Pharmaceuticals and Medical Devices Safety Information

No. 305 September 2013

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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This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information
No. 305 September 2013

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

[Outline of Information]

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

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

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

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

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

Abbreviations

ADRs	Adverse drug reactions
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BP	Bullous pemphigoid
BUN	Blood urea nitrogen
COP	Cryptogenic organizing pneumonia
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
Dsg 1	Desmoglein 1
Dsg 3	Desmoglein 3
EMA	European Medicines Agency
EPPV	Early Post-marketing Phase Vigilance
FDA	Food and Drug Administration
FY	Fiscal year
Hb	Hemoglobin
HES	Hydroxyethylated starch
HPV	Human papilloma virus
Ht	Hematocrit
ICU	Intensive care unit
IU	International unit
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MMI	Methimazole
OTC	Over-the-counter drug
PCR	Polymerase chain reaction
PLT	Platelet
POEM	Pregnancy Outcomes of Exposure to Methimazole
PRAC	Pharmacovigilance Risk Assessment Committee
RBC	Red blood cell count
SP-A	Surfactant protein A
SP-D	Surfactant protein D
SpO_2	Oxygen saturation
TEN	Toxic epidermal necrolysis
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Hydroxyethylated Starch-containing Solutions and Renal Impairment

	Active ingredient	Brand Name (name of company)
Active ingredient Brand Name (name of company)	(1) Hydroxyethylated starch 70000 (2) Hydroxyethylated starch 130000	(1) HESPANDER fluid solution, SALINHES fluid solution 6% (Fresenius Kabi Japan K.K.) (2) Voluven Fluid Solution 6% (Fresenius Kabi Japan K.K.)
Therapeutic Category	Blood substitutes	
Indications	(1) Hemodilution in extracorporeal circulation in patients with excessive bleeding (regardless of the type of disorder) (2) Maintenance of circulating volume	

1. Introduction

Hydroxyethylated starch-containing solutions (HES solutions) are blood substitutes to increase the plasma volume based on colloid osmotic action. In Japan, hydroxyethylated starch 70000 (HES 70/0.5; average molecular weight, 70000 Da) has been available since 1974. In March 2013, hydroxyethylated starch 130000 (HES 130/0.4; average molecular weight, 130000 Da) was approved (not released as of September 2013).

In June 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommended suspending marketing authorization for the HES solutions[4)] based on the results of overseas studies questioning their safety.[1-3)] After the EMA recommendation, measures to ensure the safety of HES solutions have been reviewed in the countries where the solutions are available. After reviewing the adverse reactions to the HES solutions reported in Japan and overseas, regulatory actions of foreign authorities, and relevant literature, MHLW instructed the marketing authorization holder (MAH) to revise the Precautions section of the package insert in September 2013. Details of the MHLW instruction are described below.

2. Overseas situation

In the clinical studies[1-3)] that served as the basis for the PRAC recommendation to suspend marketing authorizations for HES solutions, the risk of renal replacement therapy and death significantly increased in patients with severe sepsis and patients admitted to the intensive care unit (ICU) who treated with the HES solutions including HES 130/0.4 compared with those treated with Ringer's acetate or normal saline. A few meta-analysis studies[5-6)] published after the approval for HES 130/0.4 in Japan supported the results of the clinical studies. The US Food and Drug Administration (FDA) added a precaution against the use of the HES solution in patients with sepsis or renal impairment in the Boxed Warning section of the package insert in June 2013 based on the clinical studies.[7)] HES 70/0.5 is sold only in Japan and was not used in the clinical studies that served as the basis for the PRAC recommendation to suspend marketing authorizations for this solutions.

Several cases of serious renal impairment for which a causality to the HES 130/0.4 could not be ruled out were reported overseas.

3. Situation in Japan

(1) HES 70/0.5

As of September 2013, HES 70/0.5 is the only HES product available in Japan. Since the approved indications of HES 70/0.5 solution are "excessive bleeding regardless of type of disorder" and "hemodilution in extracorporeal circulation," use of the solution for the treatment of relative hypovolemia without hemorrhage in critically ill patients including patients with severe sepsis is not expected. No renal impairment or death has been reported in association with the use of HES 70/0.5 for the treatment of relative hypovolemia in critically ill patients including patients with severe sepsis. Based on the results of the overseas clinical studies, the MAH issued a request for proper use of the product in July 2013 for healthcare professionals to carefully check the indications in the package insert and not to use HES 70/0.5 for the treatment of relative hypovolemia in critically ill patients including patients with severe sepsis.[8)]

(2) HES 130/0.4

Unlike HES 70/0.5, HES 130/0.4 solution is indicated for "maintenance of circulation volume." Although HES 130/0.4 solution has yet to become available in Japan, its use for the treatment of relative hypovolemia in critically ill patients including patients with severe sepsis is expected. The approval review of HES 130/0.4 solution was completed before the announcement of the PRAC recommendation to suspend marketing authorizations for the solutions. The overseas studies that served as the basis for the PRAC recommendation were evaluated in the process, and no safety issue associated with renal function was identified in the study in Japanese patients who underwent elective surgeries. The results of the overseas clinical studies were included in the Important Precautions section and the Other Precautions section of the HES 130/0.4 solution package insert at the time of regulatory approval.

4. Review results and safety measures

After the PRAC recommendation to suspend marketing authorizations for HES solutions, the PMDA examined the necessary safety measures to be taken in Japan based on the overseas clinical studies, relevant literatures including the meta-analyses, cases of product-associated renal impairment reported in Japan and overseas, the clinical significance of the product as a plasma substitute and other evidence.

As a result, PMDA considered appropriate to keep the access to HES 130/0.4 for the treatment of relative hypovolemia in critically ill patients including patients with severe sepsis for cases when other treatments are not suitable, and decided to include caution that the condition of the patient may be aggravated and the product should be used only when the potential benefits outweigh the risks in the new Warning section and add renal impairment in the Clinically significant adverse reactions section in the package insert.

On the other hand, the new Precautions of Indications section was considered appropriate to additionally alert for HES 70/0.5 solution since its use for the treatment of relative hypovolemia in critically ill patients including patients with severe sepsis is not expected based on the approved indications.

Based on the PMDA's review, MHLW instructed MAH to revise the Precautions section on September 17, 2013. The current package insert includes precautions against severe sepsis as shown in the table below. Healthcare professionals are encouraged to ensure safety through promotion of proper use of HES solutions.

■ The package insert of hydroxyethylated starch 70000 (as of September 2013) -Warnings and Precautions about the treatment of patients with severe sepsis

Precautions of Indications	HES 70000 should not be used for the treatment of relative hypovolaemia in critically ill patients including patients with severe sepsis. (See "Other Precautions.")
Clinically significant adverse reactions (similar drug)	**Renal impairment**: Renal impairment including acute renal failure has been reported in patients treated with other HES-containing solutions with a different molecular weights and degrees of substitution. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.
Other Precautions	The overseas clinical studies reported that patients with severe sepsis treated with the HES solution[Note)] had a higher risk of mortality and kidney injury requiring renal replacement therapy at Day 90 than those receiving Ringer's acetate. In patients admitted to the ICU including those affected with sepsis treated with the HES solution, they did not have a higher risk of death by Day 90 but more patients were required renal replacement therapy than those receiving normal saline. (See "Precautions of Indications.") An overseas clinical study in adult patients reported that patients treated with the HES solution[Note)] had a higher risk of postoperative haemorrhage requiring blood transfusion and additional surgery due to haemorrhage than patients treated with albumin for fluid replacement during cardiac surgery using a heart-lung machine. Note) A HES solution with different molecular weight and degree of substitution from this drug

■ The package insert of hydroxyethylated starch 130000 (as of September 2013) -Warnings and Precautions about the treatment of patients with severe sepsis

Warnings	WARNING If HES 130000 is used for the treatment of relative hypovolaemia in critically ill patients including patients with severe sepsis, the condition of the patients may be aggravated. HES 130000 should therefore be used only if the potential benefits outweigh the risks. (See "Other Precautions.")
Important Precautions	Renal impairment including acute renal failure may occur and renal replacement therapy may be required. Renal function should be monitored periodically.
Clinically significant adverse reactions	**Renal impairment**: Renal impairment including acute renal failure may occur and renal replacement therapy may be required. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.
Other Precautions	The overseas clinical studies reported that patients with severe sepsis treated with the HES solution had a higher risk of mortality and kidney injury requiring renal replacement therapy at Day 90 than those receiving Ringer's acetate. In patients admitted to the ICU including those affected with sepsis treated with the HES solution, they did not have a higher risk of death by Day 90 but more patients were required renal replacement therapy than those receiving normal saline. (See "Warnings.") An overseas clinical study in adult patients reported that patients treated with the HES solution had a higher risk of postoperative haemorrhage requiring blood transfusion and additional surgery due to haemorrhage than patients treated with albumin for fluid replacement during cardiac surgery using a heart-lung machine.

<References>

1) Perner, A. et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012 ;367(2): 124-134.
2) Brunkhorst, F.M. et al. Intensive insulin therapy and pentastarch resuscitation in sever sepsis. N Engl J Med,2008 ; 358(2): 125-139.
3) Myburgh, J.A. et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012 ; 367(20): 1901-1911.
4) European Medical Agency: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001814. jsp&mid=WC0b01ac058004d5c1
5) Zarychanski, R. et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation. JAMA 2013 ; 309(7): 678-724.
6) Perel, P. et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2013 ; Issue 2.
7) U.S. Food and Drug Administration: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm
8) http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201307_2.pdf (only available in Japanese language)

2

Project of Japan Drug Information Institute in Pregnancy

1. Project of the Japan Drug Information Institute in Pregnancy

The MHLW established the Japan Drug Information Institute in Pregnancy (JDIIP) at the National Center for Child Health and Development in October 2005 to provide consultation services to pregnant women and women who wish to become pregnant based on the latest scientific evidence. The ongoing survey project introduced in the Pharmaceuticals and Medical Devices Safety Information No. 268 and 279 evaluates the pregnancy outcome in the consultation clients to establish new evidence.

- JDIIP website
  http://www.ncchd.go.jp/kusuri/index.html
- Pharmaceuticals and Medical Devices Safety Information No. 268
  http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-268.pdf
- Pharmaceuticals and Medical Devices Safety Information No. 279
  http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-279.pdf

2. Current status

(1) Consultation

The project provides consultation services for pregnant women who are concerned about the drug influence on the fetus or those who wish to become pregnant. Those women can receive the advice at the Institute or cooperating hospitals or through their physicians as well as by telephone consultation services at the Institute. We had a total of 2,386 clients seeking consultation in fiscal year (FY) 2012.

The Institute also provides information concerning drug use while breastfeeding. The importance of breastfeeding and how the risk of drug use should be viewed are described, and lists of "Drugs that can be used safely during breastfeeding" and "Drugs unsuitable for treating breastfeeding mothers" are posted on the Institute website. The lists were created based on the latest medical studies reported in Japan and overseas.

- Drugs and breastfeeding
  http://www.ncchd.go.jp/kusuri/lactation/index.html

(2) Survey of antirheumatics and pregnancy

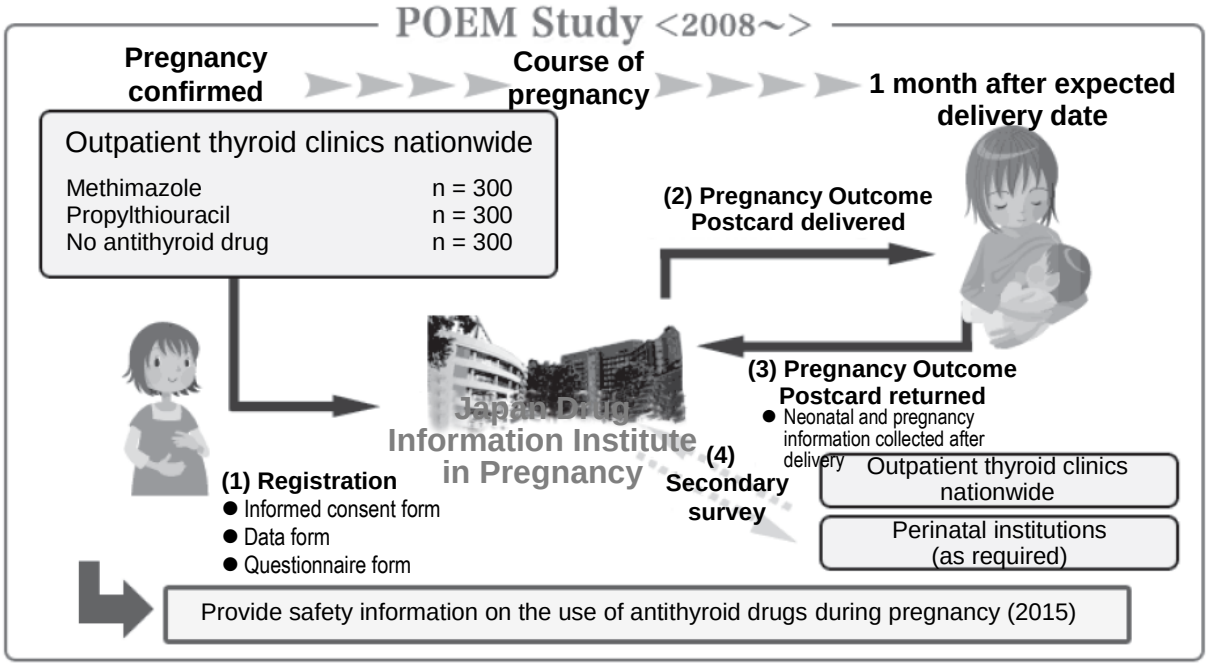
The newborn (pregnancy outcome) survey has been conducted based on the postpartum information provided by the consultation clients as part of the survey project. A new survey on registered pregnant women on antirheumatics (pregnancy outcome survey) has been conducted since June 2012. The survey aims to efficiently collect and evaluate the data on the effect of antirheumatics used during pregnancy on newborns in order to promote appropriate use of antirheumatics in pregnant women. The data of the survey are based on the information on prenatal medications and conditions of newborns provided by the mothers. The consultation services are also provided to survey participants who are concerned about using drugs during pregnancy and breastfeeding.

(3) Study of antithyroid drugs and pregnancy

In January 2008, the prospective Pregnancy Outcomes of Exposure to Methimazole (POEM) Study was started by the JDIIP and thyroid specialists at hospitals nationwide with the cooperation of

pregnant women. The POEM Study intends to see whether the frequency of methimazole (MMI)-induced malformations (congenital anomalies suspected of being associated with the exposure to MMI) increases when the expecting mother is exposed to MMI during early pregnancy. The 2011 interim analysis strongly suggested a close association between continuous use of MMI in early pregnancy and MMI-induced malformations. Available information on the safety of antithyroid drug use during pregnancy in both mothers and fetuses is still not enough. The JDIIP has been conducting the POEM Study in order to establish reliable evidence as soon as possible.

- POEM Study Interim Report
  http://www.ncchd.go.jp/kusuri/news/images/report_2011111.pdf (only available in Japanese language)



(Source: Japan Drug Information Institution in Pregnancy website)

3. Request to healthcare professionals

Healthcare professionals are encouraged to introduce the Japan Drug Information Institution in Pregnancy's consultation services to pregnant women who are concerned about the effects of drugs they have used and also to inform about the antirheumatic survey to those women who are using antirheumatics. Thyroid specialists are welcome to participate in the POEM Study.

- Consultation services and procedure
  http://www.ncchd.go.jp/kusuri/process/index.html (only available in Japanese language)
- Antirheumatic survey
  http://www.ncchd.go.jp/kusuri/news/ra.html (only available in Japanese language)
- POEM Study
  http://www.ncchd.go.jp/kusuri/news/poemstudy1.html (only available in Japanese language)

4. Cooperating hospitals

The system for consultation services and prompt information collection of the JDIIP was strengthened in FY 2013, by getting the cooperation of 4 hospitals newly joined, in order to enhance the accessibility. The 27 cooperating hospitals are listed below:

	Name of medical institution	Contact information, reception hours, etc.
1	Japan Drug Information Institute in Pregnancy	2-10-1 Okura, Setagaya-ku, Tokyo 157-8535 in National Center for Child Health and Development (NCCHD) TEL: (+81)-3-5494-7845 FAX: (+81)-3-3415-0914 Reception hours: 10:00 –12:00, 13:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.ncchd.go.jp/kusuri/index.html
Cooperating hospitals (◎: Joined since 2013)		
2	Hokkaido University Hospital	Kita 14, Nishi 5, Kita-ku, Sapporo-city, Hokkaido 060-8648 TEL: (+81)-11-716-1161 (Extension 7723 or PHS 82943) FAX: (+81)-11-706-7616 Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
3	Iwate Medical University Hospital	19-1 Uchimaru, Morioka-city, Iwate 020-8505 TEL: (+81)-19-624-5263 (Pregnancy and drugs counseling desk: Direct call) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
4 ◎	Tohoku University Hospital	1-1 Seiryo-machi, Aoba-ku, Sendai-city, Miyagi 980-8574 TEL: (+81)-22-717-7000 (Hospital's main switchboard number) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.hosp.tohoku.ac.jp/
5	Tsukuba University Hospital	2-1-1 Amakubo, Tsukuba, Ibaraki 305-8576 TEL: (+81)-29-896-7171 FAX: (+81)-29-896-7170 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
6	Maebashi Red Cross Hospital	3-21-36 Asahi-cho, Maebashi, Gunma 371-0014 TEL: (+81)-27-224-4585 (Division of Pharmacy: Extension 7709) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.maebashi.jrc.or.jp/
7	Saitama Medical University Hospital	38 Morohongo Moroyama-machi, Iruma-gun, Saitama 350-0495 TEL: (+81)-49-276-1297 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours: 15:00 – 17:00 (Monday to Saturday, excluding national holidays)
8	Chiba University Hospital	1-8-1 Inohana, Chuo-ku, Chiba-city, Chiba 260-8677 TEL: (+81)-43-226-2628 (Drug Information, Division of Pharmacy) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)

9	Toranomon Hospital	2-2-2 Toranomon, Minato-ku, Tokyo 105-8470 TEL: (+81)-3-3588-1111 (Extension 3410) FAX: (+81)-3-3505-1764 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
10	St. Luke's International Hospital	9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560 TEL: (+81)-3-5550-2412 FAX: (+81)-3-5550-2563 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
11	Yokohama City University Hospital	3-9 Fukuura, Kanazawa-ku, Yokohama-city, Kanagawa 236-0004 TEL: (+81)-45-787-2800 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.fukuhp.yokohama-cu.ac.jp/
12	Niigata University Medical & Dental Hospital	1-754 Asahimachi-dori, Chuo-ku, Niigata-city, Niigata 951-8520 TEL: (+81)-25-227-2895 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-25-227-2791 Reception hours: 13:30 – 16:00 (Monday to Friday, excluding national holidays)
13	Shinshu University Hospital	3-1-1 Asahi, Matsumoto-city, Nagano 390-8621 TEL: (+81)-263-37-3022 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-263-37-3072 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
14	National Hospital Organization Kanazawa Medical Center	1-1 Shimoishibiki-machi,Kanazawa-city, Ishikawa 920-8650 TEL: (+81)-76-262-4161 Reception hours: 9:00 – 16:30 (Monday to Friday, excluding national holidays) URL: http://www.kanazawa-hosp.jp/pv/preg.htm
15	National Hospital Organization Nagara Medical Center	1300-7 Nagara, Gifu-city, Gifu 502-8558 TEL: (+81)-58-232-7755 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-58-295-0077 Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays)
16	Japanese Red Cross Nagoya Daiichi Hospital	3-35 Michishita-cho, Nakamura-ku, Nagoya-city, Aichi 453-8511 TEL: (+81)-52-481-5111 (Division of Pharmacy: Extension 38167) FAX: (+81)-52-482-7733 Reception hours: 13:00 – 16:00 (Monday to Friday, excluding national holidays)

17	University Hospital, Kyoto Prefectural University of Medicine	465 Kajii-cho, Hirokoji agaru, Kawaramachi-dori, Kamigyo-ku, Kyoto-City, Kyoto 602-8566 TEL: (+81)-75-251-5862 (Drug Information, Division of Pharmacy) FAX: (+81)-75-251-5859 (same as above): Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
18	Osaka Medical Center and Research Institute for Maternal and Child Health	840 Murodo-cho, Izumi-city, Osaka 594-1101 TEL: (+81)-725-56-5537 (Outpatient department for pregnancy and drugs) Reception hours: 10:00 – 12:00, 14:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.mch.pref.osaka.jp/hospital/department/pharmacy/pharmacy03.html
19	Kobe University Hospital	7-5-2 Kusunoki-cho, Chuo-ku, Kobe-city, Hyogo 650-0017 TEL: (+81)-78-382-5111 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours:13:00 – 17:00 (Monday to Friday, excluding national holidays)
20	Nara Medical University Hospital	840 Shijo-cho, Kashihara-city, Nara 634-8522 TEL: (+81)-744-22-3051 (Division of Pharmacy: Extension 3565) FAX: (+81)-744-29-8027 Reception hours: 8:30 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.naramed-u.ac.jp/~gyne/kusuri.html
21 ◎	National Hospital Organization Okayama Medical Center	1711-1 Tamasu, Kita-ku, Okayama-city, Okayama 701-1192 TEL: (+81)-86-294-9556 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-86-294-9557 Reception hours: 8:30 – 18:00 (Monday to Friday, excluding national holidays) URL: http://okayamamc.jp/04_bumon/04-04_bumon/04-04_03-02yakuzai.html
22	Hiroshima University Hospital	1-2-3 Kasumi, Minami-ku, Hiroshima-city, Hiroshima 734-8551 TEL: (+81)-82-257-5079 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
23	National Hospital Organization Shikoku Medical Center for Children and Adults	2-1-1 Senyu-cho, Zentsuji-city, Kagawa 765-8507 TEL: (+81)-877-62-1000 FAX: (+81)-877-62-6311 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)

24 ◎	Tokushima University Hospital	2-50-1 Kuramoto-cho, Tokushima-city, Tokushima 770-8503 TEL: (+81)-70-6586-0831 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
25	Kyushu University Hospital	3-1-1 Maidashi, Higashi-ku, Fukuoka-city, Fukuoka 812-8582 TEL: (+81)-92-642-5900 Reception hours: 14:00 – 17:00 (Monday to Friday, excluding national holidays)
26	Kagoshima City Hospital	20-17 Kajiya-cho, Kagoshima-city, Kagoshima 892-8580 TEL: (+81)-99-224-2101 (Pharmacy department: Extension 2603) (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-99-224-9916 Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays)
27 ◎	Okinawa Chubu Hospital	281 Miyazato, Uruma-city, Okinawa 904-2293 TEL: (+81)-98-973-4111 (Please ask for "Outpatient service for pregnancy and drugs") Reception hours: 13:00 – 16:00 (Tuesday, Thursday, and Friday, excluding national holidays)

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated August 6, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Alogliptin Benzoate-containing Products

[1] Alogliptin Benzoate

Brand Name (name of company)	NESINA Tablets 6.25 mg, 12.5 mg, 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. Thiazolidinedione 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)

Careful Administration	Patients with a medical history of abdominal operation or intestinal obstruction
Adverse Reactions (clinically significant adverse reactions)	**Interstitial pneumonia**: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, or abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids 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 3 years (from initial marketing to June 2013) • Interstitial pneumonia-associated cases: 4 cases (no fatal cases) • Intestinal obstruction-associated cases: 4 cases (no fatal cases) The number of patients using this drug per year estimated by MAHs: Approximately 540,000 (April 2012 to March 2013) Launched in Japan: June 2010

[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)

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

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 9 months (from initial marketing to June 2013)

- Intestinal obstruction-associated cases: 0 cases

The number of patients using this drug per year estimated by MAHs: Approximately 68,000 (April 2012 to March 2013)

Launched in Japan: September 2011

<Alogliptin Benzoate> Case Summary

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 (diabetic retinopathy, diabetic nephropathy [stage 2], hypertension, dyslipidaemia)	25 mg for 490 days	**Interstitial pneumonia** Smoking history: 40 years Day 1 of administration: The patient started receiving alogliptin benzoate. 1 year and 3 months after administration (day of onset): Cough developed and the clinical course was monitored with an over-the-counter (OTC) drug, but no improvement was seen. 40 days after onset: Chest X-ray showed infiltrative opacities in the bilateral lower lung fields and elevations of white blood cell count ($8.9 \times 10^3/\mu L$) and C-reactive protein (CRP) (5.84 mg/dL) were found. Administration of levofloxacin (500 mg/day) was started based on the diagnosis of pneumonia. 43 days after onset (day of discontinuation): Because dyspnoea and general malaise were severe and oxygen saturation (SpO_2) was 94% (room air), administration of oxygen was started. Administration of levofloxacin was discontinued, and the patient was admitted to a hospital for detailed examinations. Krebs von den Lunge-6 (KL-6) was 2,275 U/mL, chest computed tomography (CT) showed bandlike and macular opacities in the bilateral middle and lower lung fields. Interstitial pneumonia (cryptogenic organising pneumonia, COP) was

				suspected. Administration of alogliptin benzoate was discontinued, and drip infusion of ceftriaxone (2 g/day) was started. 3 days after discontinuation: Administration of alogliptin benzoate was resumed. Day 2 of re-administration (day of discontinuation of re-administration): The patient was considered to have recovered based on chest CT, symptoms, and improvement of SpO_2. As a causal relationship with alogliptin benzoate could not be ruled out, administration of alogliptin benzoate was discontinued after administration the preceding day. 6 days after discontinuation of re-administration: The cytology of bronchoalveolar lavage fluid showed Class II, and the patient was diagnosed as having interstitial pneumonia by transbronchial lung biopsy. 8 days after discontinuation of re-administration: Administration of prednisolone (30 mg/day) was started. Starting 1 week after that, the dose of prednisolone was gradually reduced. The patient recovered and was discharged from hospital 19 days after the start of administration of prednisolone.
	Concomitant medications: voglibose, valsartan/amlodipine besilate combination tablets, rosuvastatin calcium, digoxin, tipepidine hibenzate, pronase, tranexamic acid			

Laboratory Examination

Laboratory parameter (unit)	Approx. 1 year after administration	40 days after onset	43 days after onset (day of discontinuation)	3 days after discontinu-ation	11 days after discontinuation of re-administration	53 days after discontinuation of re-administration	88 days after discontinuation of re-administration
WBC (10^3/μL)	4.5	8.9	6.6	6.8	-	-	-
CRP (mg/dL)	0.04	5.84	4.18	3.26	-	-	-
KL-6 (U/mL)	-	-	2,275	-	2,344	2,661	2,867
SP-D (ng/mL)	-	-	532.4	-	370.4	400.4	477.4
SP-A (ng/mL)	-	-	138.1	-	75.1	87.7	96.6

2 Valsartan-containing Products

[1] Valsartan

Brand Name (name of company)	DIOVAN Tablets 20 mg, 40 mg, 80 mg, 160 mg, DIOVAN OD Tablets 20 mg, 40 mg, 80 mg, 160 mg (Novartis Pharma K.K.)
Therapeutic Category	Antihypertensives
Indications	Hypertension

PRECAUTIONS (underlined parts are revised)

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.

Pemphigus, pemphigoid: Pemphigus and pemphigoid may occur. If blisters, erosion, and other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate measures such as discontinuation of administration 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 and 2 months (from April 2010 to June 2013)

- Toxic epidermal necrolysis: 0 cases
- Oculomucocutaneous syndrome: 1 case (no fatal cases)
- Erythema multiforme: 1 case (no fatal cases)
- Pemphigus: 0 cases
- Pemphigoid: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 3.6 million (January 2012 to December 2012)
Launched in Japan: November 2000
(Note) The drugs are designated as those requiring the preparation of Drug guides for patients.

[2] Valsartan/Hydrochlorothiazide

Brand Name (name of company)	Co-DIO combination Tablets MD, EX (Novartis Pharma K.K.)
Therapeutic Category	Antihypertensives
Indications	Hypertension

PRECAUTIONS (underlined parts are revised)

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.

Pemphigus, pemphigoid: Pemphigus and pemphigoid may occur. If blisters, erosion, and other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate measures such as discontinuation of administration 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 and 2 months (from April 2010 to June 2013)

- Oculomucocutaneous syndrome: 0 cases
- Erythema multiforme: 0 cases
- Pemphigus: 0 cases
- Pemphigoid: 0 cases

The number of patients using this drug per year estimated by MAHs:
Approximately 310,000 (January 2012 to December 2012)
Launched in Japan: March 2009

[3] Valsartan/Amlodipine Besilate

Brand Name (name of company)	EXFORGE Combination Tablets (Novartis Pharma K.K.)
Therapeutic Category	Antihypertensives
Indications	Hypertension

PRECAUTIONS (underlined parts are revised)

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.

Pemphigus, pemphigoid: Pemphigus and pemphigoid may occur. If blisters, erosion, and other signs and symptoms are observed, patients should be referred to dermatologist, and appropriate measures such as discontinuation of administration 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 and 2 months (from initial marketing to June 2013)

- Toxic epidermal necrolysis: 0 cases
- Oculomucocutaneous syndrome: 0 cases
- Erythema multiforme: 1 case (no fatal cases)
- Pemphigus: 0 cases
- Pemphigoid: 0 cases

The number of patients using this drug per year estimated by MAHs: Approximately 620,000 (January 2012 to December 2012)

Launched in Japan: April 2010

(Note) The drugs are designated as those requiring the preparation of Drug guides for patients.

<Valsartan> Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Hypertension (none)	80 mg for 2,568 days ↓ (discontinuation) ↓ 80 mg for 25 days	**Pemphigoid** Day 1 of administration: The patient started receiving valsartan/amlodipine besilate at 80 mg/day. Approximately Day 2,500 of administration: Erythema and blisters occurred on the patient's hands and feet (tense bulla). Day 2,530 of administration: The patient visited Hospital A and received bacitracin/fradiomycin sulfate, but no improvement was seen. Day 2,550 of administration: The patient visited Hospital B, and hydroxyzine hydrochloride and betamethasone dipropionate ointment were prescribed. Those drugs were used but no improvement was seen. Blisters also appeared on the face. Day 2,568 of administration (day of discontinuation): Large and small blisters appeared on the face and limbs (tense blisters). Because skin eruption worsened, the patient visited Hospital C. Administration of valsartan/amlodipine besilate was discontinued and valsartan/amlodipine besilate was changed to amlodipine besilate. Minocycline hydrochloride and topical steroid were prescribed. Blood sampling and skin biopsy were performed. Anti-Bullous pemphigoid (BP) 180 antibody (+). Histopathology, subepidermal blisters (+). By direct fluorescent

				antibody technique, C3 deposits were noted at the epidermal-dermal junction. 6 days after discontinuation: No nascent blisters were found, and only erosion remained. Fluocinonide cream, hydrocortisone/mixed killed bacterial suspension ointment, methylrosanilinium chloride/zinc oxide ointment, heparinoid ointment, minocycline hydrochloride, and nicotinamide powder were added. 10 days after discontinuation: Drug lymphocyte stimulation test (DLST) was performed on the day of discontinuation and the test result was positive for valsartan/amlodipine besilate. Administration of minocycline hydrochloride and nicotinamide was discontinued. Topical steroid and topical therapy with mixed killed bacterial preparation were continued. Skin eruption disappeared with no relapse and exacerbation. Histological findings were consistent with pemphigoid. Outcome, recovered. 48 days after discontinuation (Day 1 of re-administration): A trial of oral administration of valsartan/amlodipine besilate 80 mg/day was started. Day 2 of re-administration: Skin eruption was not found. Day 9 of re-administration: Erythema appeared around the mouth to lower jaw from 2 or 3 days ago. Day 25 of re-administration (day of discontinuation of re-administration): Tense blisters relapsed on the side of the right forearm flexor. Administration of valsartan/amlodipine besilate was discontinued. 7 days after discontinuation of re-administration: The patient recovered with no relapse. 84 days after discontinuation of re-administration: Relapse of symptom was not found.
	Concomitant medication: ibudilast			

Laboratory Examination

Laboratory parameter	Day of discontinuation	Day of discontinuation of readministration	33 days after discontinuation of readministration
CRP (mg/dL)	1.22	0.03	0.02
RBC ($\times 10^4$/mm^3)	435	455	470
Hemoglobin (g/dL)	12.9	13.6	13.7
Hematocrit (%)	38.3	40.3	41.6
WBC (/mm^3)	6,900	3,800	3,900
Neutrophils (%)	68.3	51.7	46.0
Eosinophils (%)	8.7	5.0	5.1
Basophils (%)	0.1	0.8	1.0
Monocytes (%)	4.3	4.5	4.1
Lymphocytes (%)	18.6	38.0	43.8

Laboratory parameter	Day of discontinuation	Day of discontinuation of readministration	33 days after discontinuation of readministration
AST (IU/L)	33	19	20
ALT (IU/L)	79	15	19
Al-P (IU/L)	360	248	222
LDH (IU/L)	237	212	203
Total bilirubin (mg/dL)	7.0	7.2	6.9
BUN (mg/dL)	20	16	17
Creatinine (mg/dL)	0.66	0.76	0.66
Blood glucose (mg/dL)	114	-	-
Serum potassium (mEq/L)	3.8	4.0	4.1
Serum sodium	146	143	145

PLT (× 10^4/mm^3)	21.4	18.5	16.9

(mEq/L)			
Anti-BP180 antibody	103	46	37
Desmoglein 1 (Dsg1)	Negative	Negative	Negative
Desmoglein 3 (Dsg3)	Negative	Negative	Negative

3 Vildagliptin

Brand Name (name of company)	Equa Tablets 50 mg (Novartis Pharma K.K)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, or abnormal chest sound (crepitations), and other signs and symptoms are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids 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 and 2 months (from initial marketing to June 2013)

- Interstitial pneumonia-associated cases: 5 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 360,000 (January 2012 to December 2012)
Launched in Japan: April 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Diabetes mellitus (angina pectoris, hypertension, hyperlipidaemia)	100 mg for 113 days	**Interstitial pneumonia** Day 1 of administration: The patient started receiving vildagliptin at 100 mg/day. Day 113 of administration (day of discontinuation): The patient visited the emergency department of this hospital due to dyspnoea. Based on blood sampling, X-ray, and CT, the patient's condition was diagnosed as interstitial pneumonia. The patient was urgently admitted to the hospital on the same day due to hypoxaemia. Steroid pulse therapy was started. 2 days after discontinuation: Steroid pulse therapy was terminated. 3 days after discontinuation: Administration of prednisolone 30 mg was started. 19 days after discontinuation: The patient had a good response to steroid, and the interstitial opacities in the lungs gradually improved. The dose of steroid was reduced, and the patient was discharged from hospital.

				DLST test was performed during hospitalization and the result was positive for vildagliptin and negative for ezetimibe .
	Concomitant medications: aspirin, ezetimibe, bisoprolol fumarate, telmisartan, isosorbide mononitrate, nifedipine, cilostazol, glimepiride, fenofibrate			

Laboratory Examination

Laboratory parameter	Day 64 of administration	Day 113 of administration (day of discontinuation)	9 days after discontinuation	17 days after discontinuation	30 days after discontinuation
RBC ($\times 10^4$/mm^3)	449	446	439	453	426
Hemoglobin (g/dL)	13.8	13.4	13.1	13.6	12.9
Hematocrit (%)	41.3	39.2	34.2	40.3	38.9
WBC (/mm^3)	6,400	8,900	9,400	11,700	8,500
Neutrophils (%)	62.9	84.9	77.8	81.6	79.2
Eosinophils (%)	10.0	2.2	1.3	0.5	1.4
Basophils (%)	0.6	0.1	0.2	0.2	6.2
Monocytes (%)	6.8	5.7	5.9	4.7	4.1
Lymphocytes (%)	19.7	7.1	14.8	13.0	15.1
PLT ($\times 10^4$/mm^3)	22.1	32.6	34.4	26.9	21.6
AST (GOT) (IU/L)	21	30	16	17	19
ALT (GPT) (IU/L)	22	13	23	23	30
γ-GTP (IU/L)	29	22	32	41	40
LDH (IU/L)	154	526	232	231	237
BUN (mg/dL)	17	11	23	20	26
Creatinine (mg/dL)	1.34	1.14	1.24	1.22	1.03
KL-6 (U/mL)	-	1,626	1,834	1,805	1,352
SP-D (ng/mL)	-	-	86.3	41.0	17.2

4 Orengedokuto, Kamishoyosan, Shin'iseihaito

[1] Orengedokuto (for ethical use)

Brand Name (name of company)	TSUMURA Orengedokuto Extract Granules for Ethical Use (Tsumura & Co.) and the others
Therapeutic Category	Kampo product
Indications	The following symptoms of those patients with a comparatively strong constitution, a touch of hot flushes, and a tendency to irritability: Haemoptysis, haematemesis, melena, cerebral haemorrhage, hypertension, palpitation, neurosis, cutaneous pruritus, gastritis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Mesenteric phlebosclerosis: Mesenteric phlebosclerosis may occur with long-term administration. If abdominal pain, diarrhoea, constipation, and abdominal distension, and other signs and symptoms repeatedly occur or if the patient tests positive for occult blood, administration of this drug should be discontinued. At the same time, examinations such as CT and colonoscopy should be performed, and appropriate measures should be taken. Intestinal resection has been reported in some cases.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 2 months (from April 2010 to June 2013)

- Mesenteric phlebosclerosis-associated cases: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 39,000 (April 2012 to March 2013)
Launched in Japan: October 1986

[2] Kamishoyosan (for ethical use)

Brand Name (name of company)	TSUMURA Kamishoyosan Extract Granules for Ethical Use (Tsumura & Co.) and the others
Therapeutic Category	Kampo product
Indications	The following symptoms of those women with a delicate constitution who are easily fatigued and are apt to have stiffness shoulder, psychoneurotic symptoms including anxiety and sometimes tendency to constipation: Oversensitivity to cold, delicate constitution, menstrual irregularity, dysmenorrhoea, climacteric disturbance, automatic imbalance syndrome peculiar to women resembling climacteric disturbance

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Mesenteric phlebosclerosis: Mesenteric phlebosclerosis may occur with long-term administration. If abdominal pain, diarrhoea, constipation, and abdominal distension, and other signs and symptoms repeatedly occur or if the patient tests positive for occult blood, administration of this drug should be discontinued. At the same time, examinations such as CT and colonoscopy should be performed, and appropriate measures should be taken. Intestinal resection has been reported in some cases.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 2 months (from April 2010 to June 2013)

- Mesenteric phlebosclerosis-associated cases: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 190,000 (April 2012 to March 2013)
Launched in Japan: October 1986

<Kamishoyosan (for ethical use)> Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Depression (hypertension, irritable bowel syndrome, bronchial asthma)	7.5 g Approx. 10 years	**Idiopathic mesenteric phlebosclerosis** 9 years before onset: The patient started receiving kamishoyosan for depression. Day of onset: Due to occurrence of abdominal pain and vomiting, the patient visited a nearby hospital. Based on abdominal X-ray, the patient's condition was diagnosed as intestinal obstruction. The patient visited and was admitted to this hospital (for 9days). After that, the patient was repeatedly admitted to and discharged from the hospital for symptoms of intestinal obstruction. 154 days after onset: The patient was admitted to the hospital with abdominal pain and vomiting (for 8 days). 164 days after onset: The patient was admitted to the hospital with abdominal pain and vomiting (for 10 days). 177 after onset (day of discontinuation): Abdominal pain and vomiting developed in the patient. She

				was admitted to the hospital for detailed examination and treatment. Abdominal X-ray showed reticular calcification in the right flank. Abdominal contrast-enhanced CT showed linear calcification in the intestinal tract wall and the mesentery in cecum to ascending colon. Barium enema examination showed diffuse narrowing in the ascending colon, and thumbprinting in cecum to right transverse colon. (definitive diagnosis: idiopathic mesenteric phlebosclerosis) Administration of kamishoyosan was discontinued. 16 days after discontinuation (day of surgery): Laparoscopic-assisted right hemicolectomy was performed. At the time of surgery: The color of cecum to serous surface of the hepatic flexure was dark purple, and hardening of the intestinal tract and mesentery was found. Histopathologic examination showed deposition of hyaline materials (Congo red stain negative) in the lamina propria to submucosal interstitium. 12 days after surgery: Symptoms improved, and the patient was discharged from hospital. 36 days after surgery: The patient recovered.
	Concomitant medications: fluvoxamine maleate, clotiazepam, bromazepam, lactomin, albumin tannate, mepenzolate bromide, etizolam, pranlukast hydrate, bunazosin hydrochloride, maprotiline hydrochloride, takadiastase/crude drug			

[3] Shin'iseihaito (for ethical use)

Brand Name (name of company)	TSUMURA Shiniseihaito Extract Granules for Ethical Use (Tsumura & Co.) and the others
Therapeutic Category	Kampo product
Indications	Nasal stuffiness, chronic rhinitis, empyema

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Mesenteric phlebosclerosis: Mesenteric phlebosclerosis may occur with long-term administration. If abdominal pain, diarrhoea, constipation, and abdominal distension, and other signs and symptoms repeatedly occur or if the patient tests positive for occult blood, administration of this drug should be discontinued. At the same time, examinations such as CT and colonoscopy should be performed, and appropriate measures should be taken. Intestinal resection has been reported in some cases.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 2 months (from April 2010 to June 2013)

- Mesenteric phlebosclerosis-associated cases: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 21,000 (April 2012 to March 2013)
Launched in Japan: October 1986

<Shin'iseihaito (for ethical use)> Case Summary

No.	Patient		Daily dose/	Adverse reactions
	Sex/	Reason for use		Clinical course and therapeutic measures

	Age	(complications)	Treatment duration	
1	Male 50s	Bronchiectasis, allergic rhinitis (none)	7.5 g Approx. 24 years	**Mesenteric phlebosclerosis** 23 years before onset: The patient started receiving shin'iseihaito for bronchiectasis and allergic rhinitis. Day of onset: Right flank pain and loose stools occurred and did not improve. 3 days after onset: The patient visited this hospital. Body temperature was 37°C, blood pressure was 97/73 mmHg, pulse rate was 92/min. Mild tenderness was noted in the right lower abdomen. Antibiotic and antiflatulent were prescribed. 4 days after onset (day of discontinuation): The right lower abdomen tenderness increased. Abdominal contrast-enhanced CT showed dilatation of cecum to ascending colon, inflammation image, and calcification of mesenteric veins. The patient was admitted to hospital. Treatment was started with fasting, fluid replacement, and cefmetazole sodium 2 g/day. Administration of shin'iseihaito was discontinued. 1 day after discontinuation: Body temperature of 37.9°C, abdominal pain increased and treatment with an analgesic drug was performed. (diagnosis: Mesenteric phlebosclerosis) After that, the symptoms gradually improved. 8 days after discontinuation: Thin rice gruel and liquid meal were started. The result of culture stool was negative. 10 days after discontinuation: The patient took porridge and semi-liquid meal. 12 days after discontinuation: The symptoms improved and the patient was discharged from hospital.
	Concomitant medications: erythromycin stearate, mequitazine, ambroxol hydrochloride, pronase			

Laboratory Examination

	Day 240 of onset	2 days after discontinuation	12 days after discontinuation
RBC (10^4cells/mm^3)	434	417	431
Hb (g/dL)	13.2	12.6	12.9
Ht (%)	40.5	37.8	39.1
PLT (10^4cells/mm^3)	18.0	23.2	29.9
WBC (cells/mm^3)	4,410	9,820	4,300
CRP (mg/dL)	≤0.05	18.94	1.40

4

Revision of Precautions (No. 249)

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 Notification dated August 6, 2013 (excluding those presented in "3. Important Safety Information" of this Bulletin).

1 General anesthetics

Isoflurane

Brand Name	Forane Inhalant Liquid (AbbVie G.K.) and the others
Careful Administration	Patients with heart disease and electrocardiogram abnormal
Adverse Reactions (clinically significant adverse reactions)	**Prolonged QT, ventricular tachycardia (including torsades de pointes), ventricular fibrillation, complete atrioventricular block, cardiac arrest**: Prolonged QT, ventricular tachycardia (including torsades de pointes), ventricular fibrillation, complete atrioventricular block, etc. may occur. Some of these cases resulted in cardiac arrest. If any abnormalities are observed, the dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be taken.

2 General Anesthetic

Desflurane

Brand Name	Suprane Inhalational Anesthetic Solution (Baxter Limited)
Adverse Reactions (clinically significant adverse reactions)	**Laryngospasm**: Laryngospasm may lead to difficulty in ventilation. If any abnormalities are observed, appropriate measures such as continuous positive airway pressure or the use of muscle relaxants should be taken. Cases that laryngospasm occurred particularly in patients using supraglottic airway devices such as laryngeal masks, resulting in difficulty in ventilation were reported. Caution should be exercised.

3 Antiparkinsonian agents

Levodopa
Levodopa/Carbidopa Hydrate
Levodopa/Benserazide Hydrochloride

Brand Name	DOPASOL TABLETS 200 mg (Daiichi Sankyo Company, Limited.), DOPASTON CAPSULES 250 mg, DOPASTON POWDER 98.5%, DOPASTON FOR INTRAVENOUS USE 25 mg, 50 mg (Ohara Pharmaceutical Co., Ltd.) NEODOPASTON COMBINATION TABLETS L100, 250 (Daiichi Sankyo Company, Limited), MENESIT Tablets 100, 250 (MSD K.K.), and the others NEODOPASOL COMBINATION TABLETS (Daiichi Sankyo Company, Limited), EC-DOPARL Tablets (Kyowa Hakko Kirin Co., Ltd.), MADOPAR

	Combination Tablet (Chugai Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Haemolytic anaemia, decreased platelets**: Haemolytic anaemia or decreased platelets may occur. Patients should be carefully monitored through periodic blood test, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

4 Hormones-Miscellaneous

Ganirelix Acetate

Brand Name	GANIREST Subcutaneous 0.25 mg Syringe (MSD K.K)
Important Precautions	The shield of the injection needle for this drug contains natural rubber latex, which may cause allergic 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.

5 Hormones-Miscellaneous

Degarelix Acetate

Brand Name	Gonax 80 mg for Subcutaneous Injection, 120 mg for Subcutaneous Injection (Astellas Pharma Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylaxis**: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

6 Habitual intoxication agents

Cyanamide

Brand Name	CYANAMIDE ORAL SOLUTION 1% "TANABE" (Mitsubishi Tanabe Pharma Corporation)
Adverse Reactions (clinically significant adverse reactions)	**Drug-induced hypersensitivity syndrome**: Rash and pyrexia may occur as the initial symptoms and signs followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, swollen lymph nodes, increased white blood cells, increased eosinocyte, and atypical lymphocytes. Patients should be carefully monitored, and if such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. The reactivation of viruses including Human Herpes virus 6 (HHV-6) frequently occurs. Symptoms and signs such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuation of administration. 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

7 Antidiabetic agents

Linagliptin

Brand Name	Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
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.

8 Miscellaneous metabolism agents-Miscellaneous

Diazoxide

Brand Name	DIAZOXIDE Capsules 25 mg "MSD" (MSD K.K)
Adverse Reactions (clinically significant adverse reactions)	**Pulmonary hypertension**: Pulmonary hypertension may occur. Some cases have been reported in newborns and children. Patients should be carefully monitored, and if any symptoms and signs including dyspnoea, cyanosis, fatigability, syncope, peripheral oedema, and chest pain are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Pediatric use	Pulmonary hypertension may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

9 Antineoplastics-Miscellaneous

Thalidomide

Brand Name	THALED CAPSULE 50, 100 (Fujimoto Pharmaceutical Corporation)
Adverse Reactions (clinically significant adverse reactions)	**Tumour lysis syndrome**: Tumour lysis syndrome may occur. Patients should be carefully monitored checking serum electrolyte levels and renal function test, etc. If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g. administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until they have recovery from such symptoms. **Hepatic dysfunction**: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), bilirubin, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as dose reduction, drug suspension, or discontinuation of administration should be taken.

10 Kampo product

Orengedokuto (OTC)

Brand Name	JPS Orengedokuto Extract Tablet N (JPS Pharmaceutical Co., Ltd.) and the others
Consultation	The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician, a pharmacist, or a registered salesperson for a consultation with this package insert. The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these symptoms and signs. **Mesenteric phlebosclerosis**: Abdominal pain, diarrhoea, constipation, abdominal distension, etc. may occur repeatedly with long-term oral administration.

11 Kampo product

Kamishoyosan (OTC)

Brand Name

Kamishoyosanryo Extract Tablet Kracie (Kracie Pharma, Ltd.) and the others

Consultation

The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician, a pharmacist, or a registered salesperson for a consultation with this package insert.
The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these symptoms.
Mesenteric phlebosclerosis: Abdominal pain, diarrhoea, constipation, abdominal distension, etc. may occur repeatedly with long-term oral administration.

12 Kampo product

Shin'iseihaito (OTC)

Brand Name

Tiknain Tablet (Kobayashi Pharmaceutical Co., Ltd.) and the others

Consultation

The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician, a pharmacist, or a registered salesperson for a consultation with this package insert.
The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these symptoms.
Mesenteric phlebosclerosis: Abdominal pain, diarrhoea, constipation, abdominal distension, etc. may occur repeatedly with long-term oral administration.

13 Over-the-counter drugs (cold medicine)

Products Containing Pseudoephedrine Hydrochloride or Pseudoephedrine Sulfate

Consultation

The following persons should consult a physician, a pharmacist, or a registered salesperson before taking the drug.

Nursing mothers.

Persons who have experienced sleep loss, dizziness, feeling of weakness, tremulousness, or palpitations after taking cold medicine, antitussive/expectorant, oral drug for rhinitis, etc.

Persons who have been diagnosed with any of the following:

Thyroid dysfunction*, diabetes mellitus*, heart disease*, hypertension*, liver disease*, kidney disease, gastric/duodenal ulcer*, glaucoma*
[*: Described based on the Guidelines for package inserts for over-the-counter drugs depending on the composition of the ingredients.]

The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician, a pharmacist, or a registered salesperson for a consultation with this package insert.

Psychoneurologic: Dizziness, convulsion

14

Over-the-counter drugs (oral medications for rhinitis)

Products Containing Pseudoephedrine Hydrochloride or Pseudoephedrine Sulfate

Consultation

The following persons should consult a physician, a pharmacist, or a registered salesperson before taking the drug.

Nursing mothers.

Persons who have experienced sleep loss, dizziness, feeling of weakness, tremulousness, or palpitations due to cold medicine, antitussive/expectorant, oral drugs for rhinitis, etc.

Persons who have been diagnosed with any of the following:

Glaucoma, diabetes mellitus*, thyroid dysfunction*, heart disease*, hypertension*, kidney disease, liver disease*

[*: Described based on the Guidelines for package inserts for over-the-counter drugs depending on the composition of the ingredients.]

The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician, a pharmacist, or a registered salesperson for a consultation with this package insert.

Psychoneurologic: Dizziness, sleep loss, nervousness, headache*, convulsion

[*: Described based on the Guidelines for package inserts for over-the-counter drugs depending on the composition of the ingredients.]

5

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of September 1, 2013)

◎: Newly-posted products, or products changed from the last Bulletin

	Nonproprietary name / Brand name	Name of the marketing authorization holder	Date of EPPV initiate
◎	Ibandronate Sodium Hydrate Bonviva IV Injection 1 mg Syringe	Chugai Pharmaceutical Co., Ltd.	August 29, 2013
◎	Levetiracetam E Keppra Dry syrup 50%	UCB Japan Co. Ltd	August 29, 2013
◎	Abatacept (Genetical Recombination) ORENCIA SYRINGE FOR S.C. INJECTION 125 mg/1 mL	Bristol-Myers K.K.	August 27, 2013
◎	Hemin Normosang Infusion 250 mg	Orphan Pacific, Inc.	August 23, 2013
◎	Palivizumab (Genetical Recombination) Synagis for Intramuscular Injection 50 mg, 100 mg*1 Synagis Intramuscular Solution 50 mg, 100 mg*1	AbbVie G.K.	August 20, 2013
◎	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*2	Novartis Pharma K.K.	August 20, 2013
	Tofacitinib Citrate XELJANZ Tablets 5 mg	Pfizer Japan Inc.	July 30, 2013
	Metreleptin (Genetical Recombination) Metreleptin for Subcutaneous Injection 11.25 mg "SHIONOGI"	Shionogi & Co., Ltd.	July 25, 2013
	Saxagliptin Hydrate ONGLYZA Tablets 2.5 mg, 5 mg	Kyowa Hakko Kirin Co., Ltd.	July 9, 2013
	Oxybutynin Hydrochloride NEOXY TAPE 73.5 mg	Hisamitsu Pharmaceutical Co., Inc.	June 27, 2013
	Clofarabine Evoltra 20 mg I.V. Infusion	Sanofi K.K.	June 21, 2013
	Lidocaine Penles Tape 18 mg*3	Nitto Denko Corporation	June 14, 2013
	Tacrolimus Hydrate Prograf Capsules 0.5 mg, 1 mg*4	Astellas Pharma Inc.	June 14, 2013

	Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*5	Chugai Pharmaceutical Co., Ltd.	June 14, 2013
	Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg*6	Nippon Shinyaku Co., Ltd.	June 14, 2013
	Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%*7	Otsuka Pharmaceutical Co., Ltd.	June 14, 2013
	Dexmedetomidine Hydrochloride (1) Precedex Intravenous Solution 200 μg "Hospira"*8 (2) PRECEDEX Intravenous Solution 200 μg "Maruishi"*8	(1) Hospira Japan Co., Ltd. (2) Maruishi Pharmaceutical Co., Ltd.	June 14, 2013
	Denosumab (Genetical Recombination) PRALIA SUBCUTANEOUS INJECTION 60 mg SYRINGE	Daiichi Sankyo Company, Limited	June 11, 2013
	Acotiamide Hydrochloride Hydrate Acofide Tablets 100 mg	Zeria Pharmaceutical Co., Ltd.	June 6, 2013
	Levetiracetam E Keppra Tablets 250 mg, 500 mg*9	UCB Japan Co. Ltd	May 31, 2013
	Istradefylline NOURIAST Tablets 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 30, 2013
	Rufinamide Inovelon Tablets 100 mg, 200 mg	Eisai Co., Ltd.	May 29, 2013
	Acamprosate Calcium Regtect Tablets 333 mg	Nippon Shinyaku Co., Ltd.	May 27, 2013
	Ofatumumab (Genetical Recombination) Arzerra for I.V. infusion 100 mg, 1000 mg	GlaxoSmithKline K.K.	May 24, 2013
	Tocilizumab (Genetical Recombination) ACTEMRA 162 mg Syringe for SC Injection, ACTEMRA 162 mg Auto-Injector for SC Injection	Chugai Pharmaceutical Co., Ltd.	May 24, 2013
	Exenatide BYDUREON for Subcutaneous Injection 2 mg	Astra Zeneca K.K.	May 16, 2013
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Stribild Combination Tab.	Japan Tobacco Inc.	May 14, 2013
	Paromomycin Sulfate AMEPAROMO capsules 250 mg	Pfizer Japan Inc.	April 12, 2013
	Botulinum Toxin Type B NerBloc for Intramuscular Injection 2500 Units	Eisai Co., Ltd.	March 27, 2013
	Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 60 μg*10	Ferring Pharmaceuticals Co., Ltd.	March 25, 2013
◎	Regorafenib Hydrate Stivarga tablets 40 mg*11	Bayer Yakuhin, Ltd.	March 25, 2013
	Methadone Hydrochloride METHAPAIN Tablets 5 mg, 10 mg	Teikoku Seiyaku Co., Ltd.	March 25, 2013
	Fesoterodine Fumarate Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	March 15, 2013
	Certolizumab Pegol (Genetical Recombination)	UCB Japan Co. Ltd	March 8, 2013

	Cimzia 200 mg Syringe for S.C. Injection		
	Insulin Degludec (Genetical Recombination) TRESIBA Injection FlexTouch, TRESIBA Injection Penfill	Novo Nordisk Pharma Ltd.	March 7, 2013
	Monobasic sodium phosphate monohydrate/Dibasic sodium phosphate anhydrous Phosribbon Combination Granules*12	Zeria Pharmaceutical Co., Ltd.	March 4, 2013
	Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg*13	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012

*1 An additional indication for "prevention of serious lower respiratory tract disease caused by respiratory syncytial (RS) virus infection in neonates and infants aged ≤24 months with immunodeficiency or Down syndrome (early stage of an epidemic of RS viral infection)"

*2 An additional indication for "treatment of patients with macular oedema with retinal vein occlusion or choroidal neovascularization with pathologic myopia"

*3 An additional indication for "relief of pain in laser irradiation treatment of the skin"

*4 An additional indication for "treatment of patients with interstitial pneumonia associated with polymyositis/ dermatomyositis"

*5 An additional indication for "treatment of patients with malignant glioma"

*6 An additional indication for "analgesia of chronic pain cannot be managed by treatments with non-opioid analgesics"

*7 An additional indication for "treatment of patients with depression/depressive state (to be used only when the patient does not sufficiently respond to conventional therapy)"

*8 An additional indication for "sedation in surgery or treatment without intubation under local anesthesia"

*9 An additional administration for "pediatrics"

*10 An additional indication for "treatment of patients with central diabetes insipidus"

*11 EPPV was initiated in August 20, 2013 for an additional indication for "treatment of patients with gastrointestinal stromal tumour that has progressed after chemotherapy"

*12 An additional indication for "treatment of patients with hypophosphataemia"

*13 An additional indication for "treatment of patients with central diabetes insipidus"