Pharmaceuticals and Medical Devices Safety Information

No. 315 August 2014

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) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

Published by
Ministry of Health, Labour and Welfare

Translated by
Pharmaceuticals and Medical Devices Agency

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

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

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. 315 August 2014

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

ADR	Adverse drug reaction
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BP	Blood pressure
CPR	Cardiopulmonary resuscitation
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
D-Bil	Direct bilirubin
DIC	Disseminated intravascular coagulation
Eos	Eosinophil
EPPV	Early Post-marketing Phase Vigilance
ER	Emergency room
FY	Fiscal year
Hb	Hemoglobin
Ht	Hematocrit
ICU	Intensive care unit
IU	International unit
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MR	Medical representative
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
RBC	Red blood cell count
SaO_2	Arterial oxygen saturation
T-Bil	Total bilirubin
WBC	White blood cell count

1

Safety Measures of New Drugs during the Early Post-marketing Phase

1. Introduction

Pre-approval safety information on pharmaceutical and other products from studies including clinical trials is not of a general nature because of the limited sample size and patient background factors such as concomitant drugs, complications, and age. Especially in post-marketing experience with a new drug, unknown serious adverse drug reactions (ADRs) may occur or ADRs may occur at unexpected frequencies since the number of patients treated with the product dramatically increases in a short time and the patient background factors diversify. Because prompt collection of accurate ADR information at medical practice is crucial to ensure post-marketing safety of pharmaceutical products, ADR reporting is required for marketing authorization holders (MAHs) and healthcare professionals as part of the regulatory measures. (Article 77-4-2 of the Pharmaceutical Affairs Act)

This article introduces "Early Post-marketing Phase Vigilance (EPPV)" conducted by MAHs and "Early Post-marketing Phase Safety Information Collection (fixed-point observation project)" carried out by the Ministry of Health, Labour and Welfare (MHLW) to ensure prompt collection of safety information and to take appropriate safety measures for new drugs during the early post-marketing phase.

2. Early post-marketing phase vigilance

2−1. Objective of Early post-marketing phase vigilance

Required by the "Ministerial Ordinance on Good Vigilance Practice for drugs, quasi-drugs, cosmetics, and medical devices" (MHLW Ordinance No. 135, 2004), EPPV is conducted by MAHs to promote the proper use of new pharmaceutical products in clinical practices and promptly collect ADR information in the first 6 months after the launch of the products (or after approval for additional indication). EPPV will be included in the condition for approval for individual pharmaceutical products if it is considered necessary during the regulatory review process.

Unlike studies such as use-results surveys and post-marketing clinical studies in which patient registration and predetermined investigational items are involved, EPPV is conducted as part of activities including collection and provision of information on proper use of drugs specified in Article 77-3-1 of the Pharmaceutical Affairs Act.

References
Past issues of Pharmaceutical and Medical Device Safety Information (PMDSI) describing EPPV
No.170 http://www.info.pmda.go.jp/iyaku_anzen/PMDSI170d.html#1 (only available in Japanese language)
No.212 http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-212.pdf

2−2. Method of Early post-marketing phase vigilance

The following is the general process of EPPV (Figure 1).

(1) The MAH sends a medical representative (MR) to provide the following explanation and to request cooperation from the medical institution using the pharmaceutical product before its delivery in principle. If a MR cannot visit a site before delivery, a written notification will be sent before product delivery and a MR will visit to provide an explanation and request for cooperation within approximately 2 weeks of delivery.

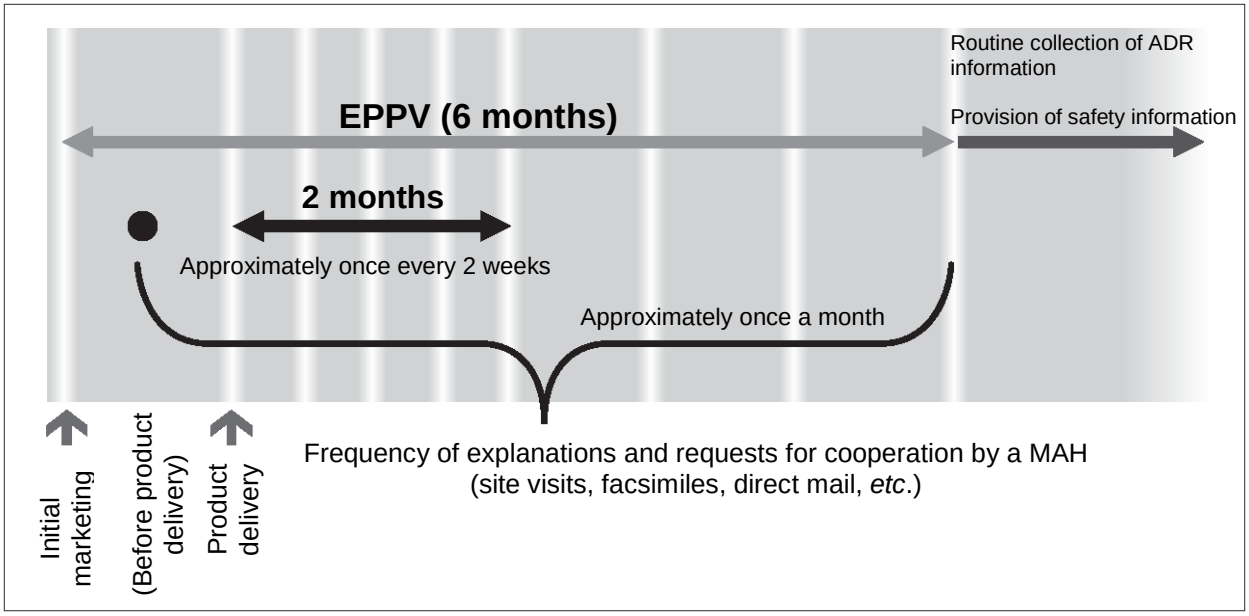
Details of the explanation and request for cooperation

- The new pharmaceutical product is subject to and is under EPPV.
- The medical institution is requested to use the new pharmaceutical product carefully and promptly report to the MAH any serious ADRs for which causal relationship with the product cannot be ruled out.

(2) The MAH provides medical institutions with the explanation and requests cooperation approximately once every 2 weeks in the first 2 months after product delivery and at an appropriate frequency (approximately once a month) after that until the end of EPPV in principle and raises cautions to ensure proper use of drug as necessary.

(3) The MAH prepares an EPPV report using the specific form and submits it to the Pharmaceuticals and Medical Devices Agency (PMDA) within 2 months after the EPPV is completed.

Figure 1. Summary of EPPV



2−3. Early post-marketing phase vigilance and safety measures

When occurrence of ADRs, including serious ADRs, is notified by a medical institution *etc*., the MAH makes an attempt to promptly collect follow-up information and file an ADR report to the PMDA in accordance with the provisions of the Pharmaceutical Affairs Act.

Examples of safety measures such as revision of package inserts and thorough notifications to medical institutions taken based on the ADR information reported by the MAHs are shown in the table below.

As with Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter), Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue Letter) is prepared and distributed by MAHs under the instructions of MHLW when certain safety measures are required more urgently compared with general revisions of precautions in a package insert. Five of 8 Blue Letters prepared and distributed in the past 5 years were issued during the EPPV period (Table 1).

Table 1. Blue Letters issued after 2008

Brand name	ADRs cautioned	Initial marketing	Blue Letter	Timing of Blue Letter issuance
Nexabar Tablets	(1) Acute lung injury, interstitial pneumonia (2) Liver failure, hepatic encephalopathy	April 2008 Additional indication, May 2009	(1) December 19, 2008 (2) November 18, 2009	(1) After EPPV (2) During EPPV
Victoza Subcutaneous Injections	Diabetic ketoacidosis, hyperglycaemia	June 2010	October 12, 2010	During EPPV
Prazaxa Capsules	Serious haemorrhage	March 2011	August 12, 2011	During EPPV
Ranmark Subcutaneous Injections	Serious hypocalcaemia	April 2012	September 11, 2012	During EPPV
Careram Tablets /Kolbet Tablets	Serious haemorrhage (interaction with warfarin)	September 2012	May 17, 2013	After EPPV
Yaz Combination Tablets	Thrombosis	November 2010	January 17, 2014	After EPPV
Xeplion Aqueous Suspension for IM Injections	Death (causal relationship unknown)	November 2013	April 17, 2014	During EPPV

3. Early Post-marketing Phase Safety Information Collection (fixed-point observation project)

For multistreaming of the safety information collection system, the MHLW started the Early Post-marketing Phase Safety Information Collection in fiscal year (FY) 2006. Early post-marketing phase safety management is especially needed for newly approved pharmaceutical products with high novelty or a few number of treated patients in Japan and overseas. In line with the duration of EPPV, the MHLW directly collects and evaluates the clinical information such as product usage and occurrences of ADRs for 6 months after the launch of the products in principle in the project. For every product (active ingredient), 4 to 6 medical institutions are asked for their cooperation for the project. Physicians and pharmacists are asked to report the following information periodically, and the MHLW takes appropriate measures including safety measures and instructions to the MAH as necessary.

- Usage and ADR occurrence of the pharmaceutical product
- Provision of information on the pharmaceutical product by the MAH (including the EPPV status)
- Use of safety information at medical institutions

A summary of the project is reported to the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council at the earliest meeting after the project completion. As of July 2014, reports have been filed for 26 active ingredients based on the information collected at 149 participating institutions.

The cooperation of institutions receiving a request for project participation from the MHLW would be appreciated to ensure proper use of pharmaceutical products.

4. Conclusion

Unknown ADRs sometimes became evident during the early post-marketing phase. EPPV is an especially important post-marketing safety system to collect accurate information, take necessary safety measures, and maintain/improve public health. Healthcare professionals such as physicians, dentists, and pharmacists are encouraged to understand the objectives of EPPV and their active cooperation for EPPV conducted by MAHs would be appreciated.

If any serious ADRs to pharmaceutical products are identified and reporting is considered necessary, report to the MHLW directly.

Drugs and Medical Devices Safety Information Reporting System
http://www.info.pmda.go.jp/info/houkoku.html (only available in Japanese language)

Pharmaceutical products subject to EPPV are shown in the "List of products subject to EPPV" in monthly PMDSI as well as on the following PMDA website with a link to "Review reports."

EPPV information
http://www.info.pmda.go.jp/shinyaku/shihan_index.html (only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated July 8, 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Inchinkoto

Brand Name (name of company)	Tsumura Inchinkoto Extract Granules for Ethical Use (Tsumura & Co.) and the others
Therapeutic Category	Kampo product
Indications	The relief of the following symptoms of those patients with a comparatively strong constitution and decreased urine volume who are somewhat likely to have constipation: Jaundice, hepatic cirrhosis, nephrosis, urticaria, and stomatitis

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, abdominal distension, and other signs and symptoms repeatedly occur, or if the patient tests positive for faecal occult blood, administration of this drug should be discontinued. At the same time, examinations such as computed tomography (CT) and large bowel endoscopy 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 (April 2011 to May 2014)
4 cases (no fatal cases)
The number of patients using this drug per year estimated by MAHs:
Approximately 13 000 (FY 2012)
Launched in Japan: October 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Biliary cirrhosis primary (atrial fibrillation paroxysmal)	7.5 g for 3 596 days	**Phlebosclerotic colitis** Approximately 10 years before onset: The patient started receiving inchinkoto for primary biliary cirrhosis. Day of onset: The patient had right flank pain and felt strange in the right lower abdomen, but did not do anything about the symptoms. 3 days after onset: The patient started to feel persistent pricking pain in the right lower abdomen after lunch. In the evening, he visited a nearby hospital because pain increased. An analgesic and a cathartic were prescribed and he returned home. After that, pain increased,

				and he visited the emergency department at night. The patient was admitted to hospital on the same day. At the internal medicine department, phlebosclerotic colitis was diagnosed. 5 days after onset: The patient was transferred to the surgery department. 15 days after onset: Subtotal colectomy was performed for phlebosclerotic colitis. 24 days after onset: All stitches were removed. 35 days after onset (day of discontinuation): Administration of inchinkoto was discontinued. 2 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: liver hydrolysate-containing preparation, polyenephosphatidyl choline, ursodeoxycholic acid, bezafibrate, itopride hydrochloride, famotidine, diastase-containing preparation (1), bifidobacterium preparation (4), atenolol, flecainide acetate, levofloxacin hydrate			

Laboratory Examination

	5 days after onset	16 days after onset	22 days after onset	Day of discontinuation	30 days after discontinuation
RBC (10^4 cells/mm^3)	455	397	311	377	387
Hb (g/dL)	14.3	12.4	9.8	11.5	11.5
Ht (%)	41.8	36.1	28.6	34.2	34.0
WBC (cells/mm^3)	23 600	18 100	9 200	8 700	4 300
CRP (mg/dL)	28.0	15.5	10.0	1.3	1.0
T-Bil (mg/dL)	5.0	2.2	1.4	0.7	0.8
D-Bil (mg/dL)	3.5	1.5	1.0	0.4	0.4

2 Simeprevir Sodium

Brand Name (name of company)	Sovriad capsules 100 mg (Janssen Pharmaceutical K.K.)
Therapeutic Category	Antivirals
Indications	Improvement of viraemia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection: (1) Treatment-naïve patients with high blood HCV RNA load (2) Patients who have failed to respond to, or have relapsed after, therapy including interferon

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Sepsis: Susceptibility to infection may be increased, resulting in serious infection leading to sepsis. Patients should be carefully monitored through periodic blood tests, *etc*. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Cerebral haemorrhage: Cerebral haemorrhage 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.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 6 months (from initial marketing to May 2014) (*i.e.*, the number of reported adverse reactions for which a causality to triple therapy with this drug, peginterferon alfa-2a [genetical recombination] or -2b [genetical recombination], and ribavirin could not be ruled out)
Infection, cerebral haemorrhage, or cerebral infarction-associated cases*: 7 cases (3 fatal cases)
* Including cases with concurrent infection and cerebral haemorrhage or infarction
The number of patients using this drug estimated by MAHs:
Approximately 15 000 (from the initial marketing to May 2014)
Launched in Japan: December 2013

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Chronic hepatitis C (dysgeusia)	100 mg for 43 days	**Septic shock, subarachnoid haemorrhage** Before administration: The patients had had mild to moderate hepatic cirrhosis. Day 1 of administration: Triple therapy with simeprevir sodium (100 mg/day), peginterferon alfa-2b (100 μg/week), and ribavirin (800 mg/day) was started. Day 2 of administration: Generalised muscle aches and cramps occurred. Day 3 of administration: Generalised muscle aches and cramps improved. Day 15 of administration: Sleepiness, diarrhoea, and tonsillar redness occurred. Day 22 of administration: Malaise, headache, and oral dryness occurred. Day 29 of administration: Stomatitis, oral redness, oral pain, and skin boils at the back of

				the throat occurred. Administration of dexamethasone, sodium gualenate hydrate, and dequalinium chloride was started for stomatitis, and administration of loxoprofen sodium hydrate for stomatitis pain. Day 31 of administration: Herpes labialis occurred. Day 35 of administration: Chilliness and pyrexia (38°C) were noted. Day 36 of administration: Final administration of peginterferon alfa-2b was performed. The influenza test result was negative. Day 41 of administration: General malaise, oedema, and myalgia occurred. The patient had been working as usual until this day. Day 42 of administration: Impaired appetite and reduced water intake occurred. The patient returned from the work location where he lived separately from his family, and attended a meeting. He was absent from a subsequent dinner party due to fatigue. He had myalgia but was able to work on a regular schedule. He woke up at midnight to drink water, and he exchanged a few words with the family, but had no particular abnormality. Day 43 of administration (day of discontinuation): Nausea, myalgia, diarrhoea, dizziness, low back pain, disturbed consciousness, and unrest occurred. In the morning, after taking simeprevir sodium and ribavirin, disturbed consciousness and increased creatinine (Cr) occurred. Generalised muscle aches continued from the morning. He seemed to have twilight state due to pain. He had diarrhoea. He was scheduled to visit this hospital on this day, but informed the hospital that he was lying down and was unable to eat due to severe myalgia and therefore could not visit the hospital. His state of consciousness deteriorated with severe pain at night. Emergency service was requested. There was no available hospital in the city. A contact was made with this hospital, and his state was checked. Pain was severe and oedema was found with no urination. Twilight state was not so severe. He was transported to this hospital. Body temperature was 36.4°C, arterial oxygen saturation (SaO_2) was 96%, blood pressure (BP) was 94/43 mm Hg, and Cr was approximately 3 mg/dL. Ammonia level was not high. Administration of simeprevir sodium and ribavirin was discontinued. Administration of peginterferon alfa-2b was scheduled on this day, but was canceled. 1 day after discontinuation: Cr was 3.3 mg/dL and white blood cell count (WBC) was 10 100/μL. The patient was transported to another hospital due to acute renal failure, bacterial infection, and suspected rhabdomyolysis. Based on the results of close examination, medical treatment was started for suspected fulminant hepatitis, suspected upper gastrointestinal haemorrhage, acute renal failure, and suspected sepsis. After that, rhabdomyolysis was ruled out. Plasma exchange, continuous hemodiafiltration, mechanical ventilation, administration of dopamine hydrochloride, noradrenaline, and vasopressin for increasing BP, and platelet transfusion were performed. 2 days after discontinuation: WBCs associated with phagocytosis of gram-positive cocci were detected from a peripheral blood smear preparation, and

				methicillin-sensitive *Staphylococcus aureus* was detected from blood culture, and consequently, staphylococcal sepsis was diagnosed. Administration of meropenem hydrate 1 g/day was started. Regarding renal failure, a consultation was made with the nephrology department, and it was decided that plasma exchange and hemodiafiltration would be performed every day. As the patient had hypoglycaemia, a consultation was made with a doctor in the nutrition support team, and a high-calorie infusion from a central vein was started. Due to concurrent disseminated intravascular coagulation (DIC), 12 800 U of thrombomodulin alfa was administered. A consultation was made with the hematology department, and 10 units of platelets were transfused (acute-phase DIC score, 8 points). In the afternoon, as the respiratory status was aggravated, intubation was performed. Mechanical ventilation was started. Concomitant use of vasopressors was started. 3 days after discontinuation: The patient had septic shock, hepatic failure, renal failure, DIC, decreased platelets, hypoglycaemia, hypocalcaemia, acidosis, and disturbed consciousness. As cardiac arrest occurred suddenly, cardiopulmonary resuscitation (CPR) was started. Asystole occurred after defibrillation for ventricular fibrillation. CPR was performed but the patient had no response and died. An autopsy was not desired. The direct cause of death was determined to be acute subarachnoid haemorrhage based on autopsy imaging.
	The other suspected medications: ribavirin, peginterferon alfa-2b (genetical recombination) Concomitant medications: cefcapene pivoxil hydrochloride hydrate, dexamethasone, sodium gualenate hydrate, dequalinium chloride, loxoprofen sodium hydrate			

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Chronic hepatitis C (platelet count decreased, obesity)	100 mg for 43 days	**Cerebral haemorrhage** Before administration: The patient had mild headache and dizziness on standing up after dual therapy (peginterferon alfa-2a and ribavirin). From the time of prior treatment, the patient had a tendency toward low platelet count. For the introduction to triple therapy including simeprevir sodium for re-treatment of chronic hepatitis C, head magnetic resonance imaging and magnetic resonance angiograph were performed in consideration of cerebrovascular risks. There were no abnormal findings such as aneurysm and stenosis. Day 1 of administration: Triple therapy with simeprevir sodium (100 mg/day), peginterferon alfa-2a (90 μg/week), and ribavirin (800 mg/day) was started. Platelet count before the start of administration of simeprevir sodium was 50 000 level/μL. Day 8 of administration: Albumin was 3.4 g/dL. The dose of peginterferon alfa-2a was reduced to 45 μg/week from the second dose. Day 18 of administration: The patient visited the hospital. He had common cold-like symptoms.

				C-reactive protein (CRP) was 3.5 mg/dL. Day 22 of administration: The patient visited the hospital. Common cold-like symptoms improved. Day 29 of administration: The patient had pyrexia. Platelet count was 68 000/μL and CRP was 0.7 mg/dL. Day 30 of administration: The patient had pyrexia. Day 32 of administration: As pyrexia persisted, the dose of ribavirin was reduced to 400 mg/day at the discretion of the patient. Day 36 of administration: Final administration of peginterferon alfa-2a was performed. Day 39 of administration: Administration of ribavirin was suspended. Day 43 of administration (day of discontinuation): The patient visited an outpatient department. Increased alanine aminotransferase (ALT or glutamate pyruvate transaminase [GPT]), increased aspartate aminotransferase (AST or glutamate oxaloacetate transaminase [GOT]), and decreased platelet count occurred. Platelet count was 39 000/μL, CRP was 6.3 mg/dL, ALT was 75 international unit (IU)/L, and AST was 208 IU/L. Peginterferon alfa-2a was suspended. Prothrombin time was 68%. There was no sign of hepatic failure. Chest X-ray showed no abnormal findings. 1 day after discontinuation: The patient's family found him lying down and requested an emergency service. As the patient was in a distant area from his hospital, he was transported to another hospital (a hospital in the neighborhood of the patient’s home), and then was dealt with in the intensive care unit (ICU). Japan coma scale was 100. Head CT showed left subcortical haemorrhage (The size and other information of haematoma were unknown). Fresh frozen plasma and platelet transfusion were performed, and craniotomy for haematoma evacuation was performed. 5 days after administration: Aspiration pneumonia concurred. Extubation was performed, but the respiratory status was aggravated again. Because chest X-ray photograph showed that the status was similar to acute respiratory distress syndrome, re-intubation was considered, but the family did not want it. 7 days after discontinuation: The patient died of postoperative aspiration pneumonia and respiratory failure. An autopsy was not performed. Cerebral haemorrhage was a subcortical haemorrhage and therefore was not considered to be traumatic. Outcomes of decreased platelet count and increased AST are unknown.
	The other suspected medications: ribavirin, peginterferon alfa-2a (genetical recombination) Concomitant medications: loxoprofen sodium hydrate, sodium rabeprazole, dextromethorphan hydrobromide hydrate			

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Chronic hepatitis C (atrial fibrillation, hypertension, diabetes mellitus)	100 mg for 36 days	**Necrotising fasciitis, severe invasive streptococcal infection, sepsis** Day 1 of administration: The patient started receiving triple therapy with simeprevir sodium (100 mg/day), peginterferon alfa-2a (180 μg/week), and ribavirin (600 mg/day). Day 36 of administration (day of discontinuation): The patient had no problem at all at the time of the medical examination. 3 days after discontinuation: Swelling of the left palm and pyrexia were noted. Severe invasive streptococcal infection occurred in the left upper limb. Pathogen, group G *Streptococcus*; Method of identifying pathogen, culture; Range of lesion, left upper limb; Clinical symptom, disturbed consciousness 4 days after discontinuation: The patient was transported by ambulance due to disturbed consciousness. Based on the results of close examination, necrotising fasciitis was diagnosed in the left upper limb. As DIC and sepsis also occurred in association with necrotising fasciitis, he was admitted to the ICU. On the same day, the status suddenly aggravated and the range of inflammation enlarged. Left upper limb amputation was performed, and intensive care was given. Plain X-ray showed no findings. CT scan showed swelling of the left forearm. Date unknown: Caution was still required after upper limb amputation. Date unknown: Multi-organ failure occurred. 23 days after discontinuation: Increased ALT, increased AST, high amylase, and hyperbilirubinaemia occurred. 24 days after discontinuation: The patient died of multi-organ failure, sepsis, severe invasive streptococcal infection in the left upper limb, DIC, and necrotising fasciitis. Risk factor for infection: History of immunosuppressive therapy (triple therapy for chronic hepatitis C). Contents of treatment for infection: Antibiotics, steroids, invasive procedure (left upper limb amputation), adjunct treatment (mechanical ventilation, dialysis, catecholamine) Outcomes of increased ALT, increased AST, high amylase, and hyperbilirubinaemia were unknown.
	The other suspected medications: ribavirin, peginterferon alfa-2a (genetical recombination) Concomitant medications: rivaroxaban, pilsicainide hydrochloride hydrate, telmisartan/hydrochlorothiazide, amlodipine besilate, loxoprofen sodium hydrate, rebamipide			

3 Teriparatide (Genetical Recombination)

Brand Name (name of company)	Forteo Subcutaneous Injection Kit 600 µg (Eli Lilly Japan K.K.)
Therapeutic Category	Thyroid and parathyroid hormone preparations
Indications	Osteoporosis at high risk for fracture

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis (dyspnoea, decreased BP, rash, *etc*.) 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.

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 (April 2011 to May 2014)
1 case (no fatal case)
The number of patients using this drug per year estimated by MAHs:
Approximately 65 000 (2013)
Launched in Japan: October 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Osteoporosis (none)	20 µg (for 1 day)	**Anaphylactic shock** Medical history: Rheumatoid arthritis Adverse reaction history: Unspecified diarrhoea due to antibiotic Allergic history: No 56 days before administration: Results of laboratory tests were WBC 8 200/µL, eosinophil (Eos) 1%, and CRP 0.68 mg/dL. Day 1 of administration (day of onset) (day of discontinuation): The patient started receiving teriparatide (genetical recombination) at 20 µg. After the first dose of the injection, difficulty in breathing and back pain occurred. There was a skin symptom of flushed face. Gastrointestinal symptoms were unknown. SaO_2 was 99%, BP was 230 mm Hg level, and pulse rate was 140/min level. Results of laboratory tests (around 10:00) were WBC 8 000/µL, Eos 1%, and CRP 0.86 mg/dL. Results of venovenous gas test (around 13:30) were pH 7.432, oxygen partial pressure 34.5 Torr, carbon dioxide partial pressure 38.7 Torr, base excess 1.6 mmol/L, and HCO_3^- 25.3 mmol/L. Results of laboratory tests (around 13:30) were WBC 15 000/µL, Eos 1%, and CRP 0.91 mg/dL. Administration of O_2 mask 2 L/min was started. The patient was transported to an emergency room (ER) due to drug shock. In ER outpatient settings, treatment with intramuscular injection of epinephrine 0.2 mL, and intravenous infusion of chlorpheniramine maleate, famotidine, and methylprednisolone sodium succinate was performed. The patient was urgently admitted to hospital for follow-up observation. Dyspnoea disappeared and vital signs became stable. BP after intramuscular injection of epinephrine 0.2 mL was

				170/90 mm Hg. On the same day, administration of teriparatide (genetical recombination) was discontinued. 1 day after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: prednisolone, magnesium oxide, omeprazole, folic acid, methotrexate, glycyrrhizin/glycine/DL−methionine, indometacin			

4 Loratadine

Brand Name (name of company)	Claritin Tablets 10 mg, Claritin Reditabs Tablets 10 mg, Claritin Dry Syrup 1% (MSD K.K.), and the others
Therapeutic Category	Allergic agents-Miscellaneous
Indications	Allergic rhinitis, urticaria, itching associated with skin disease (eczema/dermatitis, cutaneous pruritus)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Convulsion: Convulsion may occur. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 2011 to March 2014)
2 cases (no fatal cases)
The number of patients using this drug per year estimated by MAHs:
Approximately 1.7 million (FY 2013)
Launched in Japan: Tablets, September 2002
Reditabs Tablets, November 2004
Dry Syrup, January 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female Under age of 10	For the treatment of pollinosis (runny nose) (Rhinitis allergic, acute rhinitis, acute bronchitis)	0.5 g for 15 days	**Convulsion** The patient had a history of febrile convulsion. She had no history of epilepsy. 1 year before administration: The patient received loratadine (dry syrup) for 70 days, but experienced no abnormality. Day 1 of administration: Administration of loratadine was started. Day 15 of administration (day of discontinuation of this drug): The patient suddenly started crying and quivering 3 to 3.5 hours after taking loratadine at night, and this condition persisted for approximately 30 seconds. The condition improved without treatment. Administration of loratadine was discontinued. 1 day after discontinuation: Convulsion improved. 14 days after discontinuation: After that, loratadine was switched to cetirizine hydrochloride. After taking cetirizine hydrochloride at night, convulsion recurred.
	Concomitant medications: none			

3

Revision of Precautions (No. 258)

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 July 8, 2014.

1

Psychotropics

Paroxetine Hydrochloride Hydrate

Brand Name	Paxil Tablets 5 mg, 10 mg, 20 mg, Paxil CR Tablets 12.5 mg, 25 mg (GlaxoSmithKline K.K.), and the others
Adverse Reactions (clinically significant adverse reactions)	**Anaphylaxis**: Anaphylaxis (rash, angioedema, dyspnoea, *etc*.) 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.

2

Acting mainly on mold

Amphotericin B [non-liposome preparation (injections)]

Brand Name	Fungizone Infusion 50 mg (Bristol Myers K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Central nervous system disorder**: Meningitis, encephalopathy, spinal cord disorder, paraplegia, and other disorders may occur with intrathecal injection of this drug. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.

3

Over-the-counter drugs

(1) Ibuprofen/Pseudoephedrine Hydrochloride/ Chlorpheniramine Maleate/Dihydrocodeine Phosphate/ Anhydrous Caffeine

(2) Ibuprofen/Pseudoephedrine Hydrochloride/ L-carbocysteine/d-chlorpheniramine maleate/ Dihydrocodeine Phosphate/Anhydrous Caffeine

Brand Name	(1) Benza Block L, Benza Block L Tablets (Takeda Pharmaceutical Company Limited) (2) Benza Block L Plus, Benza Block L Plus Tablets (Takeda Pharmaceutical Company Limited)
Consultation	The following symptoms may be adverse reactions, therefore if the following symptoms are observed after administration of this drug, immediately discontinue this drug and contact a physician, pharmacist, or 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 signs and symptoms. **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis, acute generalised exanthematous pustulosis**: Hyperthermia, ocular

hyperaemia, eye discharge, lip erosion, pain throat, widespread skin rash/redness, small pimples (small pustules) on reddened skin, general malaise, anorexia, *etc*. may persist or suddenly worsen.

4 **Over-the-counter drugs**

Inchinkoto

Brand Name	Kracie Kampo Inchinkoto Extract Granules (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, pharmacist, or 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 signs and symptoms. **Mesenteric phlebosclerosis**: Abdominal pain, diarrhoea, constipation, abdominal distension, *etc*. may occur repeatedly with long-term oral administration.

4

List of Products Subject to Early Post-marketing Phase Vigilance

EPPV was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting the ADRs from all of the medical institutions where the drugs are used and 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 ADRs. EPPV is specified as a condition of approval.

(As of August 1, 2014)

There were no products for which EPPV was initiated after July 2, 2014

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
sorafenib tosilate Nexavar Tablets 200 mg*[1]	Bayer Yakuhin, Ltd.	June 20, 2014
pneumococcal 13-valent conjugate vaccine (diphtheria CRM_{197} protein) Prevenar 13 Suspension Liquid for Injections*[2]	Pfizer Japan Inc.	June 20, 2014
azilsartan/amlodipine besilate Zacras Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 18, 2014
natalizumab (genetical recombination) Tysabri. for I.V. Infusions 300 mg	Biogen Idec Japan Ltd.	June 4, 2014
prasugrel hydrochloride Efient Tablets 3.75 mg, 5 mg	Daiichi Sankyo Company, Limited	May 27, 2014
betaine Cystadane	ReqMed Company, Ltd.	May 27, 2014
trifluridine/tipiracil hydrochloride Lonsurf Combination Tablets T15, T20	Taiho Pharmaceutical Co., Ltd.	May 26, 2014
denosumab (genetical recombination) Ranmark Subcutaneous Injections 120 mg*[3]	Daiichi Sankyo Company, Limited	May 23, 2014
enzalutamide Xtandi Capsules 40 mg	Astellas Pharma Inc.	May 23, 2014
valsartan/cilnidipine Atedio Combination Tablets	Ajinomoto Pharmaceuticals Co., Ltd	May 23, 2014
tofogliflozin hydrate (1) Deberza Tablets 20 mg (2) Apleway Tablets 20 mg	(1) Kowa Company, Ltd. (2) Sanofi K.K.	May 23, 2014
luseogliflozin hydrate Lusefi Tablets 2.5 mg, 5 mg	Taisho Pharmaceutical Co., Ltd.	May 23, 2014
dapagliflozin propylene glycolate hydrate Forxiga Tablets 5 mg, 10 mg	Bristol-Myers K.K.	May 23, 2014
tenofovir disoproxil fumarate Tenozet Tablets 300 mg	GlaxoSmithKline K.K.	May 16, 2014

	turoctocog alfa (genetical recombination) Novoeight for Intravenous Infusions 250, 500, 1000, 1500, 2000, 3000	Novo Nordisk Pharma Ltd.	May 12, 2014
	ferric citrate hydrate Riona Tablets 250 mg	Japan Tobacco Inc.	May 12, 2014
	afatinib maleate Giotrif Tablets 20 mg, 30 mg, 40 mg, 50 mg	Nippon Boehringer Ingelheim Co., Ltd.	May 7, 2014
	trastuzumab emtansine (genetical recombination) Kadcyla Intravenous Infusions 100 mg, 160 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2014
	riociguat Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg	Bayer Yakuhin, Ltd.	April 18, 2014
	levocetirizine hydrochloride Xyzal Syrup 0.05%	GlaxoSmithKline K.K.	April 17, 2014
	dolutegravir sodium Tivicay Tablets 50 mg	ViiV Healthcare K.K.	April 17, 2014
	brentuximab vedotin (genetical recombinatin) Adcetris for Intravenous Infusions 50 mg	Takeda Pharmaceutical Company Limited	April 17, 2014
	ipragliflozin l-proline Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	April 17, 2014
	tadalafil Zalutia Tablets 2.5 mg, 5 mg	Eli Lilly Japan K.K.	April 17, 2014
	tolvaptan Samsca Tablets 7.5 mg, 15 mg, 30 mg*4	Otsuka Pharmaceutical Co., Ltd.	March 24, 2014
	fluticasone furoate Allermist 27.5μg 56 metered Nasal Spray*5	GlaxoSmithKline K.K.	March 17, 2014
	pazopanib hydrochloride Votrient Tablets 200 mg*6	GlaxoSmithKline K.K.	March 17, 2014
	mogamulizumab (genetical recombination) Poteligeo Injections 20 mg*7	Kyowa Hakko Kirin Co., Ltd.	March 17, 2014
	cinacalcet hydrochloride Regpara Tablets 25 mg, 75 mg*8	Kyowa Hakko Kirin Co., Ltd.	February 21, 2014
	ranibizumab (genetical recombination) Lucentis Solution For Intravitreal Injections 2.3 mg/0.23 mL*9	Novartis Pharma K.K.	February 21, 2014

*1 An additional indication for “the treatment of patients with radically unresectable differentiated thyroid carcinoma”

*2 An additional indication for “the prevention of infection caused by *Streptococcus pneumonia* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in elderly patients”

*3 An additional indication for “the treatment of patients with bone giant cell tumour”

*4 An additional indication for “the control of disease progression in patients with autosomal dominant polycystic kidney who already had increased kidney volume and whose kidney volume was further rapidly increasing.” Samsca tablets 30 mg was launched in May 29, 2014.

*5 An additional administration for “pediatrics”

*6 An additional indication for “the treatment of patients with radically unresectable or metastatic renal cell carcinoma”

*7 An additional indication for “the treatment of patients with relapsed or refractory CCR4-positive peripheral T-cell lymphoma and patients with relapsed or refractory CCR4-positive cutaneous T-cell lymphoma”

*8 An additional indication for “the treatment of hypercalcaemia in patients with the following diseases: parathyroid carcinoma, and primary hyperparathyroidism for which patients are unable to undergo parathyroidectomy or which relapses after operation”

*9 An additional indication for “the treatment of patients with diabetic macular oedema”