# Pharmaceuticals and Medical Devices Safety Information

**No. 318 November 2014**

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers.
The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) 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).


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# Pharmaceuticals and Medical Devices Safety Information

**No. 318 November 2014**

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


## [ Outline of Information ]


| No. | Subject | Measures | Outline of Information | Page |
|---|---|---|---|---|
| 1 | **Simeprevir Sodium and Hyperbilirubinaemia** | *P*<br>*C* | Hyperbilirubinaemia-suggested cases have been reported in patients treated with Sovriad Capsules. The MHLW ordered the marketing authorization holder of Sovriad to revise Precautions and to alert healthcare professionals with the Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter) on October 24, 2014. Details are presented in this section. | 6 |
| 2 | **Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Medical Institutions and Pharmacies** | | The PMDA has been conducting surveillance from fiscal year 2010 to understand the status of dissemination and utilization of safety information in medical institutions and to determine appropriate methods for the dissemination and utilization of the information. Based on the surveillance results of fiscal year 2013, the PMDA presented the material for appropriate management of drug safety information in this section. | 14 |
| 3 | **Adverse Reactions to Influenza Vaccine in the 2013 Season** | | Adverse reactions to influenza vaccine reported from October 1, 2013 through July 31, 2014 (the 2013 season) are presented in this section. Adverse reactions included in this section were presented on October 29, 2014 at a joint meeting of the 2014 Committee on Adverse Reactions of Immunization and Vaccine Department in the Health Science Council (the 11th meeting) and 2014 Subcommittee on Drug Safety of Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 6th meeting). | 24 |
| 4 | **Important Safety Information** | *P*<br>*C* | **enzalutamide (and 3 others):** Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated October 21 (the following No.1-3), and October 24 (the following No. 4), 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section . | 29 |
| 5 | **Revision of Precautions (No. 260)** | | Acetaminophen (and 1 other) | 41 |
| 6 | **List of Products Subject to Early Post-marketing Phase Vigilance** | | Lists products subject to Early Post-marketing Phase Vigilance as of November 2014. | 42 |


*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 |
| Alb | Albumin |
| Al-P | Alkaline Phosphatase |
| ALT (GPT) | Alanine aminotransferase (Glutamate pyruvate transaminase) |
| APTT | Activated partial thromboplastin time |
| AST (GOT) | Aspartate aminotransferase (Glutamate oxaloacetate transaminase) |
| AT-III | Antithrombin III |
| BUN | Blood urea nitrogen |
| BW | Body weight |
| C3 | Complement 3 |
| C4 | Complement 4 |
| CHE | Cholinesterase |
| CLcr | Creatinine clearance |
| Anti-CL-B2GP1 | Anticardiolipin-beta2-glycoprotein I antibody |
| CRP | C-reactive protein |
| CT | Computed tomography |
| D-Bil | Direct bilirubin |
| DIHS | Drug-induced hypersensitivity syndrome |
| DLST | Drug lymphocyte stimulation test |
| DRVVT | Diluted Russell's viper venom time test |
| DSU | Drug safety update |
| eGFR | estimated glomerular filtration rate |
| EPPV | Early Post-marketing Phase Vigilance |
| FDP | Fibrin/fibrinogen degradation product |
| FY | Fiscal year |
| Hb | Hemoglobin |
| HbA1c | Hemoglobin A1c |
| HCV-RNA | Hepatitis C virus-Ribonucleic acid |
| HDL | High-density lipoprotein |
| HHV-6 | Human herpesvirus 6 |
| HHV-6 IgG | Human herpesvirus 6-Immunoglobulin G |
| Htc | Hematocrit |
| IU | International unit |
| KL-6 | Krebs von den Lunge-6 |
| LDH | Lactate dehydrogenase |
| LDL | Low-density lipoprotein |
| MAH | Marketing authorization holder |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MHLW | Ministry of Health, Labour and Welfare |
| MRCNS | Methicillin-resistant coagulase-negative Staphylococci |
| MRSA | Methicillin-resistant Staphylococcus aureus |

| | |
|---|---|
| NGSP | National glycohemoglobin standardization program |
| OTC | Over-the-counter |
| PAIgG | Platelet-associated immunoglobulin G |
| PaO2 | Arterial oxygen partial pressure |
| PC | Platelet concentrate |
| PCR | Polymerase chain reaction |
| Plt | Platelet |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PMDSI | Pharmaceuticals and Medical Devices Safety Information |
| PT | Prothrombin Time |
| PT-INR | Prothrombin time - international normalized ratio |
| RBC | Red blood cell count |
| RDW-CV | Red cell distribution width-coefficient of variation |
| RMP | Risk Management Plan |
| SI | Stimulation index |
| SP-D | Surfactant protein D |
| SpO2 | Oxygen saturation |
| T-Bil | Total bilirubin |
| T-PSA | Total prostate-specific antigen |
| WBC | White blood cell count |
| γ-GTP | gamma-glutamyl transpeptidase |

# 1

# Simeprevir Sodium and Hyperbilirubinaemia

| | |
|---|---|
| **Active ingredient** | 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:<br>(1) Treatment-naïve patients with high blood Hepatitis C virus-Ribonucleic acid (HCV RNA) load<br>(2) Patients who have failed to respond to, or have relapsed after, therapy including interferon |

## 1. Introduction

Simeprevir sodium (Sovriad Capsules 100 mg; hereinafter referred to as Sovriad), which selectively inhibits NS3/4A protease essential for replication of hepatitis C virus, is indicated for the treatment of chronic hepatitis C. In Japan, Sovriad was approved as a drug to be used in combination therapy with peginterferon and ribavirin indicated for "improvement of viraemia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic HCV 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" in September 2013. The marketing authorization holder (MAH) estimates Sovriad has been used in approximately 18 900 patients after the launch (December 6, 2013) until September 30, 2014.

Recently, a total of 3 cases of remarkable increase in blood bilirubin levels followed by hepatic dysfunction and/or renal impairment, etc. leading to death have been reported patients treated with Sovriad in Japan. The Ministry of Health, Labour and Welfare (MHLW) instructed the MAH of Sovriad to revise the Precautions and distribute Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter).[1] Details are described below.

## 2. Background

Incidence of adverse events related to increased blood bilirubin levels in the Japanese clinical studies of Sovriad was 31.5% (104/330) in the Sovriad group and 8.2% (6/73) in the placebo group. Increase of blood bilirubin levels during the treatment with Sovriad is thought to be primarily associated with its action to inhibit the hepatic transporters (organic anion transporting polypeptide 1B1 and multidrug resistance-associated protein 2). Although the incidence of adverse events related to increased blood bilirubin levels was high in the Sovriad group in the Japanese clinical studies, most events were mild, and patients tend to recovered after completing or discontinuing the treatment. Therefore, the 3-drug combination therapy was considered safe if it was used while carefully monitoring blood bilirubin levels during the treatment. Since the launch of Sovriad in December 2013, advice to monitor blood bilirubin levels during the treatment has been included in the "Important Precautions" section. Information on "increased blood bilirubin and hyperbilirubinaemia" has also been included in the "Other Adverse Reactions" section in the package insert in order to arouse caution.

Several cases of patients whose blood bilirubin levels remarkably increased after taking Sovriad* have been reported since the marketing. The investigation of the Pharmaceuticals and Medical Devices Agency (PMDA) concluded the causal relationship between Sovriad and the event could not be denied

in 3 fatal outcomes in which patients died after having hepatic dysfunction and/or renal impairment that may have been associated with hyperbilirubinaemia. After taking Sovriad, a persistent increase in blood bilirubin levels was followed by a sudden increase in all 3 fatal cases. The blood bilirubin levels further increased even after the treatment had been discontinued. Therefore, periodic monitoring of blood bilirubin levels during the treatment courses and careful patient follow-up even after discontinuing the treatment will be necessary. Once symptoms such as jaundice and general malaise occur, it may be too late to prevent a serious outcome even with appropriate measures. Based on the necessity of an urgent response, the MHLW instructed the MAH of Sovriad on October 24, 2014 to revise the Precautions to add new Warnings section including a warning against hyperbilirubinaemia associated with Sovriad and to distribute Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter)[1] to promptly provide information on the warning.

As a result of the review at PMDA, 15 cases** (causal relationship was not denied in 12 cases) of serious hepatic disorder*** had been reported since the launch of Sovriad until October 10, 2014. Blood bilirubin levels did not increase in some of the cases. The MHLW instructed the MAH to add a warning against hepatic dysfunction separate from hyperbilirubinaemia in the of "Clinically Significant Adverse Reactions" section in the package insert.

* Blood bilirubin levels ≥10 mg/dL

** Including the 3 fatal cases with remarkably elevated blood bilirubin levels mentioned earlier

*** Aspartate aminotransferase (AST) ≥500 IU/L or alanine aminotransferase (ALT) ≥500 IU/L (including patients with no available data)

## 3. Fatal cases of hyperbilirubinaemia associated with Sovriad

Details of 3 cases of hyperbilirubinaemia with use of simeprevir sodium are shown below.

### Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 40s | Chronic hepatitis C (unknown) | 100 mg /67 days | History of hyperlipidemia. No history of hepatic impairment, no complication of biliary tract disease, no previous treatment, and no history of alcohol consumption.<br>Approx. 5 years before administration:<br>Chronic hepatitis C was diagnosed.<br>44 days before administration:<br>HCV-RNA was 5.70 log IU/mL (detected by real-time polymerase chain reaction [PCR]).<br>32 days before administration:<br>Chronic hepatitis and fatty liver were detected by echography. No splenomegaly and ascites were found.<br>Started to administer rosuvastatin calcium.<br>12 days before administration:<br>Platelet (Plt) count was $9.0 \times 10^4/mm^3$<br>1 day before administration:<br>Liver biopsy: A1F2<br>Day 1 of administration:<br>Combination therapy of 3 drugs with simeprevir sodium (100 mg/day), peginterferon alfa-2b (120 μg/week), and ribavirin (800mg/day) was started. There were no appreciable clinical symptoms such as jaundice when the combination therapy of three drugs was started.<br>Date unknown:<br>Hyperthyroidism occurred.<br>Day 21 of administration:<br>Started to administer olopatadine hydrochloride. (date unknown for discontinuation)<br>Day 42 of administration: |

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| | | | | Administration of rosuvastatin calcium was discontinued.<br>Day 56 of administration:<br>Total bilirubin (T-Bil): 3.3 mg/dL<br>Day 63 of administration:<br>General malaise occurred, no blood test. Administration of peginterferon alfa-2b was discontinued.<br>Day 67 of administration (day of discontinuation):<br>The patient felt anorexia and stopped to administer simeprevir sodium and ribavirin by himself.<br>3 days after discontinuation (10 weeks after combination therapy started):<br>The patient visited a hospital with general malaise. He was admitted to hospital on this day because laboratory tests showed an increase in T-Bil of 25.7 mg/dL.<br>Hyperbilirubinaemia occurred. Computed tomography (CT) showed no biliary obstruction but revealed ascites. Other findings included gallbladder enlargement, and hepatic cirrhosis.<br>Hepatic B virus test result was negative<br>4 days after discontinuation:<br>All of the test results of hepatitis A virus, cytomegalovirus, Epstein-Barr virus, antinuclear antibody, antimitochondrial antibody, and smooth muscle antibody were negative.<br>7 days after discontinuation:<br>Drug lymphocyte stimulation tests (DLSTs) were negative for simeprevir sodium, peginterferon alfa-2b, and olopatadine hydrochloride, and positive for ribavirin. The stimulation index (SI) for ribavirin was the highest, and the SI for simeprevir sodium was the second highest.<br>Methylprednisolone sodium succinate 1 g/day was administered from this day for 9 days after discontinuation of simeprevir sodium.<br>The patient did not respond to steroid pulse therapy.<br>10 days after discontinuation:<br>Left-hand finger cellulitis developed. Antibiotic cefazolin sodium was administered from this day up until 19 days after discontinuation of simeprevir sodium. Methylprednisolone sodium succinate 80 mg/day was administered from this day for 15 days after discontinuation of simeprevir sodium.<br>15 days after discontinuation:<br>CT scan showed hepatic atrophy, increased ascites, increased levels of mesenteric adipose tissue, gallbladder atrophy, and gallbladder wall thickening. Serious hepatitis was diagnosed (Hepatitis fulminant was suspected).<br>16 days after discontinuation:<br>Methylprednisolone sodium succinate 60 mg/day was administered from this day for 17 days after discontinuation of simeprevir sodium.<br>18 days after discontinuation:<br>Hepatic failure occurred. The cause of hepatic failure: drug-induced hepatic impairment. The clinical symptoms of hepatic failure were jaundice, fatigue, disorientation or confusion, encephalopathy, and ascites. Artificial ventilation, haemodialysis, steroid pulse therapy, and plasmapheresis were performed as ancillary therapy.<br>Prothrombin time (PT) activity was below 40%.<br>The patient experienced disturbed consciousness and decreased blood pressure. A tranquilizer was administered to the patient because he went on a rampage and took off his clothes. It was |

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| | | | | unknown whether or not the disturbed consciousness was associated with sepsis or hepatic encephalopathy.<br>Ammonia: 36μg/dL. Then the patient moved to the intensive care unit and liver transplantation was considered but denied by the patient.<br>19 days after discontinuation:<br>AST: 2 300 IU/L. T-Bil: 26.8 mg/dL. Disturbed consciousness, severe jaundice, hepatocellular necrosis were noted. HCV-RNA was not detected.<br>20 days after discontinuation:<br>Culture (blood culture from artery) revealed that the pathogen was *Serratia marcescens*.<br>Bacterial sepsis was diagnosed. Clinical findings were shock, hepatic failure, and disseminate intravascular coagulation.<br>21 days after discontinuation:<br>T-Bil: 20.2mg/dL<br>The patient died of bacterial sepsis, hepatic failure, serious hepatitis (suspected hepatitis fulminant), hepatic cirrhosis, and peritonitis.<br>The condition of the patient's liver was changed compared to that before administration of simeprevir sodium, and resulted in hepatic failure.<br>The causes of death were bacterial sepsis resulting from immunological deterioration, hepatic failure, and peritonitis.<br>The autopsy showed hepatic cirrhosis, hepatocellular necrosis, peritonitis, and acute pancreatitis. |
| | Concomitant medications: peginterferon alfa-2b, ribavirin, rosuvastatin calcium, olopatadine hydrochloride | | | |

## Laboratory Examination

| | 12 days before administration | Day 1 of administration | Day 7 of administration | Day 14 of administration | Day 28 of administration | Day 35 of administration | Day 42 of administration |
|---|---|---|---|---|---|---|---|
| Plt ($\times 10^4$/mm$^3$) | 9.0 | 8.3 | 6.7 | 6.7 | 4.8 | 6.6 | 6.8 |
| PT (%) | 77.0 | 95.0 | 103.0 | 103.0 | 100.0 | 98.0 | 103.0 |
| Alb (g/dL) | 4.2 | 3.9 | 4.1 | 3.8 | 3.8 | 3.8 | 4.0 |
| T-Bil (mg/dL) | 1.4 | 1.0 | 1.7 | 1.1 | 1.8 | 1.9 | 2.5 |
| D-Bil (mg/dL) | 0.2 | − | − | 0.2 | 0.5 | 0.7 | 0.9 |
| AST (IU/L) | 72 | 63 | 48 | 41 | 49 | 58 | 85 |
| ALT (IU/L) | 120 | 95 | 76 | 54 | 57 | 75 | 103 |
| ALP (IU/L) | 248 | 236 | 229 | 253 | 294 | 300 | 325 |
| γ-GTP (IU/L) | 39 | 34 | 39 | 34 | 36 | 36 | 42 |
| WBC (/mm$^3$) | 6 200 | 6 900 | 5 100 | 3 700 | 3 900 | 5 500 | 5 900 |

| | Day 49 of administration | Day 56 of administration | 3 days after discontinuation | 10 days after discontinuation | 15 days after discontinuation | 19 days after discontinuation | 21 days after discontinuation |
|---|---|---|---|---|---|---|---|
| Plt ($\times 10^4$/mm$^3$) | 7.4 | 6.1 | 6.2 | 11.6 | 8.3 | 3.5 | 1.3 |
| PT (%) | 116 | 131.0 | 95.0 | 95.0 | 72.0 | 34.0 | 19.0 |
| Alb (g/dL) | 3.7 | 3.5 | 2.9 | 3.3 | 3.1 | 2.6 | 2.5 |
| T-Bil (mg/dL) | 3.0 | 3.3 | 25.7 | 37.2 | 44.1 | 26.8 | 20.2 |
| D-Bil (mg/dL) | 1.3 | 1.9 | 16.7 | 24.5 | 34.5 | 18.3 | 13.0 |
| AST (IU/L) | 68 | 56 | 80 | 52 | 59 | 2 300 | 557 |
| ALT (IU/L) | 79 | 59 | 51 | 46 | 39 | 1 028 | 320 |
| ALP (IU/L) | 335 | 324 | 431 | 505 | 515 | 245 | 284 |
| γ-GTP (IU/L) | 45 | 48 | 32 | 27 | 24 | 17 | 21 |
| WBC (/mm$^3$) | 4 900 | 4 300 | 5 200 | 12 800 | 20 800 | 23 800 | 3 500 |

−: No data

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Male 60s | Chronic hepatitis C (Hepatic cirrhosis, Type 2 diabetes mellitus and duodenal ulcer) | 100 mg /84 days | Body weight (BW): approx. 70 kg, Height: approx. 160 cm, well-built.<br>Reluctant to visit the hospital. No history of chronic hepatitis C therapy. No history of allergies, no diabetic nephropathy, no history of alcohol consumption.<br>28 days before administration:<br>CT scan showed hepatic cirrhosis and no enlargement of the biliary tract. No punctuate (ascites/liver) was conducted. Plt: 8.5 × $10^4$ /$mm^3$<br>T-Bil: 1.5 mg/dL<br>Day 1 of administration:<br>Combination therapy of 3 drugs with simeprevir sodium (100 mg/day), peginterferon alfa-2a (45 μg/week), and ribavirin (800 mg/day) was started in another hospital. There were no clinical symptoms associated with liver cirrhosis when 3-drug combination therapy was started. The patient had mild but clinically-insignificant diabetes mellitus. At the initiation of administration, the white blood cell count (WBC) was 12 100/$mm^3$, however, there were no symptoms.<br>Day 57 of administration:<br>T-Bil: 4.0 mg/dL, Creatinin: 0.96 mg/dL<br>Day 72 of administration:<br>Creatinine: 0.88 mg/dL. (No data available from this day to 15 days after discontinuation of simeprevir sodium.)<br>Approx. Day 80 of administration:<br>Abnormalities had not been specified before this day. However, general malaise, anorexia, and weight loss (decreased by 7 kg in 3 weeks to 63 kg) were noted. The urine output also began to decrease.<br>Day 84 of administration (day of completion):<br>Administration of simeprevir sodium was completed.<br>15 days after completion:<br>Because the patient condition was poor, peginterferon alfa-2a was administered at the decreased dose (22.5 μg/week), then discontinued and the patient was followed up (last dose of peginterferon alfa-2a and ribavirin). No data on bilirubin.<br>22 days after completion:<br>Drug-induced cholestatic hepatic disorder and acute renal failure developed.<br>Creatinine and T-Bil increased, and cholestasis and acute renal failure concurrently developed. Because advanced cholestatic liver disorder was considered to have induced acute renal failure, intensive care such as plasmapheresis, haemodiafiltration, and steroid pulse therapy was performed. However, the patient did not respond to intensive care. Diagnostic imaging showed no biliary dilatation.<br>The clinical signs and symptoms associated with drug-induced cholestatic hepatic disorder included jaundice, fatigue, nausea, malaise, anorexia, and renal failure.<br>The clinical signs and symptoms associated with acute renal failure included oliguria, general malaise, impaired appetite, and disturbed consciousness.<br>25 days after completion:<br>Creatinine: 1.70 mg/dL<br>53 days after completion:<br>There was no improvement in the laboratory data after 3 weeks of admission to the hospital. The patient did not want to continue haemodialysis. |

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| | | | | In the afternoon, the patient died of multi-organ failure.<br>Causes of death were drug-induced cholestatic hepatic disorder, renal failure acute, and multi-organ failure.<br>An autopsy was not performed<br>Plasmapheresis, haemodiafiltration, and steroid pulse therapy were performed before death.<br>DLST: positive for simeprevir sodium |
| | Concomitant medications: rivabirin, peginterferon alfa-2a, loxoprofen sodium hydrate, and fexofenadine hydrochloride | | | |

Note: The duration of administration etc. could be modified according to the additional information obtained after preliminary safety report.

## Laboratory Examination

| | 28 days before administration | Day 1 of administration | Day 29 of administration | Day 57 of administration | Day 72 of administration | 15 days after completion |
|---|---|---|---|---|---|---|
| Plt (× $10^4$/$mm^{3)}$ | 8.5 | 8.9 | 7.6 | 7.6 | 6.8 | 13.7 |
| Alb (g/dL) | 3.9 | – | – | – | – | – |
| T-Bil (mg/dL) | 1.5 | 1.6 | 2.9 | 4.0 | – | – |
| D-Bil (mg/dL) | – | – | – | – | – | – |
| AST (IU/L) | 41 | 66 | 36 | 34 | 31 | – |
| ALT (IU/L) | 38 | 91 | 37 | 31 | 27 | – |
| ALP (IU/L) | 153 | – | – | – | – | – |
| γ-GTP (IU/L) | 44 | 85 | 70 | 63 | 72 | – |
| BUN (mg/dL) | 16 | 15 | 11 | – | – | – |
| Creatinine (mg/dL) | 1.02 | 1.06 | 0.91 | 0.96 | 0.88 | – |
| WBC (/$mm^3$) | 8 500 | 12 100 | 4 500 | 5 200 | 4 900 | 6 300 |

| | 22 days after completion | 25 days after completion | 32 days after completion | 43 days after completion | 53 days after completion |
|---|---|---|---|---|---|
| Plt (× $10^4$/$mm^3$) | 15.8 | 6.7 | 7.0 | 6.0 | 5.9 |
| Alb (g/dL) | – | 2.8 | 2.6 | 2.8 | 1.8 |
| T-Bil (mg/dL) | 37.8 | – | 16.7 | 22.0 | 25.2 |
| D-Bil (mg/dL) | – | – | 12.7 | 18.7 | 20.0 |
| AST (IU/L) | 47 | – | 23 | 37 | 607 |
| ALT (IU/L) | 27 | – | 13 | 21 | 210 |
| ALP (IU/L) | – | – | 188 | 282 | 554 |
| γ-GTP (IU/L) | 83 | – | 59 | 84 | 76 |
| BUN (mg/dL) | 89 | 12 | 12 | 24 | 94 |
| Creatinine (mg/dL) | 6.75 | 1.7 | 2.0 | 2.06 | 9.15 |
| WBC (/$mm^3$) | 7 600 | 12 600 | 9 500 | 6 900 | 16 100 |

–: No data

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 3 | Female 50s | Chronic hepatitis C (Diabetes mellitus) | 100 mg /62 days | BW: approx. 90 kg, Height: approx. 160 cm<br>History of varices oesophageal. (approx. 16.5 months ago)<br>No history of allergy. No history of alcohol consumption.<br>No history of adverse events with previous treatments.<br>Hepatic chirrhosis before initiation of simeprevir sodium: None<br>Pre-treatment: Child-pugh Score: Grade A (6 points), hepatic encephalopathy and ascites: None<br>Serum T-Bil: <2.0 mg/dL, serum albumin (Alb): 2.8-3.5 (g/dL), PT activity: >70%<br>17 days before administration:<br>Plt: $6.6 \times 10^4/mm^3$, T-Bil: 2.1 mg/dL<br>Day1 of administration:<br>Three drugs of combination therapy with simeprevir sodium (100 mg/day), peginterferon alfa-2a (180 μg/week), and ribavirin (800 mg/day) was started.<br>Day 18 of administration:<br>T-Bil: 4.8mg/dL<br>Day 54 of administration:<br>Jaundice developed.<br>Day 59 of administration:<br>Abdominal CT revealed that a finding of hepatic cirrhosis while no ascites was noted.<br>Day 62 of administration (day of discontinuation):<br>Hepatic failure developed.<br>Treatment with simeprevir sodium was discontinued, and the patient was admitted to hospital.<br>8 days after discontinuation:<br>The jaundice did not improve despite the discontinuation of the treatment with simeprevir sodium, then treatment with peginterferon alfa-2a and ribavirin was also discontinued.<br>13 days after discontinuation:<br>Abdominal CT showed pleural effusion and ascites. The patient experienced bacterial peritonitis.<br>19 days after discontinuation:<br>The jaundice did not improve. Steroid pulse therapy was started (and continued for 5 days).<br>22 days after discontinuation:<br>The jaundice and ascites retention became marked, and signs of spontaneous bacterial peritonitis were also noted, for which antibiotic treatment was intensified.<br>23 days after discontinuation:<br>The jaundice worsened, and continuous haemodiafiltration was performed (and continued for 2 days).<br>25 days after discontinuation:<br>The patient experienced hepatic encephalopathy. Plasma exchange was performed (and continued for 2 days).<br>27 days after discontinuation:<br>In the early morning, the patient died.<br>Outcome for hepatic failure and bacterial peritonitis: Death<br>DLST test: Not performed<br>Liver biopsy: Not performed |
| | Concomitant medications: rivabirin, peginterferon alfa-2a and mitiglinide calcium hydrate | | | |

### Laboratory Examination

| | 17 days before administration | Day 1 of administration | Day 18 of administration | Day 59 of administration | 9 days after discontinuation | 26 days after discontinuation |
|---|---|---|---|---|---|---|
| Plt ($\times 10^4/mm^3$) | 6.6 | 5.9 | 5.4 | 9.7 | 11.8 | 3.8 |
| Alb (g/dL) | 3.5 | 3.6 | 3.1 | 2.5 | 2.4 | 3.1 |
| T-Bil (mg/dL) | 2.1 | 2.08 | 4.8 | 11.21 | 15.61 | 21.68 |
| D-Bil (mg/dL) | 0.32 | − | 1.69 | 7.14 | 10.73 | 17.36 |
| AST (IU/L) | 30 | 29 | 23 | 45 | 56 | 748 |
| ALT (IU/L) | 23 | 22 | 18 | 23 | 27 | 181 |
| ALP (IU/L) | 339 | − | 259 | 400 | 387 | 261 |
| γ-GTP (IU/L) | 47 | 44 | 40 | 40 | 36 | 38 |
| RBC ($\times 10^4/mm^3$) | 404 | 399 | 284 | 321 | 319 | 290 |
| Hb (g/dL) | 14.2 | 14.1 | 9.8 | 11.1 | 10.9 | 10.1 |
| Htc (%) | 40.4 | 39.9 | 28.4 | 34.0 | 32.6 | 32.5 |
| WBC ($/mm^3$) | 4 600 | 4 800 | 1 500 | 3 400 | 4 600 | 17 700 |
| CRP (mg/dL) | 0.17 | 0.14 | − | 1.42 | 3.3 | 0.74 |

−: No data

## 4. Precautions against hyperbilirubinaemia

Healthcare professionals should pay due attention to the following:

(1) Blood bilirubin tests should be performed regularly during the treatment courses with this drug.

(2) If any abnormalities are observed including persistent increase in blood bilirubin levels, administration of this drug should be discontinued and appropriate measures should be taken.

(3) Blood bilirubin levels may be increased even after discontinuation of this drug. Therefore the patients' condition should be carefully observed.

(4) Patients should be advised to see their doctor immediately when colouring yellow of ocular and/or skin, brown urine, and/or general malaise, etc. are observed after the treatment courses.

## 5. Closing

For the revision of package insert, please see "4. Important Safety Information" on page 41 of this document.

Since Sovriad is a treatment of chronic hepatitis C, please make sure the patient has no cirrhosis before starting treatment. Healthcare professionals are encouraged to continuously cooperate for proper use of the drug.

### <Reference>

1) Dear Healthcare Professional Letter of Rapid Safety Communication (Blue Letter), Sovriad Capsules and Hyperbilirubinaemia
http://www.pmda.go.jp/english/service/pdf/letter/141024-sovriad.pdf
PMDA Investigation Result
http://www.pmda.go.jp/english/service/pdf/revision/20141024-simeprevir.pdf

# 2

# Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Medical Institutions and Pharmacies

## 1. Introduction

In order to ensure proper use of drugs and medical devices, MHLW and the PMDA have been jointly conducting safety measures such as revisions of the Precautions section of package inserts based on evidence including case reports of adverse reactions. Safety information on these measures is to be provided from MHLW, PMDA, and pharmaceutical companies to medical institutions via various routes. It is essential that the most up-to-date information available be disseminated to and utilized by, healthcare professionals at clinical settings in an appropriate manner.

PMDA, based on the Second and Third Mid-term Plans, has been conducting surveillance to grasp the status of the access to, dissemination, and utilization of safety information at medical institutions and pharmacies, and to propose the optimal way of information dissemination for easy access and optimal method of information sharing at clinical settings. From the results of the surveillance, PMDA aims to propose ideal ways for health care professionals to receive, distribute, and utilize safety information, thereby to help promote the safe use of drugs at clinical settings.

This section presents the results of the surveillance conducted by PMDA in fiscal year (FY) 2013.

## 2. Surveillance in FY 2013

### (1) Objective

To address the problems identified in the surveillances in the past 3 years,* the FY2013 surveillance selected and investigated good examples of access to, dissemination, and utilization of drug safety information and summarized the information, which are presented as references for other medical institutions to improve their own safety management system.

*References (past surveillances) (only available in Japanese language)

FY 2010 surveillance: http://www.info.pmda.go.jp/kyoten_iyaku/dentatsu_H22tyosa.html
FY 2011 surveillance: http://www.info.pmda.go.jp/kyoten_iyaku/dentatsu_H23tyosa.html
FY 2012 surveillance: http://www.info.pmda.go.jp/kyoten_iyaku/dentatsu_H24tyosa.html

### (2) Subjects and methods

The surveillance was conducted in 14 hospitals (including nearby clinics and pharmacies in some cases) actively promoting access to, dissemination, and utilization of drug safety information. The hospitals were selected based on the results of previous surveillances, the recommendations of the "Review Committee on the Status of the Dissemination and Utilization of Safety Information on Drugs etc. in Medical Institutions" (hereinafter referred to as "the Committee") consisting of experts on medical safety and pharmaceutical practices established in PMDA, and opinions from the relevant professional organizations.

The drug safety management supervisor or the person responsible for drug information management at the respective hospitals was interviewed about how drug safety information has been managed.

### (3) Surveillance results

Access to, dissemination, and utilization of safety information at the surveyed institutions were presented as case reports based on the interview. The educational material focusing on the role of in-house pharmacies was prepared to ensure the following activities for proper management of drug safety information based on the opinions from the Committee.

- Access to safety updates
- Risk management before a hospital allows physicians to start prescribing
- Analysis of safety information/planning of safety management measures
- Dissemination to staff in accordance with the urgency/importance of the information
- Support for safety management using electronic systems
- Post-dissemination follow-up
- Cooperation with other medical institutions/pharmacies through information sharing

Please see page 17 to 22 for the educational material.

# Proper management of drug safety information

**Pharmaceuticals and Medical Devices Agency**

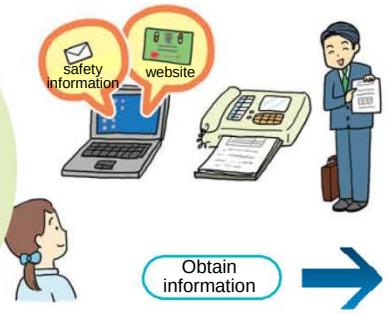
**October 2014**

## Introduction

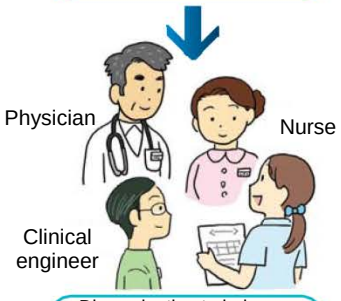
This information, prepared based on the opinions of PMDA's "Review Committee on the Status of the Dissemination and Utilization of Safety Information on Drugs, etc. in Medical Institutions," concerns proposed efforts to ensure drug safety information management at hospitals.
The entire hospital should be involved in drugs safety management. Although cooperation between the in-house pharmacy and the medical safety division is important, this information focuses on the role of hospital pharmacy.
Independent pharmacies and clinics are also encouraged to utilize this information for management of drug safety information.

**<Workflow of safety information>**

A variety of information such as Dear Healthcare Professional Letters of Emergent Safety Communications, Dear Healthcare Professional Letter of Rapid Safety Communication, information on revision of Precautions, Alert for proper use of drugs and Drug Safety Update (DSU)









## Proposed efforts to ensure drug safety information management

- Access to safety updates
- Risk management before a hospital allows physicians to start prescribing
- Analysis of safety information/planning of safety management measures
- Dissemination to staff in accordance with the urgency/importance of the information
- Support for safety management using electronic systems
- Post-dissemination follow-up
- Cooperation with other medical institutions/pharmacies through information sharing

Ensure proper management of drug safety information for safety control and improvement of healthcare quality.

# Access to safety updates

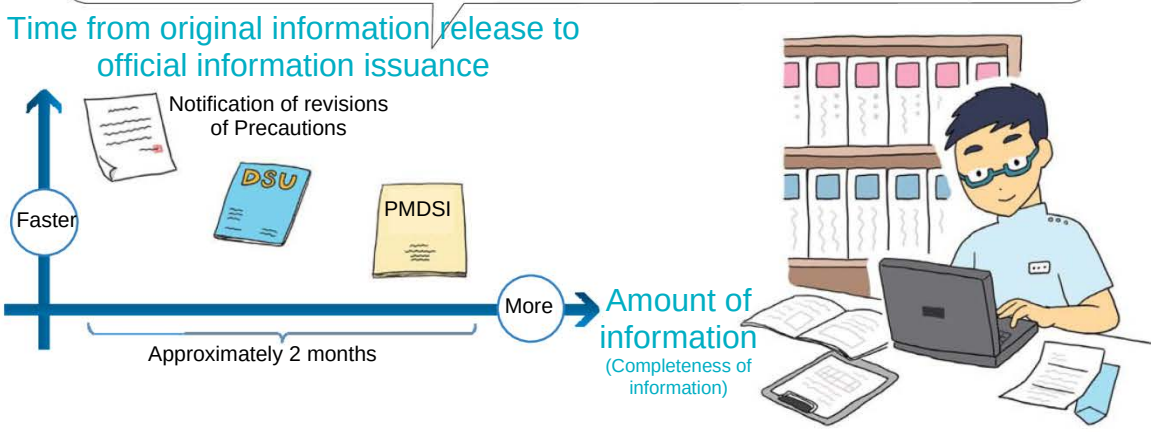
**Appoint the section/person in charge of safety information and prepare a procedure to access information to prevent information from being missed.**

**Select information sources based on the reliability, promptness, and completeness of information provided.**

**Use the Internet and e-mail to ensure efficient information collection.**

**Development of a specific information access system (section/person in charge, etc.) and securing information sources based on the characteristics of information media are crucial.**
**Assembling information on drugs prescribed exclusively for extramural dispensing and bring-in drugs as well as drugs dispensed from in-house hospital pharmacies is encouraged.**

"Notification of revisions of Precautions" will be issued first, followed by "DSU" and "Pharmaceuticals and Medical Device Safety Information (PMDSI)." The amount of information increases in the reverse order.




| | |
|---|---|
| Case 1-1: | Since a variety of drugs may be used as bring-in drugs in convalescent hospital, safety information on drugs dispensed in not only hospital pharmacy but also others is widely collected and managed. |
| Case 1-2: | Dates of checking and checking persons are documented for each information medium to prevent information from being missed. |
| Case 1-3*: | The latest information on standard drug therapies as well as drug safety information is collected to lay the groundwork for understanding and utilizing safety information. |

Please subscribe to PMDA medi-navi. You will receive all the important information without delay.

Subscribe to the PMDA medi-navi (pharmaceuticals and medical devices information e-mail alert service) and change of subscribed information are simple and easy. Visit the PMDA website for more details.

http://www.info.pmda.go.jp/info/idx-push.html

PMDA medi-navi Search

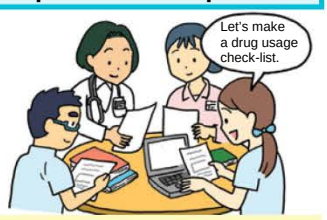
(only available in Japanese language)

*Cases presenting exceptional high-level efforts (ex. 1-3, 6-4)

## Risk management before a hospital allows physicians to start prescribing

**Develop a risk management procedure (ex. limitation of prescribing physicians, management of therapeutic regimen) based on the efficacy and safety information of the drug and the characteristics of the institution before the drug is dispensed in hospital.**

**Establish a guideline for proper use of drugs at the institution based on information on new drugs before a hospital allows physicians to start prescribing**




Case 2-1: Before dispensing a new drug, the limitation of prescriptions (limitation on quantity and prescribing physicians) and frequency of testing are discussed based on the information provided by the medical representative, Review report, overseas literature, and guidelines.

Case 2-2: Before dispensing a new drug, a drug usage manual containing a standard for proper use and a procedure for adverse reaction management as well as a drug use check-list are developed as necessary based on the clinical study data and overseas usage report.

Please utilize the risk management plan (RMP) for the discussion on safety of new drugs. The RMP is available on the PMDA website. Your cooperation in early post-marketing phase vigilance (EPPV) and use-results survey will also be appreciated.

## Analysis of safety information/planning of safety management measures

**Evaluate the level of urgency and importance of the safety information obtained based on the possible association with the drug dispensed in hospital and the characteristics of the institution and target patients.**

**Identify physicians whom the released safety information concerns and patients who may be affected using electronic medical charts, an ordering system and/or a medical affairs management system.**

**Develop appropriate safety management measures based on the characteristics of the institution and finalize it after discussing and cooperating with physicians at relevant clinical departments as necessary.**

**It is important to prepare action plans based on the in-house usage and the level of urgency and importance of the information.**
**Identifying prescribing physicians and target patients will help efficient dissemination.**


Case 3-1: The level of urgency and importance is classified based on the contents of the information obtained and the in-house usage, according to the existing information triage procedure.

Case 3-2: Prescribing physicians and target patients are identified by searching for the drug history. When information on testing is obtained, the current status of the testing and test values are checked. When information on an adverse reaction is obtained, occurrence of the adverse reaction is checked.

Different risks will be suggested by the same information depending on the institutional characteristics such as function of the hospital (ex. acute phase treatment, convalescent), location and type of patients treated there.

## Dissemination to staff in accordance with the urgency/importance of the information

**Identify the dissemination target (ex. entire hospital, relevant clinical departments, relevant professions) and the means of dissemination (ex. distribution of paper-based information, posting on the internal local area network, face-to-face explanation, real time/periodic dissemination) based on the level of urgency and importance of information in advance.**

**Determine the necessity to provide the information to in-house staffs, ensure appropriateness of dissemination target and means, disseminate information in a suitably adjusted manner, to avoid loss of important information.**

**Important information should be provided face to face to physicians and nurses by pharmacists.**

**It is important to cooperate with the medical safety division and to choose appropriate means of dissemination to physicians and nurses depending on the characteristics of the safety information.**

Case 4-1: A monthly in-house bulletin is issued to provide information on revisions of package insert and switch of the dispensed drugs available in hospital. Extra issues of the bulletin are distributed to all the departments when important information is released.
Case 4-2: Important information is provided face to face to designated prescribing physicians by ward pharmacists.
Case 4-3: Important information is provided repeatedly to prevent missing of information and forgetting.

For important safety information, be sure to use multiple means of dissemination and to provide reminders of the information after a certain amount of time has elapsed.

## Support for safety management using electronic systems

**Develop an alert system to display precautions for use when prescribing drugs by using electronic medical charts and an ordering system.**

**A reminder system to raise caution against interactions with concomitant drugs and to ensure appropriate dosage and administration and necessary testing can be incorporated by optimizing the electronic medical chart and ordering system.**


Case 5-1: When information on contraindication for co-administration is newly obtained, the master data of ordering system is renewed and set not to accept simultaneous prescription.
Case 5-2: The system is set up to give a reminder of important safety information when the user makes a prescription choice.

If electronic medical charts and an ordering system are installed in your institution, they can also be used for drug safety management.

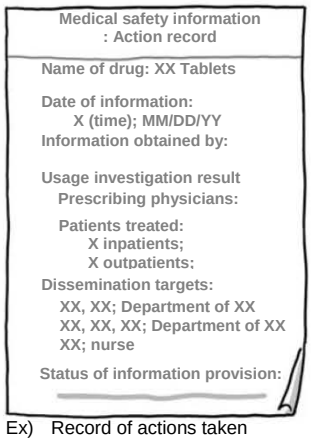
# Post- dissemination follow-up

**After dissemination of safety information, monitor the implementation of measures and give a reminder again according to the monitoring outcome.**

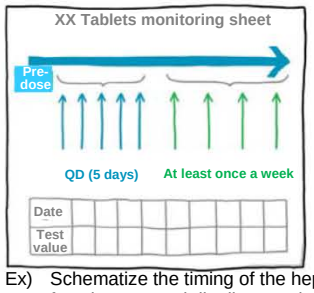
**Action should be considered to include the measures in the in-house manual and clinical path and plan periodic information provision and education/training in order to ensure continuous safety management based on the safety information.**

**Safety information disseminated within the institution should be appropriately recorded, and its utilization in the clinical practice should also be checked.**

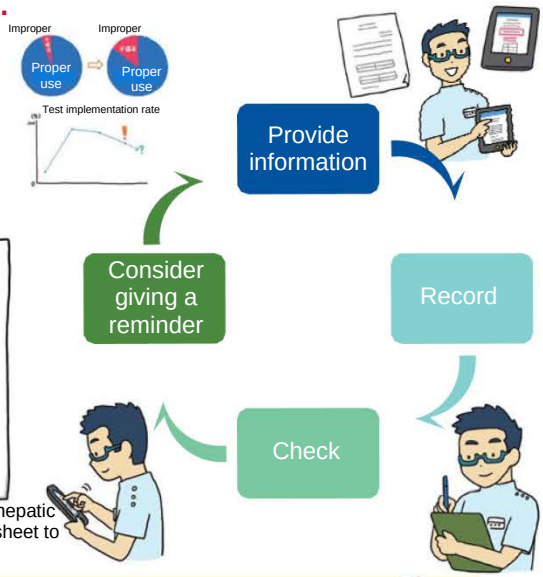
**After obtaining information on adverse reactions, check the occurrence of the reactions within the institution. Take appropriate actions if patients with suspected adverse reactions are identified.**




Ex) Record of actions taken concerning safety information




Ex) Schematize the timing of the hepatic function test and distribute a sheet to record test results




| | |
|---|---|
| Case 6-1: | Contents of safety information, results of in-house usage survey, action policy, summary of information provision by pharmacists, and reactions of information receivers are recorded to manage the dissemination of information. |
| Case 6-2: | After receiving important information, the post-dissemination change of medical care is checked based on medical charts, and implementation of actions is monitored for a specific period. The actions are evaluated based on the check results to consider correction of the actions and another reminder as necessary. |
| Case 6-3: | A check sheet has been developed to perform appropriate tests and monitor adverse reactions based on the safety information and to ensure proper use of drugs. |
| Case 6-4*: | An automatic monitoring system for test implementation and results has been developed for drugs requiring periodic testing to pick up inappropriate prescriptions. |

For ADRs, provide the information to MAHs and report it to the PMDA (medical institutions' reports) in accordance with the Drug and Medical Devices Safety Information Reporting System. If the case may be covered by the Relief System for Sufferers from ADRs, explain the system to the patient suffering from adverse health effects.


Medical certificates and medication records need to be prepared at medical institutions to apply for relief benefit. Your cooperation is necessary for prompt relief of sufferers from adverse health effects.

Please see the PMDA website (http://www.pmda.go.jp/kenkouhigai_camp/index.html) for more information (only available in Japanese language).

# Cooperation with other medical institutions/pharmacies through information sharing

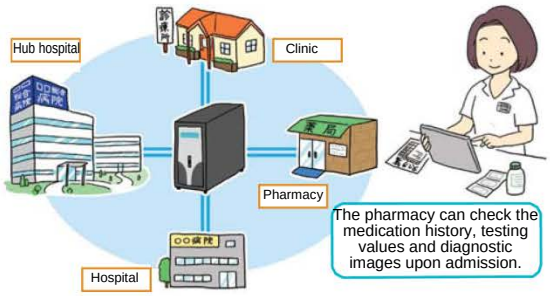
**With the consent of patients, provide information such as test values and names of disorders to dispensing pharmacies by sharing electronic medical chart information and documentation in prescription forms and medication record books.**

**Share the safety information obtained by the institution and in-house action policies with other local medical institutions and pharmacies through medical associations, pharmaceutical associations and/or societies of hospital pharmacists.**

**Accessing information on testing values and names of disorders at pharmacies is considered ideal and an effort has been made nationwide for pharmacists to effectively utilize safety information.**
**Sharing safety information with local medical institutions and pharmacies will help improve the local safety measures.**

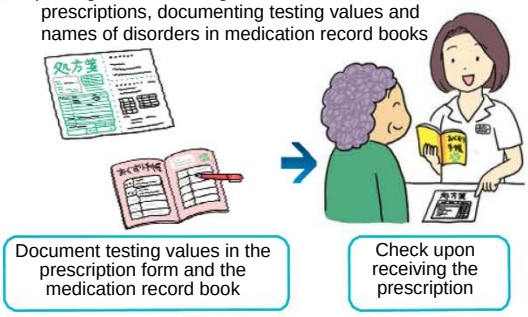
## Sharing electronic medical information

Ex: AJISAI NET (Nagasaki), "AMAKAKERU" (Onomichi, Hiroshima)




## Providing information by using external prescription forms and medication record books

Ex: printing relevant testing values on external prescriptions, documenting testing values and names of disorders in medication record books




Case 7-1: With the consent of patients, electronic medical chart information (ex. test values, diagnostic images) is shared with pre-registered local medical institutions and pharmacies.

Case 7-2: With the consent of patients, test values are documented in prescription forms as basic information for medication instructions given at pharmacies.

Case 7-3: In addition to the summary of important safety information, information on in-house actions, treated patients (if any) and occurrence of adverse reactions is provided to local pharmacies.

Case 7-4: Joint study sessions with local medical institutions and pharmacies are held to share information on proper use of drugs.

Aside from effective utilization of safety information within institutions, efforts to cooperate with other medical institutions and pharmacies are encouraged.

Please see the PMDA website for more information on the cases presented in this issue (only available in Japanese language).

**http://www.info.pmda.go.jp/kyoten_iyaku/dentatsu_katsuyou.html**

**Remarks**

This information is prepared based on the interviews with the medical institutions and pharmacies that cooperated in the FY 2013 Surveillance on Dissemination and Utilization of Safety Information in Medical Institutions and the opinions of members of the Review Committee on the Status of the Dissemination and Utilization of Safety Information on Drugs etc. in Medical Institutions.
This information is up to date at the time of preparation, and its appropriateness is not guaranteed in the future.
This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibilities on them, but is provided to support appropriate management of drug safety information.

Publisher: Pharmaceuticals and Medical Devices Agency

Contact: Investigation and Guidance Division, Office of Safety
TEL: 03-3506-9484
FAX: 03-3506-9543
http://www.info.pmda.go.jp

## 3. Closing

Appropriate access, dissemination, and utilization of the latest drug safety information in clinical practice are important to ensure proper use of drugs. The Pharmaceuticals and Medical Devices Information E-mail Alert Services (PMDA medi-navi) and the Medical Product Information website of PMDA are useful to ensure access to drug safety information in a prompter manner.

Please subscribe to PMDA medi-navi on its exclusive page at the Medical Product Information website to utilize it.

[PMDA medi-navi]
http://www.info.pmda.go.jp/info/idx-push.html (only available in Japanese language)

The results of the surveillance conducted in FY 2013 are posted on the following pages at the Medical Product Information website (only available in Japanese language).

[Outline of the Surveillance on Dissemination and Utilization of Safety Information in Medical Institutions]
http://www.info.pmda.go.jp/kyoten_iyaku/dentatsu_katsuyou.html
[Summary of the FY 2013 surveillance results (appropriate management of drug safety information)]
http://www.info.pmda.go.jp/kyoten_iyaku/file/h25_tyousa_keihatusizai.pdf
[Report on the FY 2013 surveillance results (case reports of surveyed institutions)]
http://www.info.pmda.go.jp/kyoten_iyaku/file/h25_houkoku_iyaku_yuryou.pdf

## Request for cooperation in the FY 2014 Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Medical Institutions

The PMDA has been discussing appropriate means to access to, disseminate, and utilize safety information in medical institutions and pharmacies and conducting surveillances to promote safe drug use in clinical settings. Your cooperation in the continuing surveillance in FY 2014 will be appreciated.

### Objective

The latest information on drugs and medical devices (the latest knowledge about Adverse drug reactions [ADRs]) and regulatory safety measures to be aware of provided by the MHLW, PMDA and pharmaceutical companies should be appropriately collected, disseminated and utilized at medical institutions and pharmacies.

This surveillance will provide materials for determining the optimal type of information and method of information provision to make safety information more usable in clinical settings by monitoring access to, dissemination, and utilization of safety information in medical institutions and pharmacies. The objective of this surveillance is to propose appropriate access to, dissemination, and utilization of safety information. PMDA hopes its proposal will be useful for you to promote safe drug use.

### Subjects

All hospitals in Japan (approximately 8500 institutions)

### Time of survey (tentative)

From December 2014 (approximately 6 weeks)

### Methods

Questionnaire forms will be sent to the hospital directors by post. The drug safety management supervisor or the person in charge of drug information is expected to answer the questionnaire.

Use the surveillance form on the website to answer the questionnaire in principle. You can enter the surveillance page from the PMDA website (http://www.info.pmda.go.jp/). If you do not have access to the Internet, fill out the paper questionnaire form and send it back by using the enclosed return envelope.

Your answers to the questionnaire will not be used for purposes other than to get surveillance results together and to develop safety measures to be taken by PMDA.

### Surveillance contractor

Mitsubishi Research Institute Inc.

*Surveillance activities such as mailing and collection of surveillance forms, responses to inquiries, making requests for questionnaire return and tabulation are contracted to a private company.

### Surveillance results

The results of this surveillance will be fed back to the responders and posted on the PMDA website. You are encouraged to use them as a reference for your future access to, dissemination, and utilization of drug safety information.

Past surveillance results are posted on the PMDA's information webpage.

http://www.info.pmda.go.jp/kyoten_iyaku/dentatsu_katsuyou.html (only available in Japanese language)

# 3

# Adverse Reactions to Influenza Vaccine in the 2013 Season

## 1. Introduction

This section presents adverse reactions to influenza vaccine reported from October 2013 through the end of July 2014 (hereinafter referred to as the 2013 season).

If a condition is diagnosed as an adverse reaction falling under the Reporting Criteria for adverse reactions to influenza vaccines at a medical institution, adverse reactions were to be reported from the institutions to MHLW, regardless of causality. The data of adverse reactions reported from medical institutions are tabulated and evaluated by PMDA together with those reported by MAHs as appropriate. In serious cases, etc. including fatal cases, the causalities were also evaluated based on evidence including opinions from experts. The necessity of safety measures was discussed.

These adverse reaction reports are investigated and reviewed on a regular basis at the Subcommittee of the Committee on Drug Safety under the Pharmaceutical Affairs and Food Sanitation Council and the Committee on Adverse Reactions of Immunization and Vaccine Department under the Health Sciences Council (hereinafter referred to as the Joint Meeting) to determine the necessity of safety measures.[1]

## 2. Reports of adverse reactions to influenza vaccines (2013 season)

### (1) Number of reported adverse reactions and reporting frequency

**Table 1** shows the number of reported adverse reactions to the influenza vaccines and the reporting frequency calculated from the estimated number of vaccinated persons based on the amount of vaccines distributed to the medical institutions.

**Table 1 Number of reported adverse reactions and estimated number of vaccinated persons**

| | Adverse reactions reported by medical institutions | | | Adverse reactions reported by MAHs (serious adverse reaction reports)* | |
|---|---|---|---|---|---|
| Estimated number of vaccinated persons (number of vaccinations) | Total number of reported adverse reactions (reporting frequency) | Number of reported serious cases (reporting frequency) | Number of reported deaths | Number of reported serious cases (reporting frequency) | Number of reported deaths |
| 51 731 811 (as of July 31, 2014) | 269 (0.0005%) | 84 (0.0002%) | 9 (0.00002%) | 63 (0.0001%) | 2 (0.000004%) |

* The adverse reactions reported by MAHs were determined to be serious in accordance with the Pharmaceutical Affairs Act Article 77-4-2 and may duplicate with some other cases of adverse reaction reports by the medical institutions. Duplicate reports were added up as reports by the medical institutions.

### (2) Reported adverse reactions by sex and age group

The number of reported adverse reactions to influenza vaccine is shown by sex and age group in **Tables 2** and **3**, respectively.

### Table 2 Number of reports by sex

| Sex | Number of adverse reactions reported by medical institutions | Number of adverse reactions reported by MAHs |
|---|---|---|
| Male | 127 | 27 |
| Female | 142 | 31 |
| Unknown | 0 | 5 |
| Total | 269 | 63 |

### Table 3 Number of reports by age

| Age | Number of adverse reactions reported by medical institutions | | | Number of adverse reactions reported by MAHs | |
|---|---|---|---|---|---|
| | Number of reported adverse reactions | Number of reported serious cases | | Number of reported serious cases | |
| | | | Number of reported deaths | | Number of reported deaths |
| 0-9 years | 81 | 27 | 1 | 19 | 0 |
| 10-19 years | 25 | 6 | 0 | 5 | 0 |
| 20-29 years | 16 | 1 | 0 | 8 | 0 |
| 30-39 years | 35 | 11 | 0 | 6 | 0 |
| 40-49 years | 24 | 8 | 0 | 5 | 0 |
| 50-59 years | 14 | 3 | 0 | 4 | 0 |
| 60-69 years | 20 | 5 | 0 | 0 | 0 |
| 70-79 years | 30 | 12 | 1 | 6 | 0 |
| ≥80 years | 23 | 11 | 7 | 7 | 2 |
| Unknown | 1 | 0 | 0 | 3 | 0 |
| Total | 269 | 84 | 9 | 63 | 2 |

## (3) Outline of reported adverse reactions

Adverse reactions to influenza vaccine reported for the 2013 season are presented by System Organ Class in the right column of **Table 4**. No marked difference was noted in comparison with the reports for the 2012 season.

Eleven cases of post-vaccination death were reported by the end of July 2014. Experts assessed that 10 cases were likely caused by exacerbation of an underlying disease or other factor, and that none of these deaths had a direct, clear causality to the vaccination. The following opinions on 1 fatal case of a patient with a diagnosis of encephalitis were raised from the experts; the death may be associated with the vaccination, or it was likely caused by hypertensive encephalitis. Encephalitis is one of the expected adverse reactions listed in the package inserts of influenza vaccines and subject to reporting within 28 days of onset according to the Adverse Reaction Reporting Criteria.

A total of 18 cases of adverse reactions [Note 1] were reported as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis. Of these, 7 cases and 4 cases (including cases for which a causal relationship to the vaccination could not be ruled out for Fisher syndrome, a subtype of Guillain-Barre syndrome) were determined to be Guillain-Barre syndrome and acute disseminated encephalomyelitis, respectively, and a causal relationship between their disease and influenza vaccine could not be ruled out, based on evidence including opinions of the experts.

A total of 23 cases of adverse reactions [Note 2] were reported as possible anaphylaxis. Of these, 15 cases were assessed as anaphylaxis of Level 3 or higher using Brighton Criteria.

Regarding the number of reports from MAHs by manufacturing lot, there were no specific lots in which anaphylaxis was reported more than in other lots.

At the Joint Meeting held in October 2014, it was considered that there was no new concern about the safety of vaccines, including other adverse reactions, and it was decided that taking actions such as

revision of package inserts would not be necessary at present and close attention would be continuously paid to the status of reports of adverse reactions and the contents of the reports.

Note 1: Including cases reported using the adverse reaction terms such as numbness, feeling of weakness, neuropathy, muscular weakness, and difficulty swallowing

Note 2: Includes cases reported as anaphylaxis, anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction.

### Table 4 Comparison of the number of adverse reaction reports between the 2012 season and the 2013 season (by organ)

| | 2012 season | | 2013 season | |
|---|---|---|---|---|
| | Trivalent influenza vaccine (seasonal bivalent and H1N1) | | Trivalent influenza vaccine (seasonal bivalent and H1N1) | |
| System Organ Class of adverse reaction* | Adverse reactions reported by medical institutions** | Adverse reactions reported by MAHs | Adverse reactions reported by medical institutions** | Adverse reactions reported by MAHs |
| Blood and lymphatic system disorders | 4 | 4 | 11 | 2 |
| Cardiac disorders | 1 | 3 | 4 | 1 |
| Ear and labyrinth disorders | 0 | 0 | 1 | 1 |
| Eye disorders | 1 | 0 | 2 | 1 |
| Gastrointestinal disorders | 2 | 5 | 6 | 0 |
| General disorders and administration site conditions | 19 | 35 | 21 | 24 |
| Hepatobiliary disorders | 2 | 3 | 6 | 3 |
| Immune system disorders | 10 | 11 | 9 | 5 |
| Infections and infestations | 1 | 8 | 11 | 7 |
| Investigations | 1 | 4 | 2 | 3 |
| Metabolism and nutrition disorders | 0 | 2 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 1 | 6 | 14 | 3 |
| Nervous system disorders | 27 | 32 | 32 | 16 |
| Renal and urinary disorders | 3 | 4 | 4 | 9 |
| Respiratory, thoracic and mediastinal disorders | 1 | 4 | 8 | 1 |
| Skin and subcutaneous tissue disorders | 7 | 11 | 9 | 17 |
| Endocrine disorders | 0 | 0 | 0 | 0 |
| Pregnancy, puerperium and perinatal conditions | 0 | 0 | 1 | 0 |
| Vascular disorders | 1 | 3 | 0 | 2 |
| Injury, poisoning and procedural complications | 1 | 0 | 0 | 0 |
| Reproductive system and breast disorders | 1 | 0 | 0 | 0 |
| Psychiatric disorders | 0 | 0 | 1 | 2 |
| Total | 83 | 135 | 142 | 97 |

* Adverse reaction terms were coded in accordance with the Medical Dictionary for Regulatory Activities/J Ver. 17.0.

** With regard to adverse reactions reported by the medical institutions, adverse reactions that were considered serious by the reporting physician were tabulated.

## 3. Safety measures hereafter

As provided in "Reporting Adverse Reaction for Routine Vaccination" [2], medical institutions are requested to promptly report any adverse reactions considered to meet the Adverse Reaction Reporting Criteria even if the causality is unclear.

In addition, medical institutions are requested to continue to exercise caution for the following points concerning anaphylaxis in the 2014 season:

(1) Vaccine recipients should be closely monitored for about 30 minutes after vaccination.
(2) If any symptoms suggesting anaphylaxis are observed, appropriate measures should be taken.
(3) Vaccine recipients and their guardians should be advised to consult a physician immediately if any abnormalities are observed after vaccination.

MHLW/PMDA will continue to collect safety information of influenza vaccines including adverse reaction reports and to conduct safety measures.

### <References>


1 MHLW: Distributed Materials 1-7 for the 2014 Committee on Adverse Reactions of Immunization and Vaccine Department under the Health Sciences Council (the 11th meeting) and the 2014 Subcommittee on Drug Safety of Committee on Drug Safety under the Pharmaceutical Affairs and Food Sanitation Council (the 6th meeting) (the Joint Meeting), Report of Adverse Reactions to Influenza Vaccines
http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000063515.pdf
(only available in Japanese language)

2 Reporting Adverse Reaction for Routine Vaccination: HSB Notification No. 0330-3 and PFSB Notification No. 033-1, by the Secretary-General of Health Service Bureau and Pharmaceutical and Food Safety Bureau, dated March 30, 2013 (partially amended on July 16, 2014 and September 26, 2014)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/yobou140926-6.pdf
(only available in Japanese language)
Report form: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/yobou140926-4.pdf
(only available in Japanese language)
Description guideline: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/yobou140926-5.pdf
(only available in Japanese language)

## Reference: Adverse Reaction Reporting Criteria

<Routine vaccination>

| Symptoms | Time to onset |
|---|---|
| Anaphylaxis | 4 hours |
| Hepatic dysfunction | 28 days |
| Interstitial pneumonia | 28 days |
| Acute disseminated encephalomyelitis | 28 days |
| Guillain-Barre syndrome | 28 days |
| Convulsion | 7 days |
| Vasculitis | 28 days |
| Thrombocytopenic purpura | 28 days |
| Asthmatic attack | 24 hours |
| Nephrotic syndrome | 28 days |
| Encephalitis or encephalopathy | 28 days |
| Oculomucocutaneous syndrome | 28 days |
| Other symptoms considered to be strongly associated with the vaccination by the physician and requiring hospital admission, resulting in death or physical dysfunction, or possibly resulting in death or physical dysfunction | Time frame in which the event was considered to be strongly associated with the vaccination by the physician |

Except for other reactions, any event occurring within the specific time frame is subject to mandatory reporting to the MHLW regardless of causality according to the Preventive Vaccination Law and associated related rules.

< Voluntary vaccination>

Adverse reactions or infections associated with voluntary vaccinations should be reported when reporting is necessary to prevent the occurrence or spread of a health hazards. See below for specific cases subject to reporting. Adverse reactions and infections of unclear association with vaccinations may also be subject to reporting.

(1) Death
(2) Disability
(3) Events that may result in death
(4) Events that may result in disability
(5) Requiring hospital admission or prolonged hospitalization for treatment [except for events in (3) and (4)]
(6) Serious events corresponding to those in (1) to (5)
(7) Congenital disease or anomaly in the next generation
(8) Onset of infections suspected of being caused by use of the vaccine
(9) Onset of unknown events which are non-mild and unexpected from the package insert, other than (1) to (8)

# 4

# Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated October 21 (1-3) and October 24 (4), 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

## 1 Enzalutamide

| | |
|---|---|
| **Brand Name (name of company)** | Xtandi Capsules 40 mg (Astellas Pharma Inc.) |
| **Therapeutic Category** | Antineoplastics-Miscellaneous |
| **Indications** | Castration-resistant prostate cancer |

### PRECAUTIONS (underlined parts are revised)

**Adverse Reactions (clinically significant adverse reactions)**

**Thrombocytopenia**: Thrombocytopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, 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 months (from initial marketing to August 2014)
Thrombocytopenia-associated cases: 7 cases (no fatal cases)
The number of patients using this drug per year estimated by MAHs:
Approximately 4 500 (from the initial marketing to August 2014)
Launched in Japan: May 2014

### Case Summary (thrombocytopenia)

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 80s | Castration-resistant prostate cancer, metastases to bone (none) | 160 mg for 15 days | **Thrombocytopenia**<br>Approximately 13 years before administration:<br>The patient had prostate cancer.<br>Approximately 2 years before administration:<br>Metastases to bone was found. Metastasis was confirmed in the lumbar spine (with bone scintigraphy).<br>Date unknown:<br>Chemotherapy was performed.<br>Day 1 of administration:<br>Administration of enzalutamide (160 mg, once daily) was started for castration-resistant prostate cancer.<br>Plt count was $17.6 \times 10^4/mm^3$.<br>The patient did not visit the hospital until Day 14 of administration.<br>Day 15 of administration (day of discontinuation):<br>Blood test showed Plt of $1.4 \times 10^4/mm^3$ and the patient was admitted to the hospital.<br>Thrombocytopenia developed.<br>Platelet concentrate (PC) (10 units) was transfused. |

| | | | | |
|---|---|---|---|---|
| | | | | Administration of enzalutamide was discontinued.<br>1 day after discontinuation:<br>Blood sampling was performed. Anti-platelet antibody test, *Helicobacter pylori* antibody test, and other tests were all negative.<br>PC (10 units) was transfused.<br>Plt was $1.1 \times 10^4/mm^3$ and $1.5 \times 10^4/mm^3$<br>4 days after discontinuation:<br>The patient was discharged from the hospital. Plt was $2.3 \times 10^4/mm^3$.<br>14 days after discontinuation:<br>Thrombocytopenia improved. Plt was $11.5 \times 10^4/mm^3$. |
| | Concomitant medications: celecoxib, famotidine, ketoprofen, dexamethasone, zoledronic acid hydrate | | | |

## Laboratory Examination (1)

| | Day 1 of administration | Day 15 of administration | 1 day after discontinuation -1 | 1 day after discontinuation -2 | 2 days after discontinuation | 4 days after discontinuation | 8 days after discontinuation | 14 days after discontinuation |
|---|---|---|---|---|---|---|---|---|
| Plt ($\times 10^4/mm^3$) | 17.6 | 1.4 | 1.1 | 1.5 | 1.8 | 2.3 | 6.5 | 11.5 |
| WBC ($/mm^3$) | 8 620 | 5 870 | 3 830 | 3 870 | 4 530 | 4 240 | 6 540 | 4 890 |
| RBC ($\times 10^4/mm^3$) | 360 | 400 | 364 | 358 | 363 | 360 | 359 | 366 |
| Hb (g/dL) | 11.5 | 12.7 | 11.8 | 11.5 | 11.8 | 11.8 | 11.6 | 11.8 |
| Htc (%) | 35.2 | 39.0 | 35.1 | 34.2 | 35.8 | 35.6 | 35.1 | 35.5 |
| MCV (fL) | 97.8 | 97.5 | 96.4 | 95.5 | 98.6 | 98.9 | 97.8 | 97.0 |
| MCH (pg) | 31.9 | 31.8 | 32.4 | 32.1 | 32.5 | 32.8 | 32.3 | 32.2 |
| MCHC (%) | 32.7 | 32.6 | 33.6 | 33.6 | 33.0 | 33.1 | 33.0 | 33.2 |
| RDW-CV (%) | 15.9 | 15.9 | 16.0 | 15.8 | 15.5 | 15.5 | 15.8 | 15.9 |
| Neutrophil count (mechanical value) ($/mm^3$) | 5 880 | – | – | 2 630 | – | – | – | – |
| Blasto (%) | – | – | – | 0.0 | – | – | – | – |
| Promyelo (%) | – | – | – | 0.0 | – | – | – | – |
| Myelo (%) | – | – | – | 0.0 | – | – | – | – |
| Meta (%) | – | – | – | 0.0 | – | – | – | – |
| Band (%) | – | – | – | 0.0 | – | – | – | – |
| Neutrophils (%) | 68.2 | – | – | 68.0 | – | – | – | – |
| Eosinophils (%) | 0.0 | – | – | 0.0 | – | – | – | – |
| Basophils (%) | 0.2 | – | – | 0.0 | – | – | – | – |
| Monocytes (%) | 7.0 | – | – | 9.0 | – | – | – | – |
| Lymphocytes (%) | 24.6 | – | – | 23.0 | – | – | – | – |
| Atypical lymphocytes (%) | – | – | – | 0.0 | – | – | – | – |
| Total lymphocyte count ($/mm^3$) | 2 121 | – | – | 890 | – | – | – | – |

## Laboratory Examination (2)

| | Day 1 of administration | Day 15 of administration | 1 day after discontinuation | 2 days after discontinuation |
|---|---|---|---|---|
| Total protein (g/dL) | 6.2 | 6.5 | – | – |
| Alb (g/dL) | 3.4 | 3.6 | – | – |
| AST (IU/L) | 16 | 21 | – | 15 |
| ALT (IU/L) | 10 | 10 | – | 8 |
| LDH (IU/L) | 290 | 379 | – | – |
| Al-P (IU/L) | 393 | 393 | – | – |
| γ-GTP (IU/L) | 15 | – | – | 16 |
| CHE (IU/L) | 278 | – | – | – |
| T-Bil (mg/dL) | 0.5 | – | – | – |
| Triglyceride (mg/dL) | 90 | – | – | – |
| HDL-cholesterol (mg/dL) | 65 | – | – | – |
| LDL-cholesterol (mg/dL) | 120 | – | – | – |
| BUN (mg/dL) | 18.9 | 24.2 | – | 19.4 |
| Creatinine (mg/dL) | 0.86 | 0.99 | – | 0.86 |
| eGFR (mL/min) | 55.1 | 47.2 | – | 52.5 |
| Uric acid (mg/dL) | 3.7 | 4.4 | – | – |
| Sodium (mEq/L) | 142 | 141 | – | 141 |
| Potassium (mEq/L) | 3.7 | 3.9 | – | 3.8 |
| Chloride (mEq/L) | 109 | 106 | – | 111 |
| Calcium (mg/dL) | 8.4 | – | – | – |
| Inorganic phosphorus (mg/dL) | 2.2 | – | – | – |
| CLcr (CG method) | 49.8 | 43.3 | – | 46.1 |
| PT% (%) | – | 94.3 | – | – |
| PT-INR | – | 1.01 | – | – |
| APTT (sec) | – | 31.4 | – | – |
| Fibrinogen (mg/dL) | – | 307.0 | – | – |
| FDP (μg/mL) | – | 4.8 | – | – |
| D-D dimer precise measurement (μg/mL) | – | 1.50 | – | – |
| AT-III (%) | – | 91 | – | – |
| CRP (mg/dL) | – | 0.39 | – | – |
| T-PSA (ng/mL) | 48.58 | 57.01 | – | – |
| *H. pylori* antibody (ng/mL) | – | – | (–) | – |
| Anti-platelet antibody | – | – | (–) | – |
| Antinuclear antibody (double) | – | – | <40 | – |
| Serum complement level (CH50) | – | – | 42.5 | – |
| Lupus AC (DRVVT) | – | – | 1.13 | – |
| Before neutralization (sec) | – | – | 43.9 | – |
| After neutralization (sec) | – | – | 38.8 | – |
| Anti-CL, B2GP1 antibody (U/mL) | – | – | ≤1.2 | – |
| PAIgG | – | – | 29 | – |
| C3 (mg/dL) | – | – | 109 | – |
| C4 (mg/dL) | – | – | 21 | – |

## 2 Teneligliptin Hydrobromide Hydrate

| | |
|---|---|
| **Brand Name (name of company)** | Tenelia Tablets 20 mg (Mitsubishi Tanabe Pharma Corporation) |
| **Therapeutic Category** | Antidiabetic agents |
| **Indications** | Type 2 diabetes mellitus |

### PRECAUTIONS (underlined parts are revised)

**Adverse Reactions (clinically significant adverse reactions)**

**Hepatic dysfunction:** Hepatic dysfunction with elevations of AST (glutamate oxaloacetate transaminase, GOT), ALT (glutamate pyruvate transaminase, GPT), *etc*. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

**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.

**Reference Information**

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years (from initial marketing to August 2014)
Hepatic dysfunction-associated cases: 3 cases (no fatal cases)
Interstitial pneumonia-associated cases: 4 cases (no fatal cases)
The number of patients using this drug per year estimated by MAHs:
Approximately 250 000 (August 2013 to July 2014)
Launched in Japan: September 2012

### Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 60s | Type 2 diabetes mellitus (brain neoplasm, depression) | 20 mg (for 19 days) ↓ 40 mg (for 22 days) | **Cough (interstitial pneumonia)**<br>Approximately 5 years before administration:<br>The patient had diagnosis of diabetes mellitus. She took glimepiride and metformin hydrochloride.<br>Approximately 3 years before administration:<br>Vildagliptin was administered concurrently (for 6 months).<br>Approximately 1 year before administration:<br>Vildagliptin was switched to alogliptin benzoate (due to poor adherence of taking medicine).<br>16 days before administration:<br>None of the following clinical signs and symptoms were noted:Dyspnoea, adventitious sounds, dehydration, disturbed consciousness, and swollen lymph nodes<br>From the preceding year, hemoglobin A1c (HbA1c) (national glycohemoglobin standardization program [NGSP]) had been at the 9% level, showing loss of control of blood glucose. At that time, the patient had been taking alogliptin benzoate, duloxetine hydrochloride, metformin hydrochloride, and glimepiride. With no particular symptom, blood sampling was performed.<br>Day 1 of administration:<br>Educational hospitalization was recommended due to poor |

| | | | | |
|---|---|---|---|---|
| | | | | control of blood glucose with a blood glucose level of 252 mg/dL and a HbA1c (NGSP) level of 9.6% (16 days before administration), but the patient declined it. Alogliptin benzoate was switched to teneligliptin hydrobromide hydrate (the other drugs were continued). Teneligliptin hydrobromide hydrate (20 mg/day for 19 days) was administered for type 2 diabetes mellitus.<br>Day 20 of administration:<br>The result of blood glucose self-monitoring showed that the 4-hour postprandial blood glucose level was 256 mg/dL. There were no particular symptoms. The dose of teneligliptin hydrobromide hydrate (40 mg/day for 22 days) was increased.<br>After Day 20 of administration:<br>Cough (interstitial pneumonia) occurred.<br>Day 41 of administration (day of discontinuation):<br>Blood test showed C-reactive protein (CRP) of 0.15 mg/dL and Krebs von den Lunge-6 (KL-6) of 1209 U/mL.<br>No pleural effusion was noted.<br>None of the following clinical signs and symptoms were noted: Dyspnoea, dehydration, disturbed consciousness, swollen lymph nodes Adventitious sounds (dry rales) were heard.<br>Unproductive cough occurred after Day 20 of administration. The patient said that the symptom developed 1 month before, around the time when switching to teneligliptin hydrobromide hydrate. The patient had no particular cold symptoms, without pyrexia. A chest x-ray was performed. Mild reticular opacities were noted in bilateral lower lung fields, suggesting interstitial pneumonia. The test parameter KL-6 was added.<br>The patient was instructed to discontinue oral administration of teneligliptin hydrobromide hydrate.<br>6 days after discontinuation:<br>The patient underwent CT at another hospital. Mild bronchiectasis and mild reticular opacities were noted in bilateral lower lung fields and the KL-6 level was as high as 1209 U/mL, and consequently, interstitial pneumonia was diagnosed.<br>7 days after discontinuation:<br>Cough substantially improved. The patient did not have a fit of coughing during the medical examination.<br>28 day after discontinuation:<br>None of the following clinical signs and symptoms were noted: Dyspnoea, adventitious sounds, dehydration, disturbed consciousness, and swollen lymph nodes<br>Dry cough improved. |
| | Concomitant medications: glimepiride, metformin hydrochloride, duloxetine hydrochloride | | | |

## Laboratory Examination

| Parameter \ Test date | | | 65 day before administration | 16 days before administration | Day 41 of administration (day of discontinuation) |
|---|---|---|---|---|---|
| WBC | | ($/mm^3$) | 5 100 | 4 800 | 8 000 |
| Differential leukocyte count | Neutrophils | (%) | 52 | 49 | 56 |
| | Eosinophils | (%) | 1 | 2 | 2 |
| | Basophils | (%) | 1 | 1 | 1 |
| | Lymphocytes | (%) | 41 | 43 | 36 |
| | Monocytes | (%) | 5 | 5 | 5 |

| | | | | |
|---|---|---|---|---|
| CRP | (mg/dL) | 0.07 | 0.11 | 0.15 |
| CRP | (qualitative result) | (−) | (−) | (−) |
| KL-6 | (U/mL) | − | − | 1 209 |
| AST (GOT) | (IU/L) | 18 | 20 | 19 |
| ALT (GPT) | (IU/L) | 18 | 22 | 21 |
| LDH | (IU/L) | 171 | 166 | 189 |
| γ-GTP | (IU/L) | 22 | 25 | 24 |
| Blood glucose (casual) | (mg/dL) | 228 | 252 | 148 |
| HbA1c (NGSP) | (%) | 9.5 | 9.6 | 9.1 |

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Male 80s | Diabetes mellitus (unknown) | 20 mg (for 3 days) | **Interstitial pneumonia (drug-induced pneumonia)**<br>Time unknown:<br>The patient had suspected interstitial pneumonia from before and was affected by emphysema (caused by tobacco).<br>Approximately 3 months before administration:<br>Chest X-ray findings: Reticular opacities were found in lower lung fields. Opacities spread to the area of 1/3 of the lungs.<br>Approximately 1 month and a half before administration:<br>Chest CT findings: Reticular opacities, nodular opacities, and emphysematous changes were found in right middle lower lobe and left lingular segment lower lobe.<br>Approximately 1 month before administration:<br>None of the following clinical signs and symptoms were noted: Cough, sputum, dyspnoea, dehydration, disturbed consciousness, and swollen lymph nodes. Adventitious sounds (crepitations) were heard.<br>Day 1 of administration:<br>At the gastroenterology/hepatology department of Hospital A, oral administration of teneligliptin hydrobromide hydrate (20 mg/day for 3 days) was started as it was switched from glibenclamide in the morning.<br>Day 2 of administration:<br>In the morning, pyrexia of 37.5°C occurred. Before dawn, pyrexia of 38.9°C occurred. Due to oxygen saturation (SpO2) 50%, emergency service was requested. Interstitial pneumonia (drug-induced pneumonia) occurred. The patient was transported to Hospital B before arriving at this hospital.<br>Day 3 of administration (day of discontinuation):<br>Due to acute exacerbation of chronic obstructive pulmonary disease, hydrocortisone sodium phosphate injection solution (200 mg/day) and sulbactam sodium/ampicillin sodium for injection (3 g/day) were intravenously administered at the emergency room of Hospital B.<br>In the morning, the patient was transferred to this hospital. Based on the images and clinical course, acute exacerbation of interstitial pneumonia or drug-induced pneumonia due to teneligliptin hydrobromide hydrate was suspected, and consequently, administration of steroid and oxygen was started. Teneligliptin hydrobromide hydrate was discontinued on this day. |

| | | | | |
|---|---|---|---|---|
| | | | | After hospital transfer, bacterial pneumonia could not be ruled out. Tazobactam sodium/piperacillin sodium for injection (13.5 g/day for 6 days) and levofloxacin hydrate injection (500 mg/day for 8 days) were intravenously administered.<br>Prednisolone sodium succinate for injection (40 mg/day) was intravenously administered for drug-induced pneumonia. DLST was performed to determine whether it was drug-induced interstitial pneumonia. Oxygenation was improved gradually.<br>Chest X-ray findings: Reticular opacities and ground-glass opacities (diffuse) were found in the total lung field. Opacities spread to the area of 2/3 or more of the lungs.<br>Chest CT findings Reticular opacities, ground-glass opacities (diffuse), bronchiectasis, and nodular opacities, emphysematous changes were found in the total lung field in addition to left lingular segment.<br>Cough and adventitious sounds (crepitations) were noted. None of the following clinical signs and symptoms were noted: Sputum, dehydration, disturbed consciousness, and swollen lymph nodes.<br>Bacterial and viral test: Test of sputum for viable microorganisms by smear staining method was positive for bacteria (enterobacter cloacae) (found on the day of discontinuation).<br>Test of sputum for Mycobacterium tuberculosisby smear staining methodwas negative. Tests by both PCR method and culture method (solid medium) were also negative.<br>Urinary pneumococcal antigen was negative<br>No pleural effusion was noted.<br>1 day after discontinuation:<br>For drug-induced pneumonia, prednisolone tablets (35 mg/day for 13 days) were orally administered.<br>12 days after discontinuation:<br>Chest CT findings: Mainly ground-glass opacities, seen on Day 3 of administration were improved. Reticular opacities, ground-glass opacities (localized), bronchiectasis, nodular opacities, and emphysematous changes were found.<br>13 days after discontinuation:<br>Chest X-ray findings: Reticular opacities were found in lower lung fields. . Opacities spread to the area of 1/3 of the lungs.<br>14 days after discontinuation:<br>The dose of prednisolone tablets was reduced (to 30 mg/day for 8 days). DLST was positive for teneligliptin hydrobromide hydrate.<br>20 days after discontinuation:<br>Interstitial pneumonia (drug-induced pneumonia) improved.<br>None of the following clinical signs and symptoms were noted: Cough, sputum, dyspnoea, dehydration, disturbed consciousness, and swollen lymph nodes<br>Adventitious sounds (crepitations) were heard.<br>22 days after discontinuation:<br>The dose of prednisolone tablets was set to be 25 mg, and the patient was discharged from the hospital. |
| | Concomitant medications: azilsartan, tiotropium bromide hydrate, tulobuterol, lansoprazole, glibenclamide, allopurinol, pravastatin sodium, aspirin | | | |

## Laboratory Examination

| Parameter \ Test date | | | Approximately 1 month and a half before administration | Approximately 1 month before administration | 1 day before administration | Day 3 of administration (day of discontinuation) | 1 day after discontinuation | 3 days after discontinuation | 5 days after discontinuation | 7 days after discontinuation | 10 days after discontinuation | 13 days after discontinuation | 17 days after discontinuation | 20 days after discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WBC | | (/mm$^3$) | – | 10 900 | – | 11 800 | 13 800 | 18 700 | 16 100 | 15 800 | 18 400 | 19 600 | 19 400 | 16 600 |
| Differential leukocyte count | Neutrophils | (%) | – | – | – | 72.4 | 74.5 | 66.4 | 56.5 | 57.7 | 59.2 | 62.0 | 59.4 | 60.4 |
| | Eosinophils | (%) | – | – | – | 0.3 | 0.0 | 0.1 | 0.1 | 0.2 | 0.3 | 0.1 | 0.2 | 0.2 |
| | Basophils | (%) | – | – | – | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 | 0.1 | 0.1 | 0.1 | 0.1 |
| | Lymphocytes | (%) | – | – | – | 26.0 | 23.7 | 29.9 | 39.3 | 38.2 | 36.3 | 33.7 | 37.1 | 35.0 |
| | Monocytes | (%) | – | – | – | 1.3 | 1.7 | 3.5 | 4.0 | 3.9 | 4.1 | 4.1 | 3.2 | 4.3 |
| CRP | | (mg/dL) | – | – | – | 5.41 | 8.48 | 4.61 | 1.89 | 0.89 | 0.49 | 0.67 | 0.37 | 0.61 |
| KL-6 | | (U/mL) | 873 | – | – | 1 547 | – | – | 1 465 | – | – | – | – | 1 361 |
| SP-D | | (ng/mL) | – | – | – | 300 | – | – | 361 | – | – | – | – | 93.0 |
| β-D-glucan | | (pg/mL) | – | – | – | 4.0> | – | – | – | – | – | – | – | – |
| $SpO_2$ | | (%) | 92 | – | – | 50 | – | – | 97 | – | – | – | – | 96 |
| $PaO_2$ | | (mmHg) | – | – | – | 33.4 | – | – | – | – | – | – | – | – |
| AST (GOT) | | (IU/L) | – | 28 | – | 39 | 33 | 35 | 40 | 44 | 47 | 45 | 41 | 39 |
| ALT (GPT) | | (IU/L) | – | 15 | – | 20 | 15 | 19 | 31 | 49 | 62 | 74 | 73 | 70 |
| LDH | | (IU/L) | – | 233 | – | 378 | 337 | 291 | 288 | 271 | 339 | 264 | 313 | 225 |
| γ-GTP | | (IU/L) | – | 36 | – | 35 | 32 | 31 | 39 | 45 | 52 | 65 | 71 | 67 |
| Blood glucose (fasting) | | (mg/dL) | – | – | – | 142 | – | – | – | – | – | – | – | – |
| HbA1 (c NGSP) | | (%) | – | 6.0 | 6.1 | – | – | – | – | – | – | – | – | – |

## 3 Vancomycin Hydrochloride (injectable dosage form)

| | |
|---|---|
| **Brand Name (name of company)** | Vancomycin Hydrochloride for Intravenous Infusion 0.5 g (Shionogi & Co., Ltd.) and the others |
| **Therapeutic Category** | Acting mainly on gram-positive bacteria |
| **Indications** | 1. <Applicable microorganisms><br>Vancomycin-sensitive strains of methicillin-resistant *Staphylococcus aureus* (MRSA)<br><Applicable conditions><br>Sepsis, endocarditis infective, secondary infection (from trauma, thermal burn, and surgical wound, etc.), osteomyelitis, arthritis, pneumonia, lung abscess, pyothorax, peritonitis, pyogenic meningitis<br>2. <Applicable microorganisms><br>Vancomycin-sensitive strains of methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS)<br><Applicable conditions><br>Sepsis, endocarditis infective, secondary infection (from trauma, thermal burn, and surgical wound, etc.), osteomyelitis, arthritis, peritonitis, pyogenic meningitis<br>3. <Applicable microorganisms><br>Vancomycin-sensitive strains of penicillin-resistant *Streptococcus pneumoniae* (PRSP)<br><Applicable conditions><br>Sepsis, pneumonia, pyogenic meningitis<br>4. Febrile neutropenia of suspected MRSA or MRCNS<br><br>∗ Only the product manufactured by Shionogi & Co., Ltd. has the indication shown in 3. (as of the end of October 2014). |

### PRECAUTIONS (underlined parts are revised)

**Adverse Reactions (clinically significant adverse reactions)**

**Drug-induced hypersensitivity syndrome (DIHS):** Rash and/or pyrexia may occur as the initial symptoms and signs followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, lymphadenopathy, increased white blood cells, increased eosinophils, atypical lymphocytes *etc*. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken. The reactivation of viruses including Human Herpes virus 6 (HHV-6) has been found frequently associated with DIHS. Symptoms such as rash, pyrexia, and/or hepatic dysfunction may relapse or be prolonged even after discontinuation of administration, and thus caution should be exercised.

**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 5 months (April 2011 to August 2014).
DIHS: 3 cases (no fatal cases)
The number of patients using this drug per year estimated by MAHs:
Approximately 15 000 (Original product, August 2013 to July 2014)
Launched in Japan: November 1991

### Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 60s | Skin ulcer of the right plantar, wound infection (pyrexia) | 3 g for 19 days | **Suspected DIHS**<br>Day 1 of administration:<br>The patient started receiving vancomycin hydrochloride 1.5 g × 2/day, cefazolin sodium 1 g/day (for 11 days), and |

| | | | | |
|---|---|---|---|---|
| | | | | physiological saline 50 mL × 2/day (for 19 days) for wound infection.<br>Day 5 of administration:<br>Administration of loxoprofen sodium hydrate 60 mg/day (for 19 days) and diclofenac sodium 50 mg/day (for 17 days) was started for pyrexia.<br>Day 12 of administration:<br>Cefmetazole sodium 1 g was administered once, and administration of flomoxef sodium 1 g × 2/day (for 8 days) was started.<br>Day 19 of administration (day of discontinuation):<br>Skin eruption occurred throughout the body. The patient had pyrexia of 38.4°C and swollen lymph nodes in the right inguinal region and left clavicular fossa.<br>Administration of olopatadine hydrochloride orally-disintegrating tablets 10 mg, *d*-chlorpheniramine maleate tablets 6 mg, and betamethasone butyrate propionate ointment was started.<br>2 days after discontinuation:<br>Oral administration of prednisolone tablets 30 mg was started.<br>5 days after discontinuation:<br>The dose of prednisolone tablets was increased to 40 mg.<br>6 days after discontinuation:<br>Steroid pulse therapy (for 3 days) was started.<br>Methylprednisolone 1000 mg was administered.<br>7 days after discontinuation:<br>Skin eruption tended to resolve.<br>41 days after discontinuation:<br>The result of DLST was positive for vancomycin hydrochloride (SI, 868%).<br>62 days after discontinuation:<br>Diagnosis by dermatologist: Suspected DIHS |
| | Concomitant medications: cefazolin sodium, physiological saline, loxoprofen sodium hydrate, diclofenac sodium, cefmetazole sodium, flomoxef sodium | | | |

## Laboratory Examination

| | | Day 1 of administration | 3 days after discontinuation | 6 days after discontinuation | 7 days after discontinuation | 20 days after discontinuation |
|---|---|---|---|---|---|---|
| WBC | (/mm$^3$) | 17 200 | 16 870 | − | 28 880 | − |
| Eosinophils | (%) | 0.9 | 2.7 | − | 0.2 | − |
| AST (GOT) | (IU/L) | 21 | 31 | − | 19 | − |
| ALT (GPT) | (IU/L) | 29 | 39 | − | 39 | − |
| Al-P | (IU/L) | 304 | 194 | − | 192 | − |
| LDH | (IU/L) | − | 489 | − | 220 | − |
| γ-GTP | (IU/L) | − | 30 | − | 26 | − |
| T-Bil | (mg/dL) | − | 0.4 | − | 0.4 | − |
| CRP | (mg/dL) | 6.24 | 9.69 | − | 0.79 | − |
| BUN | (mg/dL) | 13 | 30 | − | 4.3 | − |
| Serum creatinine | (mg/dL) | 0.69 | 1.52 | − | 0.95 | − |
| Urine protein | | − | (2 +) | − | − | − |
| HHV-6 IgG | | − | − | 10 | − | 640 |

# 4 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:<br>1) Treatment-naïve patients with high blood HCV RNA load<br>2) Patients who have failed to respond to, or have relapsed after, therapy including interferon |

## PRECAUTIONS (underlined parts are revised)

**Warnings**

Cases of remarkable increase in blood bilirubin levels followed by hepatic dysfunction and/or renal impairment, *etc*. leading to death have been reported in patients treated with this drug. Pay attention to the followings:

(1) Blood bilirubin tests should be performed regularly during treatment course with this drug.

(2) If any abnormalities are observed including persistent increase in blood bilirubin levels, administration of this drug should be discontinued and appropriate measures should be taken.

(3) Blood bilirubin levels may be increased even after discontinuation of this drug. Therefore the patients' condition should be carefully observed.

(4) Patients should be advised to see their doctor immediately when colouring yellow of ocular and/or skin, brown urine, and/or general malaise, *etc*. are observed after the treatment course.

**Precautions for Indications**

Prior to initiate the administration of this drug to patients, healthcare professionals should check that blood HCV RNA is positive and that hepatic cirrhosis is ruled out based on histology, residual function of the liver, Plt count, *etc*.

**Important Precautions**

~~Increased blood bilirubin levels have been reported in the treatment with this drug., Blood bilirubin level, liver function test values, and/or patients' condition should be carefully monitored during treatment courses with this drug. If hepatic function is aggravated, appropriate measures should be taken~~. (deleted)

**Adverse Reactions (clinically significant adverse reactions)**

**Hyperbilirubinaemia** (incidence unknown): Blood bilirubin levels may be markedly increased. Cases of remarkable increase in blood bilirubin levels followed by hepatic dysfunction and/or renal impairment, *etc*. leading to death have been reported. Blood bilirubin tests should be performed regularly during the treatment courses with this drug. Patients' condition should be carefully observed. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. (See Warnings section)

**Hepatic dysfunction** (incidence unknown): Hepatic dysfunction accompanied by increased AST (GOT), ALT (GPT), alkaline phosphatase (Al-P), gamma-glutamyl transpeptidase (γ-GTP), *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 10 months (from initial marketing to October 2014)

Cases with remarkable increase in blood bilirubin levels*: 7 cases (3 fatal cases)

* Cases with blood bilirubin levels of ≥10 mg/dL.

Serious hepatic dysfunction-associated cases**: 12 cases (3 fatal cases [identical with the abovementioned 3 fatal cases of remarkable increase in blood bilirubin levels])

** AST ≥500 IU/L or ALT ≥500 IU/L (including patients with no available data)

The number of patients using this drug estimated by MAHs:
Approximately 18 900 (December 2013 to September 2014)
Launched in Japan: December 2013

**Case Summary**

See the Case Summary in "1. Simeprevir Sodium and Hyperbilirubinaemia" of this issue.

# 5

# Revision of Precautions (No. 260)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated October 21, 2014.

## 1

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

## Acetaminophen

| | |
|---|---|
| **Warnings** | Serious liver disorder due to acetaminophen overdose may occur in concomitant use of other acetaminophen-combination products (including over-the-counter [OTC] drug). Concomitant use with other acetaminophen-combination products should be avoided. (See Important Precautions and Overdosage sections) |
| **Important Precautions** | Serious liver disorder due to acetaminophen overdose may occur in concomitant use of other acetaminophen-combination products (including OTC drugs). When other drugs are used concomitantly, especially when combination products such as common cold drugs and analgesics, anti-inflammatory agents are used concomitantly, healthcare professionals should check whether the concomitant drugs contain acetaminophen or not. Healthcare professionals should avoid concomitant use of acetaminophen-combination products with acetaminophen. In addition, patients should be educated to avoid concomitant use of acetaminophen-combination products with acetaminophen. (See Warnings and Overdosage sections) |

## 2

**Acting mainly on gram-positive bacteria**

## Vancomycin Hydrochloride (oral dosage form)

| | |
|---|---|
| **Brand Name** | Vancomycin Hydrochloride Powder 0.5 g (Shionogi & Co., Ltd.) and the others |
| **Adverse Reactions (clinically significant adverse reactions)** | Anaphylaxis, acute renal failure, interstitial nephritis, pancytopenia, agranulocytosis, thrombocytopenia, toxic epidermal necrolysis, oculomucocutaneous syndrome (Stevens-Johnson syndrome), dermatitis exfoliative, DIHS, VIIIth cranial nerve disorder, pseudomembranous colitis, hepatic dysfunction, and/or jaundice have been reported in patients treated with vancomycin hydrochloride intravenous infusion. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken. |

# 6

# 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 November 1, 2014)

◎: Products for which EPPV was initiated after October 2, 2014

| | Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | standardized Japanese cedar pollen extract original solution<br>Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL bottle, 2 000 JAU/mL bottle, 2 000 JAU/mL pack | Torii Pharmaceutical Co., Ltd. | October 8, 2014 |
| | bimatoprost<br>GlashVista Cutaneous Solution 0.03% 5 mL | Allergan Japan K.K. | September 29, 2014 |
| | edoxaban tosilate hydrate<br>Lixiana Tablets 15 mg, 30 mg*[1] | Daiichi Sankyo Company, Limited | September 26, 2014 |
| | voriconazole<br>Vfend Tablets 50 mg, 200 mg, Vfend for Intravenous Use 200 mg*[2] | Pfizer Japan Inc. | September 26, 2014 |
| | metronidazole<br>Anaemetro Intravenous Infusion 500 mg | Pfizer Japan Inc. | September 26, 2014 |
| | delamanid<br>Deltyba Tablets 50 mg | Otsuka Pharmaceutical Co., Ltd. | September 26, 2014 |
| | treprostinil<br>Treprost 20 mg for Injection, 50 mg for Injection, 100 mg for Injection, 200 mg for Injection | Mochida Pharmaceutical Co., Ltd. | September 26, 2014 |
| | anti-human thymocyte immunoglobulin, rabbit<br>Thymoglobuline for Intravenous Infusions 25 mg*[3] | Sanofi K.K. | September 19, 2014 |
| | donepezil hydrochloride<br>Aricept Tablets 3 mg, 5 mg, 10 mg, Aricept D Tablets 3 mg, 5 mg, 10 mg, Aricept Fine Granules 0.5%, Aricept Oral Jelly 3mg, 5mg, 10 mg, Aricept Dry Syrup 1%*[4] | Eisai Co., Ltd. | September 19, 2014 |
| | aflibercept (genetical recombination)<br>Eylea Solution for IVT inj. 40mg/mL, Eylea Solution for IVT inj. Kit 40 mg/mL*[5] | Bayer Yakuhin, Ltd. | September 19, 2014 |
| | calcipotriol hydrate/betamethasone dipropionate<br>Dovobet Ointment | Leo Pharma K.K. | September 12, 2014 |

| Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| eftrenonacog alfa (genetical recombination)<br>Alprolix Intravenous 500, 1000, 2000, 3000 | Biogen Idec Japan Ltd. | September 8, 2014 |
| alectinib hydrochloride<br>Alecensa Capsules 20 mg, 40 mg | Chugai Pharmaceutical Co., Ltd. | September 5, 2014 |
| cabazitaxel acetonate<br>Jevtana 60 mg I.V. Infusion | Sanofi K.K. | September 4, 2014 |
| umeclidinium bromide/vilanterol trifenatate<br>Anoro Ellipta 7 doses | GlaxoSmithKline K.K. | September 4, 2014 |
| (1) daclatasvir hydrochloride<br>(2) asunaprevir<br>(1) Daklinza Tablets 60 mg<br>(2) Sunvepra Capsules 100 mg | Bristol-Myers K.K. | September 3, 2014 |
| cysteamine bitartrate<br>Nicystagon Capsules 50 mg, 150 mg | Mylan Seiyaku Ltd. | September 3, 2014 |
| canagliflozin hydrate<br>Canaglu Tablets 100 mg | Mitsubishi Tanabe Pharma Corporation | September 3, 2014 |
| nivolumab (genetical recombination)<br>Opdivo Intravenous Infusion 20 mg, 100 mg | Ono Pharmaceutical Co., Ltd. | September 2, 2014 |
| ruxolitinib phosphate<br>Jakavi Tablets 5 mg | Novartis Pharma K.K. | September 2, 2014 |
| velaglucerase alfa (genetical recombination)<br>Vpriv Intravenous Injection 400 U | Shire Japan KK | September 2, 2014 |
| abiraterone acetate<br>Zytiga Tablets 250 mg | Janssen Pharmaceutical K.K. | September 2, 2014 |
| efinaconazole<br>Clenafin Topical Solution 10% for Nail | Kaken Pharmaceutical Co., Ltd. | September 2, 2014 |
| rituximab (genetical recombination)<br>Rituxan Injection 10 mg/mL*[6] | Zenyaku Kogyo Co., Ltd. | August 29, 2014 |
| phenothrin<br>Sumithrin Lotion 5% | Kracie Pharma, Ltd. | August 22, 2014 |
| tapentadol hydrochloride<br>Tapenta Tablets 25 mg, 50 mg, 100 mg | Janssen Pharmaceutical K.K. | August 18, 2014 |
| fentanyl citrate<br>Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg*[7] | Hisamitsu Pharmaceutical Co., Inc. | June 20, 2014 |
| sorafenib tosilate<br>Nexavar Tablets 200 mg*[8] | Bayer Yakuhin, Ltd. | June 20, 2014 |
| pneumococcal 13-valent conjugate vaccine (diphtheria $CRM_{197}$ protein)<br>Prevenar 13 Suspension Liquid for Injections*[9] | Pfizer Japan Inc. | June 20, 2014 |
| azilsartan/amlodipine besilate<br>Zacras Combination Tablets LD, HD | Takeda Pharmaceutical Company Limited | June 18, 2014 |
| natalizumab (genetical recombination)<br>Tysabri. for I.V. Infusions 300 mg | Biogen Idec Japan Ltd. | June 4, 2014 |
| prasugrel hydrochloride<br>Efient Tablets 3.75 mg, 5 mg | Daiichi Sankyo Company, Limited | May 27, 2014 |

| Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| betaine<br>Cystadane | ReqMed Company, Ltd. | May 27, 2014 |
| trifluridine/tipiracil hydrochloride<br>Lonsurf Combination Tablets T15, T20 | Taiho Pharmaceutical Co., Ltd. | May 26, 2014 |
| denosumab (genetical recombination)<br>Ranmark Subcutaneous Injections 120 mg*10 | Daiichi Sankyo Company, Limited | May 23, 2014 |
| enzalutamide<br>Xtandi Capsules 40 mg | Astellas Pharma Inc. | May 23, 2014 |
| valsartan/cilnidipine<br>Atedio Combination Tablets | Ajinomoto Pharmaceuticals Co., Ltd | May 23, 2014 |
| tofogliflozin hydrate<br>(1) Deberza Tablets 20 mg<br>(2) Apleway Tablets 20 mg | (1) Kowa Company, Ltd.<br>(2) Sanofi K.K. | May 23, 2014 |
| luseogliflozin hydrate<br>Lusefi Tablets 2.5 mg, 5 mg | Taisho Pharmaceutical Co., Ltd. | May 23, 2014 |
| dapagliflozin propylene glycolate hydrate<br>Forxiga Tablets 5 mg, 10 mg | Bristol-Myers K.K. | May 23, 2014 |
| tenofovir disoproxil fumarate<br>Tenozet Tablets 300 mg | GlaxoSmithKline K.K. | May 16, 2014 |
| turoctocog alfa (genetical recombination)<br>Novoeight for Intravenous Infusions 250, 500, 1000, 1500, 2000, 3000 | Novo Nordisk Pharma Ltd. | May 12, 2014 |
| ferric citrate hydrate<br>Riona Tablets 250 mg | Japan Tobacco Inc. | May 12, 2014 |
| afatinib maleate<br>Giotrif Tablets 20 mg, 30 mg, 40 mg, 50 mg | Nippon Boehringer Ingelheim Co., Ltd. | May 7, 2014 |

*1 An additional indication for “the reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and the treatment and suppression of relapse for venous thromboembolisms (deep vein thrombosis and pulmonary thromboembolism)”

*2 An additional administration for “pediatrics”

*3 An additional indication for “the treatment of acute rejection after transplantation of heart, lung, liver, pancreas, and small intestine”

*4 An additional indication for “the suppression of progression of dimentia symptoms in patients with Lewy body dementia”

*5 An additional indication for “the treatment of choroidal neovascularization in pathologic myopia”

*6 An additional indication for “the treatment of patients with refractory nephrotic syndrome (frequently relapsing or steroid-resistant)”

*7 An additional indication for “the treatment of moderate to severe chronic pain”

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

*9 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 geriatrics”

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