 cases for 4-valent HPV vaccine (as of April 9, 2012). The cause of incorrect vaccination included lack of confirmation with the recipient, lack of review of a medical record, and mix-up of HPV vaccines. Incorrect vaccination tends to occur especially when the recipient visits a different medical institution from the one she visited for the previous dose and when multiple recipients visit a medical institution simultaneously, which requires careful attention. Adverse reactions to incorrect vaccinations include 2 non-serious cases (1 case of feelings of weakness, and 1 case of myalgia, movement disorder, musculoskeletal stiffness and pain).

As a safety measure to prevent incorrect vaccination, recipients and healthcare professionals have been alerted against incorrect alternate vaccination, and use of the Mother and Child Health Handbook or a card-type portable material provided by the MAHs has been promoted to ensure that healthcare professionals can check an HPV vaccination history.

Healthcare professionals should confirm the previously-used vaccine prior to the second or third dosing, by reviewing a medical record, the Mother and Child Health Handbook, or a vaccination card or by thoroughly discussing the vaccination history with the recipient. In addition, healthcare professionals are also required to let a recipient understand the need for using the same vaccine for three doses and to instruct a recipient to bring a vaccination card, etc., prepared by the MAHs for the next dosing. If a recipient received the first or second dose at another medical institution and the name of the previously-used HPV vaccine is unknown because the recipient does not remember or has no record of vaccination or a vaccination card, please contact the medical institution to prevent incorrect vaccination.

<References> (including provisionally translated titles)

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2) Material 2-1, Reports of adverse reactions to cervical cancer prevention vaccine (Cervarix), FY 2012 Subcommittee on Drug Safety of Committee on Drug Safety (the first meeting), Influenza A (H1N1) Vaccine Adverse Reaction Review Committee (the first meeting), and the Vaccine Adverse Reaction Review Committee for Carcinoma of the Uterine Cervix (May 25, 2012) (only available in Japanese language)
http://www.mhlw.go.jp/stf/shingi/2r9852000002c06s-att/2r9852000002c0ci.pdf
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4) Material 2-3, Syncope-related adverse reactions after cervical cancer prevention vaccination, Y 2012 Subcommittee on Drug Safety of Committee on Drug Safety (the first meeting), Influenza A (H1N1) Vaccine Adverse Reaction Review Committee (the first meeting), and the Vaccine Adverse Reaction Review Committee for Carcinoma of the Uterine Cervix (May 25, 2012) (only available in Japanese language)
http://www.mhlw.go.jp/stf/shingi/2r9852000002c06s-att/2r9852000002c0cw.pdf
5) Japan Pediatric Society, Committee of Immunization and Communicative Disease; Policy statement: Caution against syncope after vaccination (September 2010) (only available in Japanese language)
http://www.jpeds.or.jp/saisin/saisin_100927.pdf
6) Cervarix®, Request for measures to prevent fall due to syncope (only available in Japanese language)
http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201202_2.pdf
7) GARDASIL® Aqueous Suspension for Intramuscular Injection Syringe/Aqueous Suspension for Intramuscular Injection, Request for measures to prevent fall due to syncope (only available in Japanese language)
http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201202_1.pdf
8) Morbidity and Mortality Weekly Report (MMWR), 59 (20); 626-629, 2010

2

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated April 24, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Alogliptin Benzoate, Alogliptin Benzoate/Pioglitazone Hydrochloride, Sitagliptin Phosphate Hydrate, Vildagliptin, Linagliptin

(1) Alogliptin Benzoate

Brand Name (name of company)	NESINA Tablets 25 mg, 12.5 mg, 6.25 mg (Takeda Pharmaceutical Company Limited)
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 treatments: (1) Diet and exercise therapies alone (2) α-glucosidase inhibitor along with diet and exercise therapies (3) Thiazolidine along with diet and exercise therapies (4) Sulfonylurea along with diet and exercise therapies (5) Biguanide along with diet and exercise therapies

PRECAUTIONS (underlined parts are revised)

Important Precautions

Acute pancreatitis may occur. Patients should be instructed to immediately consult a doctor if initial symptoms including persistent intense abdominal pain and vomiting occur.

Adverse Reactions (clinically significant adverse reactions)

Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin may occur. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Acute pancreatitis: Acute pancreatitis may occur. Patients should be carefully monitored, and if any abnormalities including persistent intense abdominal pain and vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Hepatic dysfunction, jaundice: Hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), Al-P, etc. or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Oculomucocutaneous syndrome or erythema multiforme may occur. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Clinically significant adverse reactions (similar drug)	**Intestinal obstruction**: Intestinal obstruction may occur. Patients should be carefully monitored, and if any abnormalities including severe constipation, abdominal distension, persistent abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

(2) Alogliptin Benzoate/Pioglitazone Hydrochloride

Brand Name (name of company)	LIOVEL Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus To be used only when the concomitant use of alogliptin benzoate and pioglitazone hydrochloride is considered appropriate.

PRECAUTIONS (underlined parts are revised)

Important Precautions	Acute pancreatitis may occur. Patients should be instructed to immediately consult a doctor if initial symptoms including persistent intense abdominal pain and vomiting occur.
Adverse Reactions (clinically significant adverse reactions)	**Acute pancreatitis**: Acute pancreatitis may occur. Patients should be carefully monitored, and if any abnormalities including persistent intense abdominal pain and vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken. **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Oculomucocutaneous syndrome or erythema multiforme may occur. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Clinically significant adverse reactions (similar drug)	**Intestinal obstruction**: Intestinal obstruction may occur. Patients should be carefully monitored, and if any abnormalities including severe constipation, abdominal distension, persistent abdominal pain, or vomiting 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 1 year and 8 months (from initial marketing of (1) to February 29, 2012) • Rhabdomyolysis-associated cases: 1 case (no fatal cases) • Acute pancreatitis-associated cases: 3 cases (1 fatal case) • Hepatic dysfunction/jaundice-associated cases: 7 cases (no fatal cases) • Oculomucocutaneous syndrome/erythema multiforme-associated cases: 10 cases (no fatal cases) The number of patients using this drug estimated by MAHs: (1) Approximately 237,000 (April 1, 2011 to March 31, 2012) (2) Approximately 23,000 (September 20, 2011 to March 31, 2012) Launched in Japan : (1) June 2010 (2) September 2011

(3) Sitagliptin Phosphate Hydrate

Brand Name (name of company)	GLACTIV Tablets 25 mg, 50 mg, 100 mg (Ono Pharmaceutical Co., Ltd.); JANUVIA Tablets 25 mg, 50 mg, 100 mg (MSD K.K.)

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 treatments: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies (3) Thiazolidine along with diet and exercise therapies (4) Biguanide along with diet and exercise therapies (5) α-glucosidase inhibitor along with diet and exercise therapies (6) Insulin along with diet and exercise therapies

PRECAUTIONS (underlined parts are revised)

Careful Administration	Patients with a medical history of abdominal operation or intestinal obstruction
Adverse Reactions (clinically significant adverse reactions)	**Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin may occur. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. **Intestinal obstruction**: Intestinal obstruction may occur. Patients should be carefully monitored, and if any abnormalities including severe constipation, abdominal distension, persistent abdominal pain, or vomiting 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 2 years and 2 months (from initial marketing to February 29, 2012) • Rhabdomyolysis-associated cases: 7 cases (no fatal cases) • Intestinal obstruction-associated cases: 7 cases (no fatal cases) The number of patients using this drug per year estimated by MAHs: approximately 1,400,000 (2011) Launched in Japan: December 2009

(4) Vildagliptin

Brand Name (name of company)	Equa Tablets 50 mg (Novartis Pharma K.K.)
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 treatments: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies

PRECAUTIONS (underlined parts are revised)

Careful Administration	Patients with a medical history of abdominal operation or intestinal obstruction
Important Precautions	Acute pancreatitis may occur. Patients should be instructed to immediately consult a doctor if initial symptoms including persistent intense abdominal pain and vomiting occur.
Adverse Reactions	**Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feelings of weakness,

(clinically significant adverse reactions)	increased CK (CPK), increased blood myoglobin, and increased urine myoglobin may occur. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. **Intestinal obstruction**: Intestinal obstruction may occur. Patients should be carefully monitored, and if any abnormalities including severe constipation, abdominal distension, persistent abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken. **Acute pancreatitis**: Acute pancreatitis may occur. Patients should be carefully monitored, and if any abnormalities including persistent intense abdominal pain and vomiting 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 1 year and 10 months (from initial marketing to February 29, 2012) • Rhabdomyolysis-associated cases: 6 cases (no fatal cases) • Intestinal obstruction-associated cases: 6 cases (no fatal cases) • Acute pancreatitis-associated cases: 1 case (no fatal cases) The number of patients using this drug per year estimated by MAHs: approximately 150,000 (2011) Launched in Japan: April 2010

(5) Linagliptin

Brand Name (name of company)	Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus (To be used only when the patient does not sufficiently respond to diet and exercise therapies alone)

PRECAUTIONS (underlined parts are revised)

Clinically significant adverse reactions (similar drug)	**Intestinal obstruction**: Intestinal obstruction may occur. Patients should be carefully monitored, and if any abnormalities including severe constipation, abdominal distension, persistent abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Case Summaries

Vildagliptin

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Type 2 diabetes mellitus (dyslipidaemia, angina pectoris, constipation)	50 mg for 5 days	**Rhabdomyolysis** Approximately 4 years before administration: The patient started receiving fluvastatin sodium at 30 mg/day. 1 day before administration: Lower limb oedema developed. Lower limb oedema was noted at an outpatient visit. Administration of pioglitazone hydrochloride was discontinued and pioglitazone hydrochloride was switched to vildagliptin. Day 1 of administration: Administration of vildagliptin was started at 50 mg/day. Day 5 of administration (day of discontinuation):

				Since it became difficult to stand since the morning, the patient visited the hospital. Creatine kinase (Creatine phosphokinase) (CK [CPK]) >2000 IU/L and brown urine were observed, and the patient was diagnosed with rhabdomyolysis. The patient had muscular weakness, hypotonia, and difficulty in walking. Creatinine was 1.2 mg/dL, and fluid replacement was given. Administration of vildagliptin and fluvastatin sodium was discontinued. The patient was not admitted to the hospital and underwent follow-up observation with treatment at home. 1 day after discontinuation: Muscular weakness was improved. Oedema mostly disappeared. Fluid replacement was performed. CK (CPK) 2640 IU/L (Muscle-type [MM] 98%) 2 days after discontinuation: Muscular weakness was improved. CK (CPK) 1617IU/L 3 days after discontinuation: CK (CPK) 790 IU/L 6 days after discontinuation: Mild gait disturbance still remained, but the patient could walk with a cane as usual. CK (CPK) 151 IU/L, creatinine 1.0 mg/dL
	Concomitant medications: fluvastatin sodium, pioglitazone hydrochloride, bisoprolol fumarate, lansoprazole, diltiazem hydrochloride, magnesium oxide, mitiglinide calcium hydrate, torasemide			

Laboratory Examination

	148 days before administration	Day 5 of administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	6 days after discontinuation
CK (CPK) (IU/L)	62	>2000	2640	1617	790	151
MM (%)	-	-	98	-	-	-
Creatinine (mg/dL)	1.3	1.2	1.2	1.0	0.9	1.0
BUN (mg/dL)	29.8	27.7	33.2	25.7	20.6	20.1
AST (GOT) (IU/L)	18	54	83	63	-	-
ALT (GPT) (IU/L)	18	20	34	32	-	-
LDH (IU/L)	-	-	357	-	-	-

Sitagliptin Phosphate Hydrate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Type 2 diabetes mellitus (dyslipidaemia, pruritus)	25 mg for 5 days	**Intestinal obstruction** 21 years before administration: The patient underwent gastrectomy. 15 years before administration: The patient developed intestinal obstruction, and underwent surgery. 26 months before administration: The patient had oral administration of gliclazide (40 mg × 1 time/day), metformin hydrochloride (250 mg × 3 times/day), and miglitol (50 mg × 3 times/day) for type 2 diabetes mellitus. Miglitol was prescribed by the previous doctor. 302 days before administration: The dose of gliclazide was increased to 60 mg/day. Hemoglobin A1c (HbA1c) 7.4%.

				204 days before administration: Metformin hydrochloride was switched to pioglitazone hydrochloride (30 mg/day) for type 2 diabetes mellitus. Administration of Gliclazide (60 mg/day) and miglitol (50 mg × 3 times/day) was continued. HbA1c 7.5%. Day 1 of administration: HbA1c level remained at 7.0%, and for type 2 diabetes mellitus, the dose of gliclazide was reduced to 40 mg/day. Administration of pioglitazone hydrochloride and miglitol was continued, and additional administration of sitagliptin phosphate hydrate (25 mg × 1 time/day) was started. Day 5 of administration (day of discontinuation): After intake of breakfast, the patient developed abdominal pain and vomiting, and visited the department of gastroenterological medicine at this hospital. A swollen abdomen was pointed out, and intestinal obstruction was suspected. After computed tomography (CT) examination of the abdomen and pelvic cavity (upper and lower abdomen), the patient was admitted to the hospital. Infection (-). Abdominal/pelvic cavity CT showed a finding of intestinal obstruction, with distended bowel and content retentions mainly in the jejunum. The ends of dilatation seemed to be the caudal part of the lower pole of the left kidney and the ventral part of the greater psoas muscle. Due to the period after gastric operation, postoperative adhesive ileus was suspected. With no ascites, obvious abnormal findings were not observed in the abdominal parenchymal organs. After hospital admission, the patient was put under a fasting state as a medical procedure. Fluid replacement was given and an ileus tube was inserted for medical treatment. Administration of oral medications for type 2 diabetes mellitus (sitagliptin phosphate hydrate, gliclazide, pioglitazone hydrochloride, miglitol) was temporarily discontinued, and the regimen of recombinant human insulin was changed to sliding scale injection. Vomiting remitted, and abdominal pain also gradually improved. White blood cell count (WBC) 11570/μL, C-reactive protein (CRP) 0.02 mg/dL. 1 day after discontinuation: Abdominal pain mostly disappeared. 2 days after discontinuation: The ileus tube was removed. Thin rice gruel was started from evening meal, and the amount of food was increased little by little. 3 days after discontinuation: Around this time, the patient could take meals. 6 days after discontinuation: The patient became capable of eating rice dishes. Administration of gliclazide (60 mg/day) and pioglitazone hydrochloride (30 mg/day) was resumed for type 2 diabetes mellitus. 7 days after discontinuation: The patient recovered from intestinal obstruction and was discharged from the hospital. 21 days after discontinuation: The patient visited an outpatient department and was confirmed to have a favorable clinical course with no abdominal pain, etc. HbA1c 6.9%, WBC 4510/μL, CRP 0.01 mg/dL. After that, sitagliptin phosphate hydrate was not readministered.

	Concomitant medications: miglitol, gliclazide, pioglitazone hydrochloride, rosuvastatin calcium, fexofenadine hydrochloride

Alogliptin Benzoate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Type 2 diabetes mellitus (hyperlipidaemia)	25 mg for 59 days	**Acute pancreatitis** Medical history: prostatic hyperplasia, total prostatectomy More than 10 years before administration: The patient started receiving voglibose (0.6 mg/day), pravastatin sodium (5 mg/day). Day 1 of administration: Coadministration of alogliptin benzoate was started at 25 mg. HbA1c 6.3%, blood glucose level 153 mg/dL. Day 59 of administration (day of discontinuation): A bout of abdominal pain occurred. Upper abdominal tenderness, back pain, and nausea/vomiting developed. Pancreatic enlargement was suspected by abdominal echo. Plain abdominal CT scan was performed at another hospital (Hospital A). Gallstones were not found. Imaging findings suggesting acute pancreatitis were observed, the patient was admitted to the hospital. Oral administration of alogliptin benzoate and voglibose was discontinued on this date. 1 day after discontinuation: The patient was referred and admitted to another hospital (Hospital B). Contrast-enhanced CT showed Grade 1 acute pancreatitis with a pancreatitis severity score of 0. Magnetic resonance cholangiopancreatography (MRCP) showed no involvement of gallstones. Medical treatment was started with fasting, fluid replacement, and administration of protease inhibitor. 5 days after discontinuation Abdominal pain remitted gradually, and oral intake was restarted from Day 5 of onset. After that, the contents of meals were gradually increased, but an exacerbation of the symptoms was not observed. The patient's alcohol consumption was less than 180 mL, and it was not quite excessive. No finding of chronic pancreatitis was observed, involvement of gallstones was ruled out by MRCP, immunoglobulin G-4 (IgG-4) was normal, and hyperlipidaemia was controlled. Therefore, although involvement of viruses, etc. cannot be completely ruled out, taking into account the medical history and complaints, the condition was considered to be acute pancreatitis due to dipeptidyl peptidase-4 (DPP-4) inhibitor. Oral diabetic agents were changed to sulfonylurea (SU) drug. 10 days after discontinuation: The patient recovered from acute pancreatitis and was discharged from the hospital. After that, the clinical course has been favorable.
	Concomitant medications: voglibose, pravastatin sodium			

Laboratory Examination

	193 days before administration	Day 1 of administration	Day 59 of administration (day of discontinuation)	1 day after discontinuation	5 days after discontinuation	10 days after discontinuation	34 days after discontinuation
HbA1c (%)	6.4	6.3	-	6.5	-	-	-
WBC ($\times 10^3/\mu L$)	3.21	4.11	10.11	9.8	8.8	5.3	-
Amylase (IU/L)	-	-	-	2592	92	95	-
Pancreatic amylase (IU/L)	-	-	3470	-	-	-	42
Lipase (IU/L)	31	-	7825	2317	-	-	39
Triglycerides (mg/dL)	184	220	118	55	-	-	-
CRP (mg/dL)	0.07	≤0.05	0.7	1.7	13.8	2.3	-

Alogliptin Benzoate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 60s	Type 2 diabetes mellitus (hypertension, gastritis, hyperlipidaemia, retinopathy)	25 mg for 28 days	**Hepatic dysfunction** Medical history: angina pectoris, retinal detachment surgery, Japanese cedar pollinosis HbA1c level of 6% to 6.5% was maintained by administration of glimepiride (2 mg/day), pioglitazone hydrochloride (15 mg/day), and acarbose (300 mg/day). 85 days before administration: The patient stopped receiving pioglitazone hydrochloride. HbA1c 6.4 %. 43 days before administration: HbA1c level increased to 6.7%, administration of acarbose was discontinued, and administration of sitagliptin phosphate hydrate (50 mg/day) was started. The same dose of glimepiride was continued. Day 1 of administration: HbA1c level increase to 7.0%, administration of sitagliptin phosphate hydrate was discontinued, and administration of alogliptin benzoate was started at 25 mg. Others were not changed. 2 - 3 weeks before onset: The patient had 2 glasses of Shochu (Japanese distilled beverage)/time, three times a week (usually, twice a week). 1 week before onset: The patient had 1 glass of Shochu and one glass of Oolong Hai (Shochu with oolong tea)/time, once a week. Day 28 of administration (day of discontinuation): Severe hepatic dysfunction was found at a periodic visit, the patient was urgently admitted to the hospital. Mild malaise was noted. The patient had no history of intake foods, such as raw oysters, which may cause hepatitis A. Oral administration of alogliptin benzoate was discontinued on this date. Hepatitis B surface (HBs) antigen and Hepatitis C virus (HCV) antibody: Both were negative 1 day after discontinuation: The patient showed a trend toward a rapid improvement in liver function. The dose of glimepiride (2.5 mg/day) was

				increased. 6 days after discontinuation: Laboratory test results showed rapid remission, the patient was discharged from the hospital. 14 days after discontinuation: The patient visited an outpatient department. Laboratory test values related to liver function mostly recovered to normal levels. DLST (drug lymphocyte stimulation test) results: alogliptin benzoate (-), sitagliptin phosphate hydrate (-) 35 days after discontinuation: Liver function recovered completely. Hepatitis A immunoglobulin M (HA-IgM) antibody, Cytomegalovirus immunoglobulin M (CMV-IgM), anti-Epstein-Barr virus viral capsid antigen immunoglobulin G (anti-EBV VCA-IgG), parvovirus B19-IgM, Hepatitis E virus ribonucleic acid (HEV-RNA): All were negative. Tests of virus markers other than Hepatitis B virus (HBV) and Hepatitis C virus (HCV) at the onset of liver disorder and imaging tests (abdominal echo, CT, MRI, etc.) were not performed.
	Concomitant medications: isosorbide mononitrate, sodium gualenate hydrate, famotidine, teprenone, nifedipine, glimepiride, pravastatin sodium			

Laboratory Examination

	43 days before administration	1 day before administration	Day 28 of administration (day of discontinuation)	1 day after discontinuation:	4 days after discontinuation	14 days after discontinuation	35 days after discontinuation
HbA1c (%)	6.7	7.0	6.8	-	-	6.9	-
AST (GOT) (IU/L)	36	33	2188	859	93	24	18
ALT (GPT) (IU/L)	29	27	1512	1022	425	55	14
LDH(IU/L)	179	187	425	210	164	163	170
Al-P (IU/L)	-	-	-	313	316	-	255
γ-GTP (IU/L)	58	86	613	535	463	199	82
Total bilirubin (mg/dL)	-	-	3.9	3.0	1.3	0.8	0.7
Direct bilirubin (mg/dL)	-	-	2.6	-	-	0.1	-
PT INR	-	-	1.20	-	0.91	-	-
PT (%)	-	-	71.2	82.6	119.4	-	119.4

Alogliptin Benzoate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Female 80s	Type 2 diabetes mellitus (hypertension, hyperlipidaemia)	25 mg for 15 days	Oculomucocutaneous syndrome (Stevens-Johnson syndrome: SJS) Day 1 of administration: The patient started receiving alogliptin benzoate at 25 mg. Day 5 of administration: Itching of both eyes occurred. Day 12 of administration: Urticaria-like rash occurred mainly in both gluteal regions

				and the lower limbs. Day 15 of administration (day of discontinuation): Rash spread systemically, and blisters formed at the initial site of occurrence. Conjunctivitis and stomatitis also occurred. Since alogliptin benzoate was the only new oral medication, the patient was diagnosed with Stevens-Johnson syndrome associated with alogliptin benzoate. The patient was admitted to the hospital. Pruritus was noted. On this date, administration of alogliptin benzoate was discontinued, and oral administration of prednisolone (40 mg) was started. 1 day after discontinuation: Skin eruption did not newly occur, and was partially resolving. 7 days after discontinuation: Skin eruption disappeared substantially. The regions of blistering tended to heal with desquamation. Since the patient is elderly and has diabetes mellitus, the dose of prednisolone was reduced (30 mg). 13 days after discontinuation: The dose of prednisolone was reduced (20 mg). Skin eruption disappeared steadily. 19 days after discontinuation: The dose of prednisolone was reduced (15 mg). 34 days after discontinuation: The dose of prednisolone was reduced (7.5 mg). Skin eruption disappeared. 41 days after discontinuation: The dose of prednisolone was reduced (5 mg). The patient recovered and was discharged from the hospital. (Serological viral test and biopsy skin were not performed.)
	Concomitant medications: olmesartan medoxomil, amlodipine besilate, fenofibrate			

Alogliptin Benzoate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
6	Female 60s	Type 2 diabetes mellitus (none)	25 mg for 13 days	**Erythema multiforme** Medical history: uterine cancer, hyperlipidaemia, cerebral infarction, ovarian cancer Day 1 of administration: The patient had pioglitazone hydrochloride and pioglitazone hydrochloride was changed to alogliptin benzoate 25 mg. Day 13 of administration (day of discontinuation): Generalized skin eruption and pyrexia of 38.9°C were noted at an outpatient visit. Administration of alogliptin benzoate was discontinued, and the patient was instructed to visit a dermatology department. 1 day after discontinuation: The patient was referred to and visited the dermatology department for the first time. Erythema multiforme-like eruption occurred systemically. The patient was diagnosed with erythema multiforme-type drug eruption associated with alogliptin benzoate. Topical administration of difluprednate ointment (limbs and body trunk) and hydrocortisone butyrate ointment (face) was started (used for 6 days).

				6 days after discontinuation: At a follow-up visit to the department, skin eruption resolved. Mild erythema remained but erythema remitted and healed. <Characteristics of skin eruption> Site of onset: almost the whole body (body regions exposed to sunlight and regions covered) Number of skin eruptions: many Size of skin eruption: red bean to thumb's head size Color tone of skin eruption: light red Mucosal lesion: none Shape of skin eruption: macule, exudative
	Concomitant medications: unknown			

2 **Exenatide, Liraglutide** (Genetical Recombination)

Brand Name (name of company)	**Exenatide** Byetta Subcutaneous Injection 5 μg Pen 300, 10 μg Pen 300 (Eli Lilly Japan K.K.) **Liraglutide (Genetical Recombination)** ViCTOZA Subcutaneous Injection 18 mg (Novo Nordisk Pharma Ltd.)
Therapeutic Category	Hormones-Miscellaneous
Indications	**Exenatide** Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to sulfonylurea (including concomitant use with biguanide or thiazolidinedione) along with diet and exercise therapies. **Liraglutide (Genetical Recombination)** Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies

PRECAUTIONS (underlined parts are revised)

Careful Administration

Patients with a medical history of abdominal operation or intestinal obstruction

Adverse Reactions (clinically significant adverse reactions)

Intestinal obstruction: Intestinal obstruction may occur. Patients should be carefully monitored, and if any abnormalities including severe constipation, abdominal distension, persistent abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Reference Information

Exenatide:
The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 2 months (from initial marketing to February 29, 2012)

- Intestinal obstruction-associated cases: 0 cases

The number of patients using this drug per year estimated by MAHs: approximately 14,000 (April 1, 2011 to March 31, 2012)
Launched in Japan: December 2010

Liraglutide (Genetical Recombination):
The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 8 months (from initial marketing to February 29, 2012)

- Intestinal obstruction-associated cases: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 33,000 (April 1, 2011 to March 31, 2012)
Launched in Japan: June 2010

Case Summary

Liraglutide (Genetical Recombination)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Type 2 diabetes mellitus (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, hypertension, psoriasis, tinea, constipation)	0.3-0.9 mg for 16 days	**Intestinal obstruction (paralytic ileus)** The patient was admitted to the hospital for glycaemia control. Intensive insulin therapy conducted in outpatient settings was continued. The patient has no history of laparotomy in the past. Day 1 of administration: The patient started receiving liraglutide (genetical recombination) at 0.3 mg in concomitant use with insulin. The dose was increased by 0.3 mg every week. Day 14 of administration: The dose of liraglutide (genetical recombination) was increased to 0.9 mg. The patient had vomiting before the evening meal. Although the patient had a tendency toward constipation, he continued to have bowel movements every day after the start of administration. Day 16 of administration (day of discontinuation): Vomiting occurred after lunch. CRP level was elevated to 7.46 mg/dL. Plain abdominal radiography showed niveau, the patient was diagnosed with ileus. Fasting and transfusion were started from the evening of the same day. Administration of liraglutide (genetical recombination) was discontinued. 2 days after discontinuation: Abdominal contrast-enhanced CT was performed. No obvious causative disease for obstruction was found. 6 days after discontinuation: The patient resumed eating. After that, abdominal symptoms were not aggravated. 27 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: insulin aspart (genetical recombination), insulin glargine (genetical recombination), candesartan cilexetil, amlodipine besilate, epinastine hydrochloride, terbinafine hydrochloride, magnesium oxide			

3 Mosapride Citrate Hydrate

Brand Name (name of company)	GASMOTIN Tablet 5 mg, 2.5 mg, GASMOTIN Powder 1% (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Digestive organ agents-Miscellaneous
Indications	○ Gastrointestinal symptoms associated with chronic gastritis (heartburn, nausea/vomiting) ○ Adjunction with colonic cleansing agent for a preparation prior to radiographic contrast barium enema

PRECAUTIONS (underlined parts are revised)

Important Precautions

When using this drug for gastrointestinal symptoms associated with chronic gastritis, improvement in gastrointestinal symptoms should be evaluated and the necessity of continuation of administration should be considered after administration for a certain period (usually 2 weeks).

Fulminant hepatitis, serious hepatic dysfunction, and jaundice may occur. This drug should not be excursively administered over the long-term. During administration of this drug, patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. The patient should be instructed to discontinue taking this drug and contact their physician, if any symptoms such as malaise, anorexia, dark urine, conjunctiva bulbi colouring yellow, etc. are observed after administration of this drug.

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 February 29, 2012)

- Hepatic dysfunction-associated cases: 23 cases (3 fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 9,000,000 (July 2010 to June 2011)

Launched in Japan: October 1998

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Gastritis (hypertension, hyperlipidaemia, insomnia, neck, shoulder and arm syndrome, reflux oesophagitis, pruritus, dizziness)	15 mg for 126 days	**Fulminant hepatitis** Approximately 8 months before administration: The patient underwent gastroscopy at hospital A, erosive gastritis and reflux oesophagitis were shown. After that, famotidine was changed to omeprazole. Administration of cetraxate hydrochloride was continued. Day 1 of administration: The patient was prescribed with mosapride citrate hydrate. Day 4 of administration: The patient complained of a "churning of the stomach." Day 35 of administration: Churning of the stomach improved. Day 77 of administration: The patient said, "stools became loose, but improved a little after taking cetraxate hydrochloride." Day 117 of administration: The patient complained of malaise in the body. Impaired

				appetite was noted. Purpura developed in the right thigh. The patient was referred to a dermatology department and was diagnosed with anaphylactoid purpura. The patient was scheduled to visit hospital B after 4 days. Around Day 120 of administration: Jaundice and pruritus were noted. Day 126 of administration (day of discontinuation): At a visit to hospital A, the patient had marked drug eruption, with itching all over the body. Results of blood test showed prominent hepatic disorder. The patient was referred to hospital C. 1 day after discontinuation: The patient visited hospital C with a letter of referral. The patient was admitted to the hospital. Fluid replacement (500 mL + vitamin preparation + menatetrenone 20 mg) was performed. The patient went on a diet for hepatic failure, and blood tests were performed every day. 5 days after discontinuation (day of onset): The patient was diagnosed as fulminant hepatitis. ♦ Systemic management in intensive care unit (particularly for hepatic encephalopathy) • Plasma exchange was performed. [fresh frozen plasma (FFP) 40 units/day] 5, 7, 9, 11, 24, 29, 32, 36, 39, and 45 days after discontinuation • Steroid pulse therapy [Methylprednisolone sodium succinate] 5-7 days after discontinuation: 1 g/day 8-10 days after discontinuation: 500 mg/day 11-13 days after discontinuation: 250 mg/day 14-16 days after discontinuation: 125 mg/day • Infection prophylaxis (Antibiotics were changed, if appropriate, and administered.) [Cefmetazole sodium 2 g/day] 16-28 days after discontinuation; 43-49 days after discontinuation [Piperacillin sodium 2 g/day] 29-42 days after discontinuation; 50-52 days after discontinuation • Administration of hemostatic agent and anti-ulcer agent for haemorrhage prophylaxis of digestive tract [Coinjection of carbazochrome sodium sulfonate hydrate 100 mg + tranexamic acid 500 mg] 28-52 days after discontinuation [Famotidine 2A/day] 16-27 days after discontinuation [Lansoprazole 60 mg/day] 28-52 days after discontinuation • Glucose/insulin therapy as hepatic adjuvant therapy 52 days after discontinuation: The patient died.
	Concomitant medications: spironolactone, epinastine hydrochloride, ethyl icosapentate, omeprazole, mequitazine, oxazolam, bepotastine besilate, losartan potassium, sennoside, nitrazepam, eperisone hydrochloride, betahistine mesilate, bifidobacteria preparation, loxoprofen sodium hydrate			

Laboratory Examination
(Hospital A: the prescribing institution)

	Day 4 of administration	Day 126 of administration (day of discontinuation)
AST (GOT) (U/L)	19	1381
ALT (GPT) (U/L)	13	1031
LDH (U/L)	-	542
Al-P (U/L)	272	829
Total bilirubin (mg/dL)	-	12.13

(Hospital C)

	1 day after discontinuation	5 days after discontinuation (day of onset)	10 days after discontinuation	15 days after discontinuation	45 days after discontinuation
AST (GOT) (U/L)	1363	962	58	31	49
ALT (GPT) (U/L)	1150	771	61	47	40
LDH (U/L)	595	465	169	187	286
γ-GTP (U/L)	388	234	30	64	63
Al-P (U/L)	1043	1253	220	289	373
Total bilirubin (mg/dL)	19.06	23.46	9.65	11.27	33.69
Albumin (g/dL)	3.9	2.9	2.5	2.4	2.6
PT (%)	44	40	58	47	37

4 Iodine

(1) **Iodine** (PREPODYNE solution)

Brand Name (name of company)	PREPODYNE solution 1% (Maruishi Pharmaceutical Co., Ltd.)
Therapeutic Category	Local Antimicrobial agents
Indications	Disinfection of the skin at surgical sites (surgical fields), disinfection of the mucous membrane at surgical sites (surgical fields) Disinfection of wound sites of the skin/mucous membrane, disinfection of burned skin surfaces

PRECAUTIONS (underlined parts are revised)

Contraindications	Patients with a history of hypersensitivity to this drug or iodine

(2) **Iodine** (drugs with the indication and dosage and administration for "use for dispensing of iodine tincture, diluted iodine tincture, compound iodine glycerin, etc.")

Brand Name (name of company)	Iodine "Kozakai M" (Kozakai Pharmaceutical Co., Ltd.), IODINE NIKKO (Nikko Pharmaceutical Co., Ltd.), Iodine "Yamazen" (Yamazen Pharmaceutical Co., Ltd.)
Therapeutic Category	Local Antimicrobial agents, Dispensing medicines-Miscellaneous
Indications	Use for dispensing of iodine tincture, diluted iodine tincture, compound iodine glycerin, etc.

PRECAUTIONS (underlined parts are revised)

Contraindications

Patients with a history of hypersensitivity to this drug or iodine

Adverse Reactions (clinically significant adverse reactions)

Anaphylactoid symptoms: Anaphylactoid symptoms (dyspnoea, laryngeal oedema, wheezing, urticaria, flushing, etc.) may occur. Patients should be carefully monitored, and if such symptoms 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, 2009 to January 31, 2012)

- Anaphylactoid symptoms: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAH(s):

(1) Approximately 300,000 (April 1, 2011 to March 31, 2012)

(2) Approximately 93,250 (April 1, 2011 to March 31, 2012)

Launched in Japan:

(1) January 1987

(2) August 1949

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Medical observation: early-stage carcinoma of middle third of oesophagus (colon adenoma, bronchial asthma)	Unknown; Once, for 1 day	**Status Asthmaticus** Day of administration (day of completion): Lugol's solution was prepared using iodine in the hospital pharmacy, and the test was completed after the patient underwent an endoscopy for oesophageal carcinoma with Lugol staining. 30 minutes after completion: Dyspnoea occurred following the onset of cough. Oxygen saturation (SpO_2) was 80%-82%, oxygen mask 10 L was started. 35 minutes after completion: Wheezing was noted on auscultation in the chest and back during oxygen inhalation. The patient had a history of bronchial asthma. An asthmatic attack was suspected, electrolyte solution (lactate Ringer's solution) 500 mL + aminophylline injection 250 mg, hydrocortisone sodium succinate injection 300 mg + physiological saline 20 mL were administered. SpO_2 was 79%-80%. The patient did not respond to her name when called. Cyanosis progressed, and the respiratory conditions also worsened. 50 minutes after completion: Intubation was performed. 60 minutes after completion: Blood pressure was 105/82 and pulse rate was 116, 500 mL of electrolyte solution (lactate Ringer's solution) was infused in the dorsum of the right foot. Vomiting occurred. Aspiration was performed. SpO_2 98% 65 minutes after completion: SpO_2 was 98%, the patient moved her arms/legs, and nodded in response to her name being called. 90 minutes after completion: 10 mL of propofol injection 500 mg was injected. 1 day after completion: Extubation was performed

				7 days after completion: The patient was discharged from the hospital.
	Concomitant medications: potassium iodide			

Laboratory Examination

	130 minutes after completion	8 hours after completion	1 day after completion	2 days after completion	6 days after completion
WBC ($\times 10^3/\mu L$)	15.1	10.5	9.5	6.8	5.8
RBC ($\times 10^4/mm^3$)	348	338	314	321	328
Hemoglobin (g/dL)	11.0	11.0	9.9	10.2	10.5
Hematocrit (%)	34.4	33.3	31.4	32.1	31.7
PLT ($\times 10^4/\mu L$)	20.4	20.3	16.8	16.2	17.5

3

Revision of Precautions (No. 236)

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 April 24, 2012 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1

Antipyretics and analgesics, anti-inflammatory agents

Ibuprofen (oral dosage form)

Brand Name	BRUFEN Tablets 100, 200, BRUFEN Granule 20% (Kaken Pharmaceutical Co., Ltd.) and the others
Contraindications	Women in their third trimester of pregnancy [Refer to the section "Use in Pregnant, Parturient And Nursing Women"]
Use in Pregnant, Parturient And Nursing Women	This drug should not be administrated in the third trimester of pregnancy. [Foetal ductus arteriosus stenosis was reported in studies in which the drug was administered to rats in their third trimester of pregnancy. In addition, persistent foetal circulation (PFC) has been reported after other antipyretics, analgesics, anti-inflammatory agents were administered in the third trimester of pregnancy.] Pregnant women (at a stage other than their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Reduced number of implantations and live births were observed at a high-dose (60 mg/kg or higher) in a group of rats.]

2

Antipyretics and analgesics, anti-inflammatory agents

Ibuprofen (suppository)

Brand Name	UNIPRON Supp. 50, 100 (Showa Yakuhin Kako Co., Ltd.)
Contraindications	Women in their third trimester of pregnancy [Refer to the section "Use in Pregnant, Parturient And Nursing Women"]
Use in Pregnant, Parturient And Nursing Women	This drug should not be administrated in the third trimester of pregnancy. [Foetal ductus arteriosus stenosis was reported in studies in which the drug was administered to rats in their third trimester of pregnancy.] Animal studies showed fetotoxicity (reduced number of implantations and live births were observed in a high-dose group), and the safety has not been established for administration during pregnancy in humans. Pregnant women (at a stage other than the third trimester of pregnancy) or women who may be pregnant are not recommended to be administered this drug.

3 Antipyretics and analgesics, anti-inflammatory agents

Flurbiprofen (oral dosage form)

Brand Name	FROBEN Tab. 40, FROBEN Gr. 8% (Kaken Pharmaceutical Co., Ltd.) and the others
Contraindications	Women in their third trimester of pregnancy [Refer to the section "Use in Pregnant, Parturient And Nursing Women"]
Use in Pregnant, Parturient And Nursing Women	This drug should not be administrated in the third trimester of pregnancy. [Delayed delivery and foetal ductus arteriosus stenosis were reported in studies in which the drug was administered to rats in their third trimester of pregnancy.] Pregnant women (at a stage other than their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established.]

4 Antipyretics and analgesics, anti-inflammatory agents

Flurbiprofen Axetil

Brand Name	ROPION Intravenous 50 mg (Kaken Pharmaceutical Co., Ltd.)
Contraindications	Women in their third trimester of pregnancy [Refer to the section "Use in Pregnant, Parturient And Nursing Women"]
Use in Pregnant, Parturient And Nursing Women	This drug should not be administrated in the third trimester of pregnancy. [Delayed delivery and foetal ductus arteriosus stenosis were reported in studies in which the drug was administered to rats in their third trimester of pregnancy.] Pregnant women (at a stage other than their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established.]

5 Miscellaneous metabolism agents-Miscellaneous

Canakinumab (Genetical Recombination)

Brand Name	ILARIS for s.c. injection 150 mg (Novartis Pharma K.K.)
Important Precautions	Neutropenia may occur in association with administration of this drug. Neutrophil count should be measured before the initial injection, about one month after the injection, and then periodically during administration of this drug.
Adverse Reactions (clinically significant adverse reactions)	**Neutropenia**: Neutropenia may occur. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

6 Synthetic antibacterials

Lomefloxacin Hydrochloride (oral dosage form)

Brand Name	Bareon Capsule 100 mg, Bareon Tablet 200 mg (Abbott Japan Co., Ltd.), Lomebact Capsule 100 mg (Shionogi & Co., Ltd.)
Adverse Reactions (clinically significant	**Prolonged QT, ventricular tachycardia (including Torsades de pointes)**: Prolonged QT or ventricular tachycardia (including torsades de pointes) may occur.

adverse reactions)	Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

7 **Antivirals**

Raltegravir Potassium

Brand Name	ISENTRESS Tablets 400 mg (MSD K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Drug-induced hypersensitivity syndrome**: Rash and pyrexia may occur as the initial symptoms followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, swollen lymph nodes, leukocytosis, eosinophilia, and 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. The reactivation of viruses including Human Herpesvirus 6 (HHV-6) has been found to be frequently associated with drug-induced hypersensitivity syndrome. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised.
Reference Information	Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

8 **Antipyretics and analgesics, anti-inflammatory agents**

Acetaminophen

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
Use in Pregnant, Parturient And Nursing Women	Foetal ductus arteriosus stenosis may occur in women treated with this drug in their third trimester of pregnancy. Weak foetal ductus arteriosus stenosis was reported in studies in which the drug was administered to rats in their third trimester of pregnancy.

9 **Antipyretics and analgesics, anti-inflammatory agents**

Isopropylantipyrine/Acetaminophen/Allylisopropylacetylurea/ Anhydrous Caffeine

Brand Name	SG Combination Granule (Shionogi & Co., Ltd.)
Use in Pregnant, Parturient And Nursing Women	Foetal ductus arteriosus stenosis may occur in women treated with this drug in their third trimester of pregnancy. Weak foetal ductus arteriosus stenosis was reported in studies in which isopropylantipyrine or acetaminophen was administered to rats in their third trimester of pregnancy.

10 **Antipyretics and analgesics, anti-inflammatory agents**

Tramadol Hydrochloride/Acetaminophen

Brand Name	TRAMCET Combination Tablets (Janssen Pharmaceutical K.K.)
Use in Pregnant, Parturient And	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant

Nursing Women	women has not been established. It has been reported that tramadol passes the placental barrier resulting in convulsive seizure, physical dependence, and drug withdrawal syndrome in neonates as well as foetal death or stillbirth. Animal studies showed tramadol had an impact on organogenesis, ossification, and newborn survival. It has been reported that acetaminophen causes mild foetal ductus arteriosus stenosis in rats in their third trimester of pregnancy. Foetal ductus arteriosus stenosis may occur in women treated with acetaminophen in their third trimester of pregnancy.

11 **Common cold drugs**

Salicylamide/Acetaminophen/Anhydrous Caffeine/Chlorpheniramine Maleate (for adult)

Brand Name	Pelex combination granule (Taiho Pharmaceutical Co, Ltd.) and the others
Use in Pregnant, Parturient And Nursing Women	Pregnant women (within 12 weeks or in their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [Teratogenicity was reported in animal studies (rats) for salicylic acid preparations (e.g. aspirin), and abnormal haemorrhage in humans was reported in patients who were administered the drug in their third trimester of pregnancy and their newborns.] Foetal ductus arteriosus stenosis may occur in women treated with acetaminophen in their third trimester of pregnancy. Weak foetal ductus arteriosus stenosis was reported in studies in which acetaminophen was administered to rats in their third trimester of pregnancy.

12 **Common cold drugs**

Salicylamide/Acetaminophen/Anhydrous Caffeine/Chlorpheniramine Maleate (for pediatric)

Brand Name	Pediatric Pelex combination granule (Taiho Pharmaceutical Co., Ltd.), LL COMBINATION SYRUP FOR PEDIATRIC (Daiichi Sankyo Company, Limited)
Use in Pregnant, Parturient And Nursing Women	Pregnant women (within 12 weeks or in their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [Teratogeniity was reported in animal studies (rats) for salicylic acid preparations (e.g. aspirin), and abnormal haemorrhage in humans was reported in patients who were administered the drug in their third trimester pregnancy and their newborns.] Foetal ductus arteriosus stenosis may occur in women treated with acetaminophen in their third trimester pregnancy. Weak foetal ductus arteriosus stenosis was reported in studies in which acetaminophen was administered to rats in their third trimester of pregnancy. Long-term continued use should be avoided in nursing women. [The caffeine is easily transferred into breast milk.]

13 **Common cold drugs**

Salicylamide/Acetaminophen/Anhydrous Caffeine/Promethazine Methylenedisalicylate (for adult)

Brand Name	PL Combination Granules (Shionogi & Co., Ltd) and the others
Use in Pregnant, Parturient And	Pregnant women (within 12 weeks or in their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits

Nursing Women	outweigh the risks. [Teratogenicity was reported in animal studies (rats) for salicylic acid preparations (e.g. aspirin), and abnormal haemorrhage in humans was reported in patients who were administered aspirin in their third trimester of pregnancy and their newborns.] Foetal ductus arteriosus stenosis may occur in women treated with acetaminophen in their third trimester of pregnancy. Weak foetal ductus arteriosus stenosis was reported in studies in which acetaminophen was administered to rats in their third trimester pregnancy.

14 **Common cold drugs**

Salicylamide/Acetaminophen/Anhydrous Caffeine/Promethazine Methylenedisalicylate (for pediatric)

Brand Name	PL Combination Granules for Infant (Shionogi & Co., Ltd)
Use in Pregnant, Parturient And Nursing Women	Pregnant women (within 12 weeks or in their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [Teratogenicity was reported in animal studies (rats) for salicylic acid preparations (e.g. aspirin), and abnormal haemorrhage in humans was reported in patients who were administered aspirin in their third trimester of pregnancy and their newborns.] Foetal ductus arteriosus stenosis may occur in women treated with acetaminophen in their third trimester of pregnancy. Weak foetal ductus arteriosus stenosis was reported in studies in which acetaminophen was administered to rats in their third trimester of pregnancy. Long-term use should be avoided in nursing women. [The caffeine in this drug is easily secreted into breast milk.]

15 **Antitussives**

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

Brand Name	Coughcode-N Combination Tablets (Mylan Seiyaku Ltd.)
Use in Pregnant, Parturient And Nursing Women	Pregnant women (within 12 weeks or in their third trimester of pregnancy) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [Teratogenicity was reported in animal studies (rats) for salicylic acid preparations (e.g. aspirin), and abnormal haemorrhage in humans was reported in patients who were administered aspirin in their third trimester of pregnancy and their newborns.] Foetal ductus arteriosus stenosis may occur in women treated with acetaminophen in their third trimester of pregnancy. Weak foetal ductus arteriosus stenosis was reported in studies in which acetaminophen was administered to rats in their third trimester of pregnancy.

16 **Alkylating agents**

Bendamustine Hydrochloride

Brand Name	TREAKISYM Injection 100 mg (SymBio Pharmaceuticals Limited)
Important Precautions	Decreased lymphocytes may occur at a high frequency after administration of this drug and then severe immune deficiency may worsen or occur. Close examination should be performed for signs of immune deficiency through frequent laboratory tests (e.g. blood tests), etc. If any abnormalities are observed, appropriate measures such as

	dose reduction or drug suspension should be taken and attention should be paid to severe opportunistic infection due to fungi such as candida, viruses such as cytomegalovirus and Pneumocystis. Hepatitis due to reactivation of hepatitis B virus may occur in association with administration of this drug. Prior to treatment, the patient should be checked for hepatitis virus infection, and appropriate measures should be taken before administration of this drug. After the start of administration of this drug, attention to the occurrence of signs or symptoms related to reactivation of hepatitis B virus should be paid by continuously monitoring results of liver function tests or hepatitis virus markers.
Adverse Reactions (clinically significant adverse reactions)	**Infection**: Severe infections including sepsis and pneumonia may occur. Hepatitis due to reactivation of hepatitis B virus may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

17 **Antineoplastics-Miscellaneous**

Azacitidine

Brand Name	Vidaza for Injection 100 mg (Nippon Shinyaku Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Interstitial lung disease**: Interstitial lung disease may occur. Patients should be carefully monitored for clinical symptoms such as cough, dyspnoea, and pyrexia. If any abnormalities are observed, examinations such as chest X-ray and chest CT should be performed. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

18 **Antineoplastics-Miscellaneous**

Sorafenib Tosilate

Brand Name	Nexavar Tablet 200 mg (Bayer Yakuhin, Ltd.)
Important Precautions	Hand and foot syndrome, exfoliative dermatitis, toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), or erythema multiforme may occur. Patients should be instructed to consult a dermatologist as necessary.
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Toxic epidermal necrolysis, oculomucocutaneous syndrome or erythema multiforme 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.

19 **Acting mainly on gram-negative bacteria**

Pivmecillinam Hydrochloride

Brand Name	MELYSIN TABLETS 50 mg (Takeda Pharmaceutical Company Limited)
Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester of pregnancy and their neonates.]
Pediatric use	Hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (preparations for pediatric) to children (particularly infants).

Other Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of this drug. In children (particularly infants), hypoglycaemia (convulsions, disturbed consciousness, etc.) associated with hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (cefditoren pivoxil, cefcapene pivoxil hydrochloride hydrate, cefteram pivoxil, tebipenem pivoxil).

20 **Acting mainly on gram-positive and gram-negative bacteria**

Cefcapene Pivoxil Hydrochloride Hydrate (tablet)

Brand Name	Flomox Tablet 75 mg, 100 mg (Shionogi & Co., Ltd.) and the others
Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester of pregnancy and their neonates.]
Pediatric use	In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (preparations for pediatric use).
Other Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of antibiotics with a pivoxil group including this drug (cefcapene pivoxil hydrochloride hydrate, cefditoren pivoxil, cefteram pivoxil, tebipenem pivoxil). In children (particularly infants), hypoglycaemia associated with hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (preparations for pediatric). Attention should be paid to decreased carnitine when administering antibiotics with a pivoxil group.

21 **Acting mainly on gram-positive and gram-negative bacteria**

Cefcapene Pivoxil Hydrochloride Hydrate (fine granule for pediatric)

Brand Name	Flomox Fine Granule for Pediatric 100 mg (Shionogi & Co., Ltd.) and the others
Important Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of antibiotics with a pivoxil group including this drug (cefcapene pivoxil hydrochloride hydrate, cefditoren pivoxil, cefteram pivoxil, tebipenem pivoxil). In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group. Attention should be paid to decreased carnitine when administering antibiotics with a pivoxil group.
Adverse Reactions (clinically significant adverse reactions)	**Hypoglycaemia associated with hypocarnitinemia**: Hypoglycaemia resulting from hypocarnitinemia may occur in children (particularly infants) treated with antibiotics with a pivoxil group. If any hypoglycaemic symptoms including convulsions and disturbed consciousness are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester of pregnancy and their neonates.]

22 **Acting mainly on gram-positive and gram-negative bacteria**

Cefditoren Pivoxil (tablet)

Brand Name	MEIACT MS TABLETS 100 mg (Meiji Seika Pharma Co., Ltd.) and the others
Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester pregnancy and their neonates.]
Pediatric use	In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (preparations for pediatric).
Other Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of antibiotics with a pivoxil group including this drug (cefditoren pivoxil, cefcapene pivoxil hydrochloride hydrate, cefteram pivoxil, tebipenem pivoxil). In children (particularly infants), hypoglycaemia associated with hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (preparations for pediatric). Attention should be paid to decreased carnitine when administering antibiotics with a pivoxil group.

23 **Acting mainly on gram-positive and gram-negative bacteria**

Cefditoren Pivoxil (fine granule for pediatric)

Brand Name	MEIACT MS FINE GRANULES 10% for Pediatric (Meiji Seika Pharma Co., Ltd.) and the others
Important Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of antibiotics with a pivoxil group including this drug (cefditoren pivoxil, cefcapene pivoxil hydrochloride hydrate, cefteram pivoxil, tebipenem pivoxil). In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group. Attention should be paid to decreased carnitine when administering antibiotics with a pivoxil group.
Adverse Reactions (clinically significant adverse reactions)	**Hypoglycaemia associated with hypocarnitinemia**: Hypoglycaemia resulting from hypocarnitinemia may occur in children (particularly infants) treated with antibiotics with a pivoxil group. If any hypoglycaemic symptoms including convulsions and disturbed consciousness are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester of pregnancy and their neonates.]

24 **Acting mainly on gram-positive and gram-negative bacteria**

Cefteram Pivoxil (tablet)

Brand Name	TOMIRON tablet 50, 100 (Toyama Chemical Co., Ltd.)

Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester pregnancy and their neonates.]
Pediatric use	In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (preparations for pediatrics).
Other Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of antibiotics with a pivoxil group including this drug (cefteram pivoxil, cefditoren pivoxil, cefcapene pivoxil hydrochloride hydrate, tebipenem pivoxil). In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group (preparations for pediatric). Attention should be paid to decreased carnitine when administering antibiotics with a pivoxil group.

25 **Acting mainly on gram-positive and gram-negative bacteria**

Cefteram Pivoxil (fine granule for pediatric)

Brand Name	TOMIRON fine granule 10% for pediatric (Toyama Chmical Co., Ltd.) and the others
Important Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of antibiotics with a pivoxil group including this drug (cefteram pivoxil, cefditoren pivoxil, cefcapene pivoxil hydrochloride hydrate, tebipenem pivoxil). In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a pivoxil group. Attention should be paid to decreased carnitine when administering antibiotics with a pivoxil group.
Adverse Reactions (clinically significant adverse reactions)	**Hypoglycaemia associated with hypocarnitinemia**: Hypoglycaemia associated with hypocarnitinemia may occur in children (particularly infants) treated with antibiotics with a pivoxil group. If any hypoglycaemic symptoms including convulsions and disturbed consciousness are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester pregnancy and their neonates.]

26 **Acting mainly on gram-positive and gram-negative bacteria**

Tebipenem Pivoxil

Brand Name	ORAPENEM FINE GRANULES 10% FOR PEDIATRIC (Meiji Seika Pharma Co., Ltd.)
Important Precautions	Decreased serum carnitine resulting from metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group) was reported in association with administration of antibiotics with a pivoxil group including this drug (tebipenem pivoxil, cefditoren pivoxil, cefcapene pivoxil hydrochloride hydrate, cefteram pivoxil). In children (particularly infants), hypoglycaemia resulting from hypocarnitinemia may occur in association with administration of antibiotics with a

	pivoxil group. Attention should be paid to decreased carnitine when administering antibiotics with a pivoxil group.
Adverse Reactions (clinically significant adverse reactions)	**Hypoglycaemia associated with hypocarnitinemia**: Hypoglycaemia resulting from hypocarnitinemia may occur in children (particularly infants) treated with antibiotics with pivoxil group. If any hypoglycaemic symptoms including convulsions and disturbed consciousness are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Use in Pregnant, Parturient And Nursing Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. [The safety of this drug in pregnant women has not been established. Occurrence of hypocarnitinemia was reported in pregnant women treated with antibiotics with a pivoxil group in their third trimester pregnancy and their neonates.]

27 Synthetic antibacterials

Moxifloxacin Hydrochloride (oral dosage form)

Brand Name	Avelox Tablets 400 mg (Bayer Yakuhin, Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Fulminant hepatitis, hepatitis (mainly cholestatic), hepatic dysfunction, jaundice:** Fulminant hepatitis, hepatitis (mainly cholestatic), hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), etc. or jaundice 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.

28 Vaccines

Live Attenuated Human Rotavirus Vaccine, Oral

Brand Name	Rotarix Oral Solution (GlaxoSmithKline K.K.)
Precautions of Dosage and Administration	Individuals who receive vaccinations and timings of vaccinations: Initial vaccination should be started at 6 weeks after birth and the second vaccination should be completed with an interval of at least 4 weeks. Vaccinations should be completed no later than 24 weeks after birth. This drug may be administered to pre-trem infants in a similar manner. Initial vaccination by 14 weeks and 6 days after birth is recommended.
Reference Information	Centers for Disease Control and Prevention (CDC): Morbidity and Mortality Weekly Report (MMWR) Recomm. Rep. 2009 ; 58(RR-2): 1-25

29 Vaccines

Rotavirus Vaccine, Live, Oral, Pentavalent

Brand Name	RotaTeq Oral Solution (MSD K.K.)
Precautions of Dosage and Administration	Individuals who receive vaccinations and timings of vaccinations: This drug should be orally administered to infants aged 6 to 32 weeks after birth. Initial vaccination should be administered at 6 weeks or more of age, and this drug should be orally administered 3 times by 32 weeks of age with intervals of 4 weeks or more. This drug may be administered to premature infants in a similar manner. Initial vaccination by 14 weeks and 6 days after birth is recommended.
Reference Information	CDC: MMWR Recomm. Rep. 2009 ; 58(RR-2): 1-25

30

Over-the-counter drugs

Preparations containing ibuprofen

Brand Name	EVE (SSP Co., Ltd.) and the others
When not to use the product	This product should not be used in the following persons. Pregnant women whose estimated delivery date is within 12 weeks.

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 a new drug. It is mandatory 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 serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of June 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
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*[1]	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*[2, 3]	Shionogi & Co., Ltd.	May 25, 2012
Thyrotropin Human Alfa (Genetical Recombination) THYROGEN for Intramuscular Injection 0.9 mg*[4]	Sato Pharmaceutical Co., Ltd.	May 25, 2012
Mometasone Furoate Hydrate NASONEX Nasal 50 μg 56 sprays, NASONEX Nasal 50 μg 112 sprays*[3]	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
Caspofungin Acetate CANCIDAS for Intravenous Drip Infusion 50 mg, 70 mg	MSD K.K.	April 19, 2012
Eszopiclone Lunesta Tablets 1 mg, 2 mg, 3 mg	Eisai Co., Ltd.	April 18, 2012
Rivaroxaban Xarelto Tablets 10 mg, 15 mg	Bayer Yakuhin Ltd.	April 18, 2012

Atovaquone SAMTIREL Oral Suspension 15%	GlaxoSmithKline K.K.	April 17, 2012
Denosumab (Genetical Recombination) RANMARK SUBCUTANEOUS INJECTION 120 mg	Daiichi Sankyo Company, Limited	April 17, 2012
Crizotinib XALKORI Capsules 200 mg, 250 mg	Pfizer Japan Inc.	March 30, 2012
Duloxetine Hydrochloride Cymbalta Capsules 20 mg, 30 mg*5	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*6	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*7	Novartis Pharma K.K.	December 22, 2011
Everolimus Certican Tablets 0.25 mg, 0.5 mg, 0.75 mg*8	Novartis Pharma K.K.	December 22, 2011
Pranlukast Hydrate ONON drysyrup 10%*9	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*10	MSD K.K.	December 22, 2011
Ribavirin REBETOL Capsules 200 mg*11	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

*1 An additional indication for “erythema nodosum leprosum”

*2 An additional indication for “pyogenic meningitis”

*3 An additional administration for “pediatrics”

*4 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”

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

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

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

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

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

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

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