# Pharmaceuticals and Medical Devices Safety Information

**No. 320 January 2015**

## Table of Contents



This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers.
The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).


**Published by**
**Ministry of Health, Labour and Welfare**

**Translated by**
**Pharmaceuticals and Medical Devices Agency**



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

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

# Pharmaceuticals and Medical Devices Safety Information

No. 320 January 2015

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


## [ Outline of Information ]



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

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

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

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

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

## Abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| Alb | Albumin |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| BP | Blood pressure |
| BS | Blood sugar |
| BT | Body temperature |
| BUN | Blood urea nitrogen |
| CK | Creatine kinase |
| Cr | Creatinine |
| CRP | C-reactive protein |
| CRPC | Castration-resistant prostate cancer |
| CT | Computed tomography |
| CTR | Cardio-thoracic ratio |
| DBP | Diastolic blood pressure |
| EPPV | Early Post-marketing Phase Vigilance |
| FN | Febrile neutropenia |
| G-CSF | Granulocyte colony-stimulating factor |
| Glu | Glucose |
| Hb | Hemoglobin |
| HbA1c | Hemoglobin A1c |
| IU | International unit |
| KL-6 | Krebs von den Lunge-6 |
| LDH | Lactate dehydrogenase |
| Lt | Left |
| MAH | Marketing authorization holder |
| MHLW | Ministry of Health, Labour and Welfare |
| MRI | Magnetic resonance imaging |
| NCCN | National Comprehensive Cancer Network |
| NGSP | National glycohemoglobin standardization program |
| PD | Progressive disease |
| PLT | Platelet |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| $PCO_2$ | Carbon dioxide partial pressure |
| $PO_2$ | Oxygen partial pressure |
| PS | Performance status |
| PSA | Prostate-specific antigen |
| RBC | Red blood cell count |
| Rt | Right |
| SBP | Systolic blood pressure |
| $SpO_2$ | Oxygen saturation |
| TEN | Toxic epidermal necrolysis |
| TNM | Tumour- node-metastasis |
| T-P | Total protein |
| UA | Uric acid |
| WBC | White blood cell count |

# 1

# Cabazitaxel Acetonate and Severe Febrile Neutropenia

| | |
|---|---|
| **Active ingredient** | Cabazitaxel acetonate |
| **Brand Name (name of company)** | Jevtana 60 mg I.V. Infusion (Sanofi K.K.) |
| **Therapeutic Category** | Antineoplastics-Plant extract preparations |
| **Indications** | Prostate cancer |

## 1. Introduction

Cabazitaxel acetonate (Jevtana 60 mg I.V. Infusion, hereinafter referred to as Jevtana) is a taxane antineoplastic thought to suppress tumor growth by accelerating tubulin polymerization and stabilizing microtubules to inhibit cell division. In Japan, Jevtana was approved for the indication for "prostate cancer" in July 2014. For febrile neutropenia (FN) associated with Jevtana, cautions have been included since approval in the package insert as well as in the guide for proper use included in the information materials prepared by the marketing authorization holder (MAH) based on the incidence reported in the clinical trials submitted for approval review.

Since the launch on September 4 until December 17, 2014, Jevtana has been used in 208 patients, and serious FN has been reported in 28 cases, including 5 fatalities (including cases with causal relationship unknown due to insufficient information). Based on the reported serious cases, the Ministry of Health, Labour and Welfare (MHLW) instructed the MAH to revise the Precautions section of the package insert and take safety measures such as distribution of information materials to promote proper use of Jevtana on December 22, 2014.
Details are described below.

## 2. Background

The incidence of FN from the clinical trials submitted for approval review of Jevtana was 54.5% (24/44) in patients treated with cabazitaxel 25 mg/m$^2$ in the Japanese phase I study (TED11576) and 7.5% (28/371) in the overseas phase III study (EFC6193). Based on the reported results, cautions against FN were included in the sections of Warnings, Important Precautions, and Clinically Significant Adverse Reactions of the package insert at the time of approval. Although no fatal case was reported in the Japanese phase I study, fatal FN cases were reported in the overseas phase III study; therefore, the Warnings section mentions the fatal case reports to raise caution.

Since the launch in September 2014, cases of patients who had FN after using Jevtana have been reported in Japan and cases with fatal outcome have also been reported. As a result of thorough review of the fatal cases, appropriate antibiotics were not immediately used based on the FN treatment guidelines[1-2] in some cases. Under instructions from the Pharmaceuticals and Medical Devices Agency (PMDA), the MAH prepared the material "Information on Proper Use of Jevtana"[3] and has been distributing it to medical institutions since December 8, 2014 to advice on appropriate treatment of FN.

After discussing about the necessity of further safety measures, the PMDA decided that the descriptions of antibiotic use against FN and proper use of granulocyte colony-stimulating factor (G-CSF) product in the package insert should be more elaborate and specific to supplement the current cautions. The proposed revision of the package insert was determined appropriate after a discussion among attendees, including specialists, at the seventh meeting of 2014 Subcommittee on Drug Safety of Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council on December 19, 2014. On December 22, 2014, the MHLW instructed the MAH to revise the Precautions section of the

Jevtana package insert and take safety measures such as distribution of information materials for proper use.

The MAH revised the Precautions section and started distributing information "Information on Proper Use of Drug; Precautions against Bone Marrow Depression and FN"[4)] including reported cases of patients who died of FN to raise caution on December 22, 2014.

## 3. Febrile neutropenia associated with Jevtana

### (1) Reported cases of febrile neutropenia

A total of 28 cases of serious FN, including 5 fatal cases, have been reported after the launch of Jevtana until December 17, 2014. Of these, 5 fatal cases in which the causal relationship of FN with Jevtana could not be denied are presented below.

**Case Summaries**

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 60s | Prostate cancer (hypertension, interstitial lung disease) | 30mg/dose 1 dose/4 weeks × 2 | **Lobar pneumonia, interstitial pneumonia, FN**<br>Approximately 3 and a half months before initial dose:<br>The patient had taken enzaltamide for approximately 1 month.<br>Approximately 3 months before initial dose:<br>White blood cell count (WBC) never decreased to ≤3 000/mm$^3$ (until the month of cabazitaxel treatment initiation).<br>Approximately 2 months before initial dose:<br>Blood transfusion was performed for anaemia (to supplement red blood cell [RBC] and decrease dyspnoea) once or twice a month. Interstitial pneumonia associated with docetaxel occurred (treatment, the dose of prednisolone increased).<br>61 days before initial dose:<br>Krebs von den Lunge-6 (KL-6) was 1 340 U/mL.<br>44 days before initial dose:<br>KL-6 was 2 090 U/mL.<br>15 days before initial dose:<br>Prostate-specific antigen (PSA) was 10 000 ng/mL, KL-6 was 3 200 U/mL.<br>1 day before initial dose:<br>The patient was admitted to hospital. WBC was 6 100/mm$^3$.<br>Cycle 1 Day 1:<br>Administration of cabazitaxel 30 mg/day was started in the patient with originally elevated KL-6.<br>Day 4:<br>The patient was discharged from the hospital. WBC was 3 940/mm$^3$.<br>Day 6:<br>WBC was 3 040/mm$^3$. G-CSF was administered for prophylactic purpose.<br>Day 14:<br>PSA was 21 000 ng/mL. WBC was 6 210/mm$^3$.<br>Date unknown<br>Performance status (PS) remained 0 and metastasis to liver was found.<br>Day 28:<br>WBC was 5 790/mm$^3$.<br>Cycle 2 Day 1:<br>The patient received the second dose of cabazitaxel.<br>Day 6:<br>Difficulty in breathing and pyrexia developed. Vital signs: Blood pressure (BP), 110/60 mmHg; body temperature (BT), 36.1°C; oxygen saturation ($SpO_2$), 97% (with |

| | | | | |
|---|---|---|---|---|
| | | | | oxygen 3 L/min). The patient was fully conscious.<br>Lobar pneumonia and aggravation of interstitial pneumonia were diagnosed. FN also occurred.<br>WBC was 1 000/mm$^3$ (differential leukocyte count was not measured), KL-6 was 8 010 U/mL.<br>Blood culture and sputum culture were not performed because the samples were not submitted. Only biochemical test, complete blood counts, and computed tomography (CT) were performed and exclusion test (fungi) was not performed.<br>No surfactant protein A or surfactant protein D was measured for interstitial pneumonia.<br>Day 7:<br>BT was 36.6°C. Meropenem 1 g (3 days) and G-CSF (lenograstim) were administered. Corticosteroid pulse therapy with methylprednisolone sodium succinate 500 mg (3 days) was performed. Corticosteroid was administered until Day 8 but was ineffective.<br>Day 8:<br>BT was 34.0°C. Morphine was administered for severe dyspnoea.<br>Day 9:<br>WBC was 3 760/mm$^3$. BT was 38.6°C. Meropenem alone was administered.<br>14:30<br>BP decreased and respiratory arrest was found.<br>14:50<br>Cardiac arrest occurred. Cause of death included lobar pneumonia, aggravation of interstitial pneumonia, primary disorder, and FN.<br>An autopsy was not performed. |
| | Concomitant medications; prednisolone, chlorpheniramine maleate, dexamethazone sodium phosphate, ranitidine hydrochloride, granisetron hydrochloride, lenograstim (genetical recombination) | | | |

## Laboratory Examination

| | 61 days before administration | 15 days before administration | 1 day before administration | Cycle 1 Day 6 | Cycle 1 Day 14 | Cycle 1 Day 28 | Cycle 2 Day 6 |
|---|---|---|---|---|---|---|---|
| WBC (/mm$^3$) | - | - | 6 100 | 3 040 | 6 210 | 5 790 | 1 000 |
| KL-6 (U/mL) | 1 340 | 3 200 | - | - | - | - | 8 010 |

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Male 60s | Castration-resistant prostate cancer (CRPC) (metastases to bone) | 22.5 mg/m$^2$ Single dose | **Cardio-pulmonary arrest, FN, malaise, decreased appetite, vomiting, increased bronchial secretion**<br>Approximately 3 years and 5 months before initial dose:<br>Prostate cancer was diagnosed (tumour-node-metastasis [TNM] staging, T4N1M1). The patient received hormone therapy at this hospital and at another hospital, and after that, CRPC developed. Other treatment included irradiation to the bone marrow, pelvis, and para-aortic lymph nodes.<br>Approximately 1 year and 5 and a half months before initial dose:<br>Administration of prednisolone 10 mg/day was started (until approximately 2 months before cabazitaxel treatment).<br>Approximately 1 year and 5 and a half months before initial dose:<br>Administration of docetaxel (50-70 mg/m$^2$) was started (16 |

| | | | | |
|---|---|---|---|---|
| | | | | cycles in total), the dose per cycle was reduced to 50 mg/m$^2$ because of repeated neutropenia. Neutropenia improved in response to G-CSF.<br>Then, although enzaltamide and abiraterone were administered, the patient had progressive disease (PD). Primary disorder gradually progressed. Although baseline TNM staging was T4N1M1 (unchanged from the initial consultation), metastases to intrapelvic lymph nodes, para-aortic lymph nodes, bilateral inguinal lymph nodes, and bone (sternum, spine, and ischium) and bladder wall infiltration were noted. General condition was good enough for chemotherapy and the patient had good appetite.<br>48 days before initial dose:<br>Administration of dexamethazone 2 mg/day was started (until 4 days before initial cabazitaxel dose).<br>4 days before initial dose:<br>Administration of prednisolone 16 mg/day was started (until Day 7).<br>Cycle 1 Day 1:<br>Administration of cabazitaxel was started. Pretreatment with famotidine, dexamethazone, and chlorpheniramine maleate was performed. Degarelix was concomitantly administered.<br>WBC was 6 500/mm$^3$ and neutrophil sequestration was 73.3%.<br>Day 4:<br>WBC was 5 600/mm$^3$ and neutrophil sequestration was 84.9%.<br>Day 6:<br>WBC was 4 600/mm$^3$ and neutrophil sequestration was 88.1%.<br>Day 7:<br>The patient did not complain of any symptoms and had normal appetite and good swallowing since initial dose of cabazitaxel, but neutropenia was found in morning blood test (no pyrexia).<br>WBC was 1 300/mm$^3$ and neutrophil sequestration was 70.7%.<br>Morning<br>Administration of G-CSF was instructed.<br>Around noon<br>Pyrexia (38.5-38.9°C) and FN developed (treatment, G-CSF [renograstim 0.1 mg/dose, once daily for 2 days until Day 8]).<br>Day 8:<br>Antibiotic was administered (cefepime 2 000 mg/dose, twice daily for 1 day, Day 8).<br>08:59<br>WBC was 100/mm$^3$ and neutrophil sequestration was 62.5%.<br>Morning<br>Pyrexia (39°C levels), remarkable malaise (worst in life, makes the patient want to kill himself), and impaired appetite developed.<br>Noon<br>Vomiting was found several times but the patient was fully conscious. No respiratory or gastrointestinal symptom other than vomiting was found.<br>Around 19:05<br>The patient complained of "sputum stuck in the airway" with nurse call. Respiratory arrest with mydriasis was noted. Excessive airway secretion was suctioned and heart beat |

| | | | | |
|---|---|---|---|---|
| | | | | resumed after endotracheal intubation and resuscitation, but no spontaneous breathing improved. Because mydriasis remained with loss of light reflex, clinical brain death was judged. Death was confirmed after extubation. An autopsy was not performed. |
| | Concomitant medications: prednisolone, famotidine, dexamethazone sodium phosphate, chlorphenylamine maleate, denosumab (genetical recombination), degarelix acetate | | | |

## Laboratory Examination

| | Cycle 1 Day 1 | Day 4 | Day 6 | Day 7 | Day 8 |
|---|---|---|---|---|---|
| WBC (/mm$^3$) | 6 500 | 5 600 | 4 600 | 1 300 | 100 |
| Neutrophil (%) | 73.3 | 84.9 | 88.1 | 70.7 | 62.5 |

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 3 | Male 70s | Prostate cancer, GS4 + 5 (type 2 diabetes mellitus, hyperlipidaemia, hepatic function abnormal, metastases to bone, hepatic steatosis) | 25 mg/m$^2$ 1 dose/3 weeks × 1 | **FN, septic shock**<br>Approximately 3 years and 10 months before initial dose:<br>Initial consultation<br>PSA was 3 200 ng/mL.<br>Approximately 3 years and 9 months before initial dose:<br>Diagnosis, Stage 4 prostate cancer, TxNxM1b; histology, G5, 4+5. The patient started receiving estramustin.<br>Approximately 1 year and 3 months before initial dose:<br>The first cycle of docetaxel 75 mg/m$^2$ was performed.<br>Approximately 1 year and 2 months before initial dose:<br>The second cycle of docetaxel 75 mg/m$^2$ was performed.<br>Approximately 1 year and 1 month before initial dose:<br>The third cycle of docetaxel 75 mg/m$^2$ was performed. PSA decreased from 25.5 ng/mL to 6.3 ng/mL. Administration of docetaxel was suspended and administration of degarelix/dexamethazone was started.<br>Approximately 9 months before initial dose:<br>Because PSA increased, administration of docetaxel 75 mg/m$^2$ was resumed.<br>Date unknown:<br>G-CSF was administered for FN. Administration of docetaxel was terminated.<br>Approximately 6 and a half months before initial dose:<br>Metastases to bone were aggravated, the patient was judged as PD (femur, sternum, lumbar spine, etc.).<br>Approximately 6 and a half months before initial dose:<br>The patient participated in a cancer peptide vaccine trial. PSA was 82.8 ng/mL.<br>Approximately 3 and a half months before initial dose:<br>PSA was 147.9 ng/mL.<br>34 days before initial dose:<br>The patient was judged as PD. Administration of enzaltamide was started. PSA increased to 334 ng/mL.<br>28 days before initial dose:<br>PSA was 298.5 ng/mL.<br>14 days before initial dose:<br>WBC was 5 300/mm$^3$ and neutrophil was 3503/mm$^3$.<br>Cycle 1 Day 1:<br>Administration of cabazitaxel 39 mg (25 mg/m$^2$) was started for CRPC. Twice-daily administration of prednisolone 5 mg was also started. Baseline WBC was 3 800/mm$^3$ and neutrophil was |

| | | | | |
|---|---|---|---|---|
| | | | | 2 078/$mm^3$.<br>Patient had been on ursodeoxycholic acid for hepatic steatosis (hepatic dysfunction) associated with hyperlipidaemia for approximately 2 years before cabazitaxel treatment. The patient was strongly advised to admit hospital but strongly requested for outpatient treatment. Other than flushed face at the time of treatment, no remarkable change was noted. Patient went home after the attending outpatient physician found no problem with his condition.<br>No remarkable change noted at home<br>Day 7:<br>PSA was 382.4 ng/mL.<br>Around noon<br>The patient could not stand up.<br>22:15<br>The hospital was notified that tendency toward somnolence occurred since early evening. The patient was transported by ambulance.<br>At visit<br>Japan Coma Scale, 3; BT, 39.3°C; BP, 90/53 mmHg; $SpO_2$, 95% (room); blood gas normal; WBC, 500/$mm^3$; neutrophil, 0/$mm^3$; C-reactive protein (CRP), 9.67 mg/dL; procalcitonin, 1.17 ng/mL. FN and sepsis were diagnosed.<br>Administration of fluid replacement, antibacterial, immunoglobulin, and G-CSF was started.<br>Day 8:<br>Bacterial test in arterial/venous blood showed negative. *Escherichia Coli* was detected in catheter urine. No virus check was performed.<br>Around 01:30<br>Because BP decreased and state of shock was found, administration of inotropic agent was started.<br>Around 03:40<br>The patient got into a state of respiratory failure (blood gas [arterial] oxygen partial pressure [$PO_2$], 70.8 mmHg; carbon dioxide partial pressure [$PCO_2$], 24.6 mmHg). Tracheal intubation was decided to be needed and family was explained but treatment/intubation at emergency center was not requested. Treatment with oxygen administration was continued but respiratory condition worsened. WBC was 500/$mm^3$, neutrophil was 20/$mm^3$. Bacterial test in arterial/venous blood showed negative.<br>12:00<br>The patient died. An autopsy was not performed |
| | Concomitant medications: prednisolone, chlorphenylamine maleate, famotidine, dexamethazone sodium phosphate, denosumab (genetical recombination) | | | |

## Laboratory Examination

| | 14 days before administration | Cycle 1 Day 1 | Day 7 | Day 8 |
|---|---|---|---|---|
| WBC (/$mm^3$) | 5 300 | 3 800 | 500 | 500 |
| Neutrophil (/$mm^3$) | 3 503 | 2 078 | 0 | 20 |

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 4 | Male 60s | CRPC (multiple bone metastases, paraplegia [due to metastases to spinal of primary disease], decubitus ulcer [sacral decubitus , epidermolysis], cholelithiasis) | 25 mg/m$^2$ Single dose | **FN, agranulocytosis, pyrexia, diarrhoea**<br>Approximately 3 years before initial dose:<br>Diagnosis (initial onset): TNM staging, T3bN1M1c; Stage, -; metastases, present (para-aortic lymph nodes, lung)<br>Diagnosis methods; CT (lower abdomen), magnetic resonance imaging (MRI) (spine), needle biopsy (sampled from 6 areas each on left and right lobes [12 areas in total], all positive)<br>Gleason Score, 10 (5 + 3, 5 + 3, 5 + 4, 5 + 5)<br>Tissue diagnosis, adeno<br>Approximately 1 year and 2 months before initial dose:<br>The patient started receiving docetaxel.<br>Date unknown:<br>Neutropenia developed but improved with G-CSF.<br>Approximately 5 months before initial dose:<br>Administration of docetaxel was completed (10 cycles in total).<br>Approximately 2 months before initial dose:<br>Administration of enzaltamide was started (until 47 days before cabazitaxel treatment).<br>42 days before initial dose:<br>Administration of abiraterone was started (until 10 days before cabazitaxel treatment).<br>Cycle 1 Day 1:<br>PSA increase was not inhibited and clinical symptom (cancer pain) continued to be aggravated despite all hormone therapies and systemic chemotherapies other than treatment with cabazitaxel. Administration of cabazitaxel (25 mg/m$^2$) was started as the last systemic therapy for CRPC. No symptom was noted other than fever of 37°C levels at the start of treatment. Sacral decubitus was merely epidermolysis with no pyrexia. PS was 3 (at the start of treatment).<br>Day 7:<br>Impaired appetite, large amounts of diarrhoea, decreased BP, and pyrexia occurred (treatment for pyrexia, ceftazidime).<br>Date unknown:<br>Bacterial infection associated with bone marrow depression occurred.<br>Date unknown:<br>Scheduled bacterial test in arterial blood was not performed on this day.<br>Day 8:<br>FN, agranulocytosis, and thrombocytopenia occurred. (treatment for agranulocytosis, ceftazidime; treatment for FN, ceftazidime and G-CSF)<br>WBC was 350/mm$^3$ (neutrophil estimated at ≤19/μL based on lymphocyte subsets 94.5%), CRP was 15.35 mg/dL, hemoglobin (Hb) was 7.7 g/dL, platelet (PLT) was 49 000/mm$^3$.<br>On the same day, the patient died. |
| | Concomitant medications: ceftazidime hydrate, metoclopramide, fentanyl citrate, prednisolone, zolpidem tartrate, famotidine, loxoprofen sodium hydrate, prochlorperazine maleate, sennoside, magnesium oxide | | | |

## Laboratory Examination

| | 13 days before administration | 1 day before administration | Cycle 1 Day 8 |
|---|---|---|---|
| WBC (/mm$^3$) | 4 760 | 4 270 | 350 |
| Neutrophil (%) | 57.7 | 51 | 2 |
| Hb (g/dL) | 9.5 | 9.3 | 7.7 |
| PLT count (× 10$^4$/mm$^3$) | 17.5 | 16.7 | 4.9 |
| Na (mEq/L) | 134 | 134 | 126 |
| Cl (mEq/L) | 99 | 99 | 93 |
| K (mEq/L) | 4.0 | 4.1 | 5.0 |

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 5 | Male 70s | CRPC (diabetes mellitus, hypertension, hyperlipidaemia) | 20 mg/m$^2$ for 1 day | **FN, sepsis, diarrhoea**<br>Approximately 7 years and 5 months before initial dose:<br>The patient experienced leg paralysis and visited the orthopedic department for the first time. Prostate cancer was clinically diagnosed based on multiple bone metastasis (cervical, thoracic and lumbar spine, etc.) and elevated PSA of 3 093 ng/mL. Various hormone therapies were ineffective.<br>Neutropenia may have occurred during the subsequent 25 cycles of docetaxel (60 mg/m$^2$) but G-CSF was not required.<br>Approximately 3 years before initial dose:<br>Right hemicolectomy was performed.<br>Approximately 5 months before initial dose:<br>The 26th cycle of docetaxel was started but PSA tended to increase (597.29 ng/mL).<br>Approximately 4 months before initial dose:<br>Administration of enzaltamide was started.<br>33 days before initial dose:<br>Administration of enzaltamide was discontinued due to trend towards an increase in PSA (1 049.88 ng/mL).<br>32 days before initial dose:<br>Administration of prednisolone was started.<br>31 days before initial dose:<br>Administration of abiraterone was started.<br>4 days before initial dose:<br>Administration of abiraterone was discontinued due to increased PSA (1 699.05 ng/mL).<br>Total protein (T-P) was 6.48 g/dL, albumin (Alb) was 3.02 g/dL.<br>Cycle 1 Day 1:<br>Administration of cabazitaxel 20 mg/m$^2$ was started for CRPC.<br>PS was 1, but food intake decreased to 1/2 to 1/4 due to anorexia.<br>Clinical chemistry immediately before cabazitaxel treatment: WBC, 6 700/mm$^3$; neutrophil, 82%; CRP, 16.07 mg/dL (no infection, neoplastic inflammation); T-P, 5.89 g/dL; Na, 122 mEq/L; Cl, 92 mEq/L; K, 5.9 mEq/L<br>Metastases to bone (bone scintigraphy found countless hot spots in the ribs, sternum, and clavicle as well as several hot spots in the spine, right proximal femur, and pelvis; extent of disease, 3)<br>Day 4:<br>WBC was 3 200/mm$^3$.<br>Day 6:<br>Morning<br>WBC was 1 300/mm$^3$, absolute neutrophil count (ANC) was 800/mm$^3$, CRP was 3.19 mg/dL. Pyrexia did not occur. |

| | | | | |
|---|---|---|---|---|
| | | | | Noon<br>The patient could not eat solid food due to anorexia. Diarrhoea developed.<br>Evening<br>Pyrexia of 38°C levels occurred. G-CSF was administered (twice).<br>Night<br>Antibiotic (ceftriaxone) was administered.<br>Day 7:<br>WBC was 200/mm$^3$, ANC was 60/mm$^3$ (28%), CRP was 17.19 mg/dL. Pyrexia of 38.4°C occurred. Thrombocytopenia (97 000/mm$^3$) occurred. Cardio-thoracic ratio (CTR) was 53.3%. $SaPO_2$ decreased to 80 levels and maintained at 95% to 96% with oxygen 1 L.<br>Administration of cefozopran (1 g, 3 times daily) was started.<br>Day 8:<br>Pyrexia of 37°C levels occurred and venous blood culture was gram-negative bacillus positive, thus, sepsis was diagnosed.<br>Day 9:<br>Fecal culture showed only resident bacteria.<br>Night<br>BT decreased to 36°C levels but diastolic BP decreased to 80 levels.<br>$PCO_2$ was 23.1 mmHg, $PO_2$ was 67.1 mmHg, PLT was 20 000/mm$^3$, CTR was 53.8%.<br>Midnight<br>Cardio-respiratory arrest developed. Blood test upon resuscitation showed WBC of 2 800/mm$^3$, PLT of 20 000/mm$^3$. Chest x-ray showed CTR of 53.3% and pulmonary oedema.<br>Day 10:<br>01:48<br>Death was confirmed (cause of death, sepsis). |
| | Concomitant medication: prednisolone | | | |

**Laboratory Examination**

| | Cycle 1 Day 1 (immediately before administration) | Day 4 | Day 6 | Day 7 | Day 8 | Day 9 (morning) |
|---|---|---|---|---|---|---|
| WBC (/mm$^3$) | 6 700 | 3 200 | 1 300 | 200 | 200 | 100 |
| Neutrophil (%) | 82 | - | 75 | 28 | 13 | 26 |
| Neutrophil (/mm$^3$) | - | - | 800 | 60 | - | - |
| PLT (/mm$^3$) | 180 000 | 192 000 | 154 000 | 97 000 | 84 000 | 40 000 |

## (2) Antibiotic use for febrile neutropenia

For infections with serious bone marrow depression, relevant information has been provided since approval to ensure proper use of antibiotics. The Important Precautions section of the cabazitaxel acetonate package insert includes precautions "Careful attention should be paid specifically to infection. Signs and symptoms such as decreased neutrophil counts, increased levels of CRP, and pyrexia should be monitored. If infection occurred or was aggravated, appropriate measures such as administration of antibiotics should be taken immediately." The guide for proper use of cabazitaxel acetonate includes an FN treatment algorithm.

However, a review result of fatal cases involving FN reported post-marketing showed that appropriate antibiotics were not used immediately based on the FN treatment guidelines[1-2)] in some cases. A precaution "If FN occurred, the current guidelines or recommendations should be referred for proper use of antibiotics" was added to the Important precautions section of the package insert, and preparation and distribution of information material for healthcare professionals ("Information on Proper Use of cabazitaxel acetonate," "Information on Proper Use of Drugs; Precautions against Bone Marrow

Depression and FN") was advised to ensure thorough provision of information on treatment of FN.

When FN occurs in a patient, healthcare professionals should immediately perform blood culture and start appropriate antibiotics based on the current guidelines to ensure optimal treatment for the patient's condition.

### (3) Prophylactic use of G-CSF against febrile neutropenia (primary prevention)

Primary prevention with G-CSF product means using G-CSF product to prevent FN from the first cycle of cancer chemotherapy when the patient has no neutropenia or pyrexia.[5)]

Regarding the use of G-CSF product with cabazitaxel acetonate, a precaution "When cabazitaxel acetonate is administered, proper use of G-CSF should be considered" has been included in the Important Precautions section of the package insert since approval. In the guide for proper use of cabazitaxel acetonate, information on the prophylactic use of G-CSF is provided based on the guidelines for proper use of G-CSF.[5-8)]

Post-marketing incidence of FN, including non-serious cases, is 16.8% (35/208; cases with unknown causality due to insufficient information also included) as of December 17, 2014. Although the incidence is lower than 20% at which primary prevention with G-CSF is recommended in all patients by the guidelines,[5-8)] all patients who died of FN reported post-marketing had FN risk factors listed in the guidelines.

Therefore, the MHLW concluded that specific FN risk factors (≥65 years old, poor PS, medical history of FN, potent pretreatment history such as extended radiation exposure, and bone marrow tumor cell infiltration) should be listed, and advice to consider prophylactic use of G-CSF (primary prevention) in patients with the risk factors should be included in the Important precautions section of the package insert. Also, preparation and distribution of information material for healthcare professionals ("Information on Proper Use of Drugs; Precautions against Bone Marrow Depression and FN") have been instructed to minimize the FN risks.

Healthcare professionals should consider prophylactic use of G-CSF (primary prevention) based on the current guidelines and FN risk factors when using cabazitaxel acetonate.

Pegfilgrastim (genetical recombination, G-Lasta Subcutaneous Injection 3.6 mg), a long-acting G-CSF, has been approved for the indication of "prevention of FN during cancer chemotherapy." Healthcare professionals are encouraged to thoroughly read the package insert before using G-Lasta Subcutaneous Injection 3.6 mg.

## 4. Precautions against febrile neutropenia

Based on the above, Precautions for cabazitaxel acetonate was revised on December 22, 2014. Specifically, the following precautions were added to the Important precautions section.

(1) When cabazitaxel acetonate is administered, proper use of G-CSF should be considered by referring to the current guidelines or recommendations.
(2) Primary prophylaxis with G-CSF product should be considered especially in patients with risk factors for FN.
(3) If FN occurred, the current guidelines or recommendations should be referred for proper use of antibiotics.

Cautions against FN are included in the sections of Warnings, Important precautions, and Clinically significant adverse reactions in the latest package insert with revised Precautions as shown in the table below. (See "3. Information Safety Information" (page 19) for the Precautions revised on December 22, 2014.)

**Table**

| | |
|---|---|
| Warnings | Serious bone marrow depression such as neutropenia, FN, and anaemia may occur and some cases of severe infections leading to fatal outcome have been reported. This drug should be administered only to patients who are considered to be suitable, at a medical institution capable of appropriately handling emergencies and under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy. Patients should be carefully selected for treatment with this drug. The following patients should be excluded:<br>• Patients with serious bone marrow depression<br>• Patients with concurrent infection<br>• Patients with pyrexia suggestive of infection<br>• Patients with hepatic dysfunction<br>Patients and/or families should be thoroughly informed of the potential efficacy and risks of this drug. Informed consent should be obtained before administration of this drug. |
| Important precautions | Serious bone marrow depression may frequently occur. Caution should be exercised for the following points (A higher incidence of bone marrow depression such as neutropenia and FN has been reported especially in patients whose body surface area is small or geriatrics.):<br>a. When this drug is administered, proper use of G-CSF should be considered by referring to the current guidelines or recommendations. Primary prophylaxis with G-CSF product should be considered especially in patients with risk factors for FN (ex. ≥65 years old, poor PS, medical history of FN, potent pretreatment history such as extended radiation exposure, and bone marrow tumor cell infiltration).<br>b. Patients should be carefully monitored by frequent laboratory tests (ex. blood tests) after administration of this drug. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, or discontinuation of administration should be taken.<br>c. Careful attention should be paid especially for infection. Signs and symptoms such as decreased neutrophil counts, increased levels of CRP, and pyrexia should be monitored. If infection occurred or was aggravated, appropriate measures such as administration of antibiotics should be taken immediately. If FN occurred, the current guidelines or recommendations should be referred for proper use of antibiotics. |
| Clinically significant adverse reactions | Bone marrow depression: bone marrow depression such as neutropenia (30.1%), FN (12.5%), anemia (10.6%), leucopenia (7.0%), lymphopenia (0.2%) and thrombocytopenia (5.5%) may occur. In some cases, neutropenic sepsis (0.7%) and septic shock (0.7%) may concurrently occur.<br>Blood tests should be periodically performed during treatment with this drug. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, or discontinuation of administration should be taken. |

As described in the Warnings section of the package insert, cabazitaxel acetonate "should be administered only to patients who are considered to be suitable, at a medical institution capable of appropriately handling emergencies and under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy." The incidence of FN associated with cabazitaxel acetonate was especially high in the Japanese phase I study. The post-marketing surveillance reported fatal cases, including those involving inadequate FN management. Cabazitaxel acetonate should be used by physicians and at institutions experienced with FN management. When selecting patients for cabazitaxel acetonate treatment, healthcare professionals should make sure cancer chemotherapy is generally indicated for them. Whether cabazitaxel acetonate is an appropriate treatment should be carefully determined based on thorough consideration of the need for treatment and the information provided in the Contraindications and Careful administration sections.

As described in the Important precautions section of the package insert, "frequent laboratory tests (ex. blood test)" are required during cabazitaxel acetonate treatment. Since FN occurred after the first

cycle of treatment in 4 of 5 fatal cases reported post-marketing, healthcare professionals are encouraged to ensure careful patient monitoring especially after the initial dose.

Healthcare professionals should thoroughly read the package insert, the guide for proper use of cabazitaxel acetonate prepared by the MAH and the newly prepared/distributed information material ("Information on Proper Use of Drugs; Precautions against Bone Marrow Depression and FN") to ensure careful monitoring, prevention and treatment for FN associated with cabazitaxel acetonate.

Other than FN, various adverse reactions may be expected during cabazitaxel acetonate treatment. Healthcare professionals are encouraged to cooperate the proper use of cabazitaxel acetonate based on a thorough understanding of its safety profile.

**<References>** (including provisionally translated titles)


1) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56-e93.
2) FN Treatment Guideline, Japanese Society of Medical Oncology
3) Information on Proper Use of Jevtana 60 mg I.V. infusion
http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201412_1.pdf
(only available in Japanese language)
4) Proper Drug Use Information; Precautions against Bone Marrow Depression and FN (Jevtana 60 mg I.V. Infusion)
http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201412_2.pdf
(only available in Japanese language)
5) Guideline for Proper Use of G-CSF, Japan Society of Clinical Oncology
http://www.jsco-cpg.jp/guideline/30.html
(only available in Japanese language)
6) American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol. 2006;24:3187-3205.
7) 2010 update of European Organisation for Research and Treatment of Cancer guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47:8-32.
8) National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Myeloid Growth Factors. Version 2. 2014

# 2

# Use of Capsule Endoscope for Small Intestine screening in Pediatrics and Geriatrics

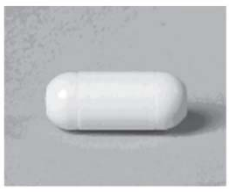
## 1. Introduction

A capsule endoscope for small intestine (hereinafter referred to as a capsule endoscope) is an encapsulated medical device used for gastrointestinal observation and diagnosis. With its wireless transmitter, the capsule endoscope non-invasively sends image data to the receiver outside the body as it moves along the intestinal tract with peristalsis. Four types of products to capture images of small intestinal mucosa for diagnosis are currently available from 2 MAHs. (See **Table 1**)

Use of the capsule endoscope in "patients aged <18 years" and "patients aged <22 and >84 years" has been advised against in "Applicable patients" under the Warnings section because the safety has not been established. However, the capsule endoscope may be necessary in some pediatrics and geriatrics. Use of the capsule endoscope and treatment outcomes have been reported by several institutions. After reviewing the current situation and the malfunctions of the capsule endoscopes reported to the PMDA and other relevant information, the PMDA instructed a revision of the Precautions to ensure consistent precautions for use, in place of the specific age groups to be avoided, among all available products. Details are presented below to widely raise caution among healthcare professionals.

**Table 1 Types of capsule endoscopes**

<table>
<tr><td colspan="2">Covidien Japan Inc.</td><td>Olympus Medical Systems Corp.</td></tr>
<tr><td colspan="2">Given Patency Capsule Endoscopy (22400BZX00106000)<br>PillCam SB 3 Capsule Endoscopy System (22500BZX00411000)</td><td>Olympus Capsule Endoscopy System (22000BZX01300000)<br>Endocapsule Small Intestinal Capsule Endoscope Olympus EC-S10 (22500BZX00304000)</td></tr>
<tr><td> 

(PillCam ®SB 3 Capsule)<br>Source, Package insert</td><td> 
(PillCam® Patency Capsule)<br>Source, Package insert</td><td> 
(Small Intestinal Capsule Endoscope Olympus EC Type 1)<br>Source, Product catalog</td></tr>
</table>

## 2. Reported device malfunctions

As of the end of December 2014, a total of 179 cases of capsule endoscope malfunction have been reported to the PMDA in Japan. A device malfunction was reported in only 1 case of a patient aged <18 years: transit abnormalities of Given Patency Capsule Endoscopy (22400BZX00106000; Covidien Japan Inc.) in the intestine in a 5-year-old Crohn's disease patient with possibly weak gastric peristalsis who had hardly eaten solid food since birth. Device malfunctions and adverse events involving transit abnormalities including retention were reported in 17 cases of patients aged ≥80 years. The incidence was comparable to that among patients aged ≥18 and <80 years regardless of product type. Aspiration of Olympus Capsule Endoscopy System (22000BZX01300000; Olympus Medical Systems Corp.) was reported in an 81-year-old patient. The endoscope entered into the trachea of the semi-bedridden patient.

Re-examination results are available for Given Image Diagnostic System (21900BZY00045000; Given Imaging Ltd.) and Olympus Capsule Endoscopy System. Among patients who underwent re-examination, those who were aged <18 years were approximately 1% to 2% and those who were aged ≥80 years were approximately 13%. No malfunction or adverse event was reported in patients aged <18 years. The incidence of adverse events in patients aged ≥80 years was not remarkably different from that among patients aged <80 years and no specific problems were found.

The 2013 retrospective survey on capsule endoscopy in 252 pediatrics (10 months to 18 years of age) was conducted by the Japan Pediatric Small-bowel Endoscopy Study Group (Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition) at 17 institutions nationwide, as a result, a retention rate was 1.6 % (n = 4), no other serious complication was reported, and safety and efficacy were not different from that shown in adult patients. Daisuke Tokuhara (Osaka City University) and Manari Oikawa (Saiseikai Yokohama City Eastern Hospital) reported the safety and usefulness of capsule endoscopy in 12 patients (10 to 17 years of age, 19 cases)[1)] and 26 patients (10 months to 16 years of age),[2)] respectively.

## 3. Safe use of capsule endoscope

### (1) Precautions to be taken when using the capsule endoscope

Frequent malfunctions of the capsule endoscopes include “aspiration” and “transit abnormalities including retention.” “Aspiration” risks can be reduced by appropriately checking to see if the patient is able to swallow before the procedure. The swallowing function of the patient should be evaluated regardless of age.

Precautions against “transit abnormalities including retention” are provided in the package insert of each product together with the risk of capsule endoscope retention and actions to be taken when retention occurs. The precautions should also be taken in all patients regardless of age. Use of the capsule endoscope should be carefully considered based on the potential risks of retention and following treatments.

The review of the post-marketing data concluded that the use of the capsule endoscope in patients aged <18 years and those aged ≥80 years is not necessarily unsafe. The MHLW instructed the MAHs of the capsule endoscopes to include the following statements as Important precautions in place of the current precautions concerning a patient’s age.

Patients’ ability to swallow should be checked before using the product. The risk of measures to be taken at the time of retention should be thoroughly considered and the product should be used carefully.

### (2) Special precautions for the use in pediatrics and geriatrics

In addition to the cautions described in (1), several points should be carefully considered when using the capsule endoscope in pediatrics and geriatrics.

A retained capsule endoscope can be endoscopically or surgically collected. While endoscopic collection will be the first choice in general, the approach may not be indicated for pediatrics depending on their physical development. Special cautions should be paid since surgical collection may be needed in some cases.

Transit abnormalities caused by anatomical features may occur frequently in pediatrics with an underdeveloped gastrointestinal tract. Healthcare professionals should use the capsule endoscope carefully in patients to whom the endoscope is still indicated after considering their anatomical features as well as their ability to swallow and risks of retention and actions to be taken at the time of retention.

Aspiration may also be frequent in pediatrics and geriatrics. The swallowing function should be evaluated carefully in advance.

Thus, the following cautions should be paid thoroughly to ensure careful use of the capsule endoscope in pediatrics and geriatrics.

<Pediatrics>

Pediatrics may have underdeveloped swallowing function or inadequate patency. The capsule endoscope should be used carefully.

<Geriatrics>

Geriatrics may have decreased peristalsis or impaired swallowing function. Capsule endoscope should be used carefully.

The small intestinal endoscopy study group of Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition is currently conducting a prospective study of capsule endoscopy in pediatrics to establish its further safety. The MHLW will take safety actions as necessary in cooperation with relevant medical associations in the future.

## <References>


1) Tokuhara D, Watanabe K, Okano Y, Tada A, Yamato K, Mochizuki T, et al. Wireless capsule endoscopy in pediatric patients: the first series from Japan. J Gastroenterol. 2010;45(7):683-691.
2) Oikawa-Kawamoto M, Sogo T, Yamaguchi T, Tsunoda T, Kondo T, Komatsu H, et al. Safety and utility of capsule endoscopy for infants and young children. World J Gastroenterol. 2013;19(45):8342-8348.

# 3 Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated December 22, 2014 (1) and January 9, 2015, (2-4) the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

## 1 Cabazitaxel Acetonate

| | |
|---|---|
| **Brand name (name of company)** | Jevtana 60 mg I.V. Infusion (Sanofi K. K.) |
| **Therapeutic category** | Antineoplastics-Plant extract preparations |
| **Indications** | Prostate cancer |

### PRECAUTIONS (underlined parts are revised)

**Important precautions**

Serious bone marrow depression may frequently occur. Caution should be exercised for the following points (A higher the incidence of bone marrow depression such as neutropenia and febrile neutropenia has been reported especially in patients whose body surface area is small or geriatrics.):

a. When this drug is administered, proper use of G-CSF should be considered by referring to the current guidelines or recommendations. Primary prophylaxis with G-CSF product should be considered especially in patients with risk factors for febrile neutropenia (ex. ≥65 years old, poor PS, medical history of febrile neutropenia, potent pretreatment history such as extended radiation exposure, and bone marrow tumor cell infiltration).

b. Patients should be carefully monitored by frequent laboratory tests (ex. blood tests) after administration of this drug. If any abnormalities are observed, appropriate measures such as drug suspension, dose reduction, or discontinuation of administration should be taken (See Precautions of dosage and administration section).

c. Careful attention should be paid specifically for infection. Signs and symptoms such as decreased neutrophil counts, increased levels of CRP, and pyrexia should be monitored. If infection occurred or was aggravated, appropriate measures such as administration of antibiotics should be taken immediately. If febrile neutropenia occurred, the current guidelines or recommendations should be referred for proper use of antibiotics.

**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 December 2014)

Cases of adverse events suggestive of febrile neutropenia: 5 fatal cases

The number of patients using this drug per year estimated by MAHs: Approximately 208 (from initial marketing to December 17, 2014)

Launched in Japan: September 2014

**Case summary**

See the case summaries in “1. Cabazitaxel Acetonate and Severe febrile neutropenia” in this document.

## 2 Sodium-glucose Co-transporter 2 Inhibitors

**(1) Ipragliflozin L-Proline**
**(2) Empagliflozin**
**(3) Canagliflozin Hydrate**
**(4) Dapagliflozin Propylene Glycolate Hydrate**
**(5) Luseogliflozin Hydrate**

| | |
|---|---|
| **Brand name (name of company)** | (1) Suglat Tablets 25 mg and 50 mg (Astellas Pharma Inc.)<br>(2) Jardiance Tablets 10 mg and 25 mg (Nippon Boehringer Ingelheim Co., Ltd.)<br>(3) Canaglu Tablets 100 mg (Mitsubishi Tanabe Pharma Corporation)<br>(4) Forxiga Tablets 5 mg and 10 mg (Bristol-Myers K.K.)<br>(5) Lusefi Tablets 2.5 mg and 5 mg (Taisho Pharmaceutical Co., Ltd.) |
| **Therapeutic category** | Antidiabetic agents |
| **Indications** | Type 2 diabetes mellitus |

### PRECAUTIONS (underlined parts are revised)

**Careful administration**

Patients who are susceptible to dehydration (ex. patients with poor blood glucose control, geriatric patients, and patients who are concomitantly administered diuretics)

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

**Dehydration**: Dehydration may occur. Patients should be advised on appropriate water intake and carefully monitored. If symptoms including thirst, polyuria, pollakiuria, and decreased blood pressure are observed and dehydration is suspected, appropriate measures such as drug suspension and fluid replacement should be taken. Careful attention should be exercised because cases of dehydration followed by thromboembolism including cerebral infarction and other diseases have been reported.

**Reference information**

The number of adverse reactions (for which a causality to the drug could not be ruled out) reported recently (from initial marketing to October 2014)

Cases of adverse events suggestive of dehydration*:

(1) 13 cases (no fatal cases)
(2) -
(3) 0 cases
(4) 2 cases (no fatal cases)
(5) 0 cases

* Cases of dehydration in which serious events resulting from dehydration (thromboembolism, diabetic ketoacidosis, hyperosmolar hyperglycaemic syndrome, arrhythmia, cardiac failure, renal impairment, mental disorder, and loss of consciousness) were observed.

The number of patients using this drug estimated by MAHs (from the initial marketing to August 2014):

(1) Approximately 70 000
(2) -
(3) -
(4) Approximately 24 000
(5) Approximately 10 000

Launched in Japan:

(1) April 2014
(2) Not launched as of January 1, 2015
(3) September 2014
(4) May 2014
(5) May 2014

## (6) Tofogliflozin Hydrate

| | |
|---|---|
| **Brand name (name of company)** | (6) Apleway Tablets 20 mg (Sanofi K. K.), Deberza Tablets 20 mg (Kowa Company, Ltd.) |
| **Therapeutic category** | Antidiabetic agents |
| **Indications** | Type 2 diabetes mellitus |

### PRECAUTIONS (underlined parts are revised)

**Careful administration**

Patients who are susceptible to dehydration (ex. patients with poor blood glucose control, geriatric patients, and patients who are concomitantly administered diuretics)

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

**Dehydration**: Dehydration may occur. Patients should be advised on appropriate water intake and carefully monitored. If symptoms including thirst, polyuria, pollakiuria, and decreased blood pressure are observed and dehydration is suspected, appropriate measures such as drug suspension and fluid replacement should be taken. Careful attention should be exercised because cases of dehydration followed by thromboembolism including cerebral infarction and other diseases have been reported.

**Pyelonephritis**: Pyelonephritis 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 adverse reactions (for which a causality to the drug could not be ruled out) reported recently (from initial marketing to October 2014)

Cases of adverse events suggestive of dehydration*: 3 cases (no fatal cases)

Cases of adverse events suggestive of pyelonephritis: 2 cases (no fatal cases)

* Cases of dehydration in which serious events resulting from dehydration (thromboembolism, diabetic ketoacidosis, hyperosmolar hyperglycaemic syndrome, arrhythmia, cardiac failure, renal impairment, mental disorder, and loss of consciousness) were observed.

The number of patients using this drug estimated by MAHs (from initial marketing to August 2014): Approximately 14 000

Launched in Japan: May 2014

### Ipragliflozin L-Proline: Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 70s | Type 2 diabetes mellitus (hypertension, dyslipidaemia) | 50 mg for 10 days | **Dehydration, cerebellar/brain stem infarction**<br>Pre-treatment clinical laboratory values; Body mass index 20.1, Hemoglobin A1c (HbA1c) 11.0%<br>Day 1 of administration:<br>The patient started receiving ipragliflozin L-proline 50 mg (once daily) for type 2 diabetes mellitus at Hospital A.<br>The physician in charge at Hospital A strongly recommended management with insulin but ipragliflozin L-proline was prescribed in response to the patient's strong desire. From the day of oral administration, the patient had thirst and pollakiuria. Fluid intake was performed.<br>Date unknown:<br>During several days after the start of administration, the patient had severe thirst and urination 20 times/day. Fluid was taken |

| | | | | |
|---|---|---|---|---|
| | | | | frequently.<br>Day 9 of administration:<br>Feelings of weakness, tinnitus, and vertigo occurred. Since symptoms did not improve after rest and vomiting occurred, emergency service was requested. At the visit, the symptoms reduced and head CT showed no abnormalities, so an anti-vertigenous drug and antiemetic were prescribed. The patient returned home.<br>Day 10 of administration (day of discontinuation):<br>Dehydration developed. Since tinnitus and vertigo occurred again, emergency service was requested.<br>The patient was transported to Hospital B. Head MRI showed cerebellar/brain stem infarction and the patient was admitted to the hospital. Acute-phase treatment for cerebral infarction (administration of edaravone and concentrated glycerin, and hyperbaric oxygen therapy) was started. Also, fluid infusion was performed for dehydration. Administration of ipragliflozin L-proline was discontinued (no re-administration was performed).<br>4 days after discontinuation:<br>Thirst, pollakiuria, and dehydration resolved (no treatment for thirst and pollakiuria was performed).<br>7 days after discontinuation:<br>Rehabilitation was started.<br>Date unknown:<br>Numbness, etc. did not remain.<br>13 days after discontinuation:<br>Oral administration of an antiplatelet drug (clopidogrel) was started.<br>41 days after discontinuation:<br>The symptom improved, but vertigo remains. The patient had been treated in hospital while doing rehabilitation.<br>Cerebellar/brain stem infarction improved. |
| | Concomitant medications: glimepiride, alogliptin benzoate/pioglitazone, valsartan/hydrochlorothiazide, amlodipine besilate | | | |

## Laboratory examination

| | 56 days before administration | Day 10 of administration | 1 day after discontinuation | 4 days after discontinuation | 34 days after discontinuation |
|---|---|---|---|---|---|
| ALB (g/dL) | - | 4.3 | - | 3.6 | 3.6 |
| T-P | - | 7.9 | - | 6.4 | 6.2 |
| CRP (mg/dL) | 0.82 | 0.75 | - | 0.75 | 0.75 |
| BUN (mg/dL) | 23.3 | - | 25 | 16 | 12 |
| Glu (serum) (mg/dL) | 209 | 185 | - | 219 | 139 |
| Na (mEq/L) | - | 139 | - | 135 | 136 |
| HbA1c (NGSP) (%) | 11.0 | 9.8 | - | - | 8.7 |
| Ht (%) | 35.3 | 40.6 | - | 38.9 | 34.8 |
| Hb (g/dL) | 11.0 | 13.4 | - | 12.8 | 11.5 |

## Ipragliflozin L-Proline: Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Male 40s | Type 2 diabetes mellitus (hypertension, dyslipidaemia, hyperuricaemia, hepatic function abnormal) | 50 mg for 6 days | **Acute renal failure due to dehydration**<br>Approximately 11 years before administration:<br>The patient experienced Type 2 diabetes mellitus.<br>Date unknown:<br>Clinical laboratory values; Blood urea, 15.2 mg/dL<br>19 days before administration:<br>Clinical laboratory values; Blood creatinine (Cr), 0.77 mg/dL<br>14 days before administration:<br>Clinical laboratory values; Blood glucose (Glu), 261 mg/dL, glycohemoglobin, 14.2%<br>Day 1 of administration:<br>From before, the patient had been using glimepiride and metformin hydrochloride for diabetes mellitus, but test results at the visit (14 days before the start of administration) showed aggravated diabetes mellitus, so additional administration of ipragliflozin L-proline 50 mg (once daily) was started for diabetes mellitus for the purpose of further control. Due to working in a hot environment, the patient was instructed to be adequately hydrated with a substantial amount of fluid. When ipragliflozin L-proline was to be administered, the patient was given thorough guidance about water drinking.<br>Day 5 of administration:<br>The patient became aware of headache dull and dizziness on standing up from around 10 am.<br>Day 6 of administration (day of discontinuation):<br>The patient stayed at home to see whether the symptoms would resolve, but the symptoms did not improve. He visited this hospital with a complaint of physical deconditioning. At the visit, the patient was fully conscious without pathological neurological finding and with BP of 113/73 mmHg, but blood urea nitrogen (BUN) and Cr rapidly increased to 49.9 mg/dL and 2.7 mg/dL, respectively. Abdominal ultrasound showed collapsed bladder and mild enlargement of bilateral kidney, acute renal failure due to dehydration was diagnosed, and the patient was admitted to the hospital on the same day. Administration of ipragliflozin L-proline was discontinued. Because dietary intake was almost impossible, administration of metformin hydrochloride and glimepiride was discontinued.<br>2 days after discontinuation:<br>High-volume fluid replacement and whole-body management were performed from immediately after hospital admission, and consequently, the symptoms disappeared. As BUN and Cr decreased to 26.6 mg/dL and 0.8 mg/dL, respectively, the patient was discharged from the hospital. The events improved.<br>9 days after discontinuation:<br>At the time of an outpatient visit, dietary intake was improved. Because fasting blood sugar was 147mg/dL, administration of glimepiride and metformin hydrochloride was resumed. The patient had no symptoms at the time of the outpatient revisit, but had BUN of 39.0 mg/dL and Cr of 1.17 mg/dL, showing no recovery to the state before the events. Subsequently, a follow-up observation was performed.<br>44 days after discontinuation:<br>With no abnormality in the general status, BUN and Cr decreased to 25.0 mg/dL and 0.91 mg/dL, respectively, but these |

| | | | | |
|---|---|---|---|---|
| | | | | did not recover to levels before administration of ipragliflozin L-proline, and follow-up observation was scheduled to be continued.<br>Date unknown:<br>After the recovery, administration of glimepiride and metformin hydrochloride has been continued. |
| | Concomitant medications: doxazosin mesilate, nifedipine, valsartan, glimepiride, amlodipine besilate, indapamide, metformin hydrochloride | | | |

## Laboratory examination

| | 19 days before administration | 14 days before administration | Day 1 of administration | Day 6 of administration (day of discontinuation) | 2 days after discontinuation | 9 days after discontinuation | 44 days after discontinuation |
|---|---|---|---|---|---|---|---|
| Cr (mg/dL) | 0.77 | - | - | 2.7 | 0.8 | 1.17 | 0.91 |
| BS (mg/dL) | - | 261 | - | - | - | - | - |
| BUN (mg/dL) | - | - | - | 49.9 | 26.6 | 39.0 | 25.0 |
| UA (mg/dL) | 7.4 | - | - | 11.9 | - | 11.0 | 7.2 |
| HbA1c (%) | - | 14.2 | - | - | - | - | - |
| Ht (%) | 43.9 | - | - | 44.3 | - | 43.8 | 45.7 |
| Hb (g/dL) | 14.5 | - | - | 15.8 | - | 14.6 | 14.9 |
| RBC ($10^4/\mu L$) | 495 | - | - | 521 | - | 492 | 505 |
| DBP (mmHg) | - | - | 73 | - | - | - | - |
| SBP (mmHg) | - | - | 113 | - | - | - | - |

## Dapagliflozin Propylene Glycolate Hydrate: Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 50s | Type 2 diabetes mellitus (gallbladder polyp, hypertension) | 5 mg for 43 days | **Thirst, pollakiuria, polyuria, cerebral infarction**<br>12 years before administration:<br>Type 2 diabetes mellitus was diagnosed.<br>Body height, approximately 170 cm; body weight, approximately 90 kg<br>Family history: Father, diabetes mellitus; Uncle, subarachnoid haemorrhage<br>Day 1 of administration:<br>For type 2 diabetes mellitus, additional administration of dapagliflozin propylene glycolate hydrate (5 mg/day) was started.<br>Day 15 of administration:<br>The patient complained of pollakiuria, thirst, and polyuria.<br>Day 42 of administration:<br>In the summer, around 4 pm, during agricultural work in the open air, the patient became aware of weakness of the lower left limb with lack of movement in the left leg, and began to drag his leg.<br>Day 43 of administration (day of discontinuation):<br>Because the symptom spread to the left upper limb from the time of awakening, the patient visited the hospital in the morning. At the visit, paresis was found in the left upper and lower limbs. |

| | | | | |
|---|---|---|---|---|
| | | | | Grip strength was 29 kg in the right hand and 19 kg in the left hand. The patient was right-handed.<br>He could not stand on his left leg alone. His speech was clear. Patellar tendon reflex was increased on the left; achilles tendon reflex, right (rt) = left (lt); biceps tendon reflex, rt = lt; triceps tendon reflex, rt = lt. His consciousness was normal.<br>For suspected cerebral infarction, the patient was transported by ambulance to another hospital, and was urgently admitted to the stroke department.<br>With glimepiride, alogliptin benzoate, voglibose, and dapagliflozin propylene glycolate hydrate, HbA1c at the time of hospital admission was 7.3%.<br>The patient was fully conscious, with high levels of BP of 187/82 mmHg. In addition, as neurological symptoms, he was ambulatory, was unable to stand on his left leg alone, and had sensory aberrations in the left part of his face. Head MRI showed infarction inside the lower right part of the pons and brain stem infarction was diagnosed. Administration of dapagliflozin propylene glycolate hydrate was discontinued. Because there was a possibility that symptoms might become exacerbated, the patient was monitored in the neurosurgical care unit for several days. Medical treatment was started with argatroban hydrate, edaravone, and fluid replacement.<br>Date unknown:<br>During hospitalization, the patient also visited the department of diabetes mellitus, where hypertension and diabetes mellitus had been controlled with oral administration. Nutritional guidance was performed by limiting caloric intake to less than 1 600 kcal and salt intake to less than 6 g. The patient generally had a favorable clinical course.<br>Assessment of cardiac function, etc. was also performed, but no particular abnormality was found. Severe arteriosclerosis of the cerebral blood vessels due to diabetes mellitus and hypertension was strongly suspected.<br>13 days after discontinuation:<br>The clinical course of blood Glu has been favorable. The doses of oral drugs were reduced. With mitiglinide calcium hydrate/voglibose combination tablets (1 tablet × 3 times/day, immediately before meal), acceptable blood Glu control was achieved (blood Glu levels; 104 mg/dL in the morning, 141 mg/dL in the daytime, 128 mg/dL in the evening, 147 mg/dL before sleep).<br>14 days after discontinuation:<br>In rehabilitation, the patient tended to lean slightly toward the left, but was able to walk without assistance, and consequently was discharged to his home.<br>Medications prescribed: clopidogrel 75 mg × 1 time/day after breakfast, captopril 12.5 mg × 1 time/day after breakfast, amlodipine 5 mg × 2 times/day after breakfast and evening meal, mitiglinide calcium hydrate/voglibose combination tablets 1 tablet × 3 times/day immediately before meal.<br>21 days after discontinuation:<br>The patient recovered from pollakiuria, thirst, and polyuria.<br>58 days after discontinuation:<br>Without paresis, the patient said “I feel I returned to the state before the onset of cerebral infarction.” |
| | Concomitant medications: voglibose, enalapril maleate, amlodipine besilate, alogliptin benzoate, glimepiride | | | |

## Laboratory examination

| | 14 days before administration | Day 15 of administration | Day 43 of administration (day of discontinuation) | 28 day after discontinuation | 63 days after discontinuation |
|---|---|---|---|---|---|
| SBP (mmHg) | 147 | 126 | 187 | 101 | 117 |
| DBP (mmHg) | 93 | 80 | 82 | 61 | 70 |
| HbA1c (%) | 9.0 | 8.3 | 7.3 | 6.6 | 6.2 |
| Blood Glu (mg/dL) | 231 (90 min. after breakfast) | 168 (FBG) | - | 113 (120 min. after breakfast) | 131 (150 min. after breakfast) |
| Grip strength (kg) | - | - | Rt, 29;Lt, 19 | - | - |

## 3 Freeze-dried Live Attenuated Mumps Vaccine

| | |
|---|---|
| **Brand name (name of company)** | Freeze-dried Live Attenuated Mumps Vaccine "Kitasatodaiichisankyo" (Kitasato Daiichi Sankyo Vaccine Co., Ltd), Dried Live Attenuated Mumps Vaccine "Takeda" (Takeda Pharmaceutical Company Limited.) |
| **Therapeutic category** | Vaccines |
| **Indications** | Prevention of mumps |

### PRECAUTIONS (underlined parts are revised)

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

**Acute pancreatitis:** Acute pancreatitis may occur. Patients should be carefully monitored. If any abnormalities such as abdominal pain, pyrexia, nausea, vomiting, and increased serum amylase are observed, appropriate measures should be taken.

**Reference information**

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 5 months (April 2011 to August 2014)
Pancreatitis acute: 1 case (no fatal cases)
The number of patients using this drug per year estimated by MAH: Approximately 990 000 (fiscal year 2013).
Launched in Japan: May 1982

### Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 10s | Prevention of mumps (none) | 0.5 mL for 1 day | **Pancreatitis acute, meningitis aseptic**<br>Day of vaccination:<br>The patient received freeze-dried live attenuated mumps vaccination at another hospital.<br>20 days after vaccination:<br>From the evening, the patient had pyrexia at 38-38.5°C, headache, and vomiting.<br>21 day after vaccination:<br>The patient was referred and admitted to this hospital from the other hospital.<br>Parotid swelling was not found. Nuchal rigidity (++), Kernig's sign (+), cerebrospinal fluid cell count 488/3.<br>With a diagnosis of aseptic meningitis, the patient received transfusion and was kept at rest on the bed.<br>Treatment was started with concentrated glycerin/fructose, famotidine, and cefotaxime sodium.<br>The patient complained of tenderness in the whole abdomen secondarily to pyrexia, headache, and vomiting.<br>23 days after vaccination:<br>Serum amylase was as high as 168 IU/L (pancreatic amylase, 127 IU/L) and concomitant acute pancreatitis was suspected.<br>The patient was placed under a fasting state, and intravenous ulinastatin (50 000 units × 3/day) was administered, and scopolamine butylbromide was intravenously administered when abdominal pain occurred.<br>Abdominal CT and abdominal echo showed normal results.<br>Abdominal pain gradually improved, but pyrexia was persistent.<br>27 days after vaccination:<br>Diet for pancreatitis was started.<br>28 days after vaccination:<br>Pyrexia resolved.<br>33 days after vaccination: |

| | | | | |
|---|---|---|---|---|
| | | | | The intravenous infusion was discontinued.<br>36 days after vaccination:<br>The patient was discharged from the hospital.<br>Viral isolation (date unknown)<br>Mumps virus was isolated from the cerebrospinal fluid. It matched the vaccine strain. |
| | Concomitant medications: none | | | |

Note: This case is an adverse reaction reported before April 2011 and for which a causal relationship cannot be ruled out.

## Laboratory examination

| Laboratory parameter (unit) | 21 day after vaccination | 23 days after vaccination | 25 days after vaccination | 33 days after vaccination |
|---|---|---|---|---|
| Amylase (IU/L) | 89 | 168 | 155 | 98 |
| Pancreatic amylase (IU/L) | - | 127 | 80 | 48 |

## Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Female 10s | Prevention of mumps (none) | 0.5 mL for 1 day | **Pancreatitis acute, meningitis aseptic**<br>Day of vaccination:<br>The patient received freeze-dried live attenuated mumps vaccination at other hospital A.<br>23 days after vaccination:<br>As the patient had pyrexia, headache, and abdominal pain, an influenza test was performed at other hospital A, but the result was negative.<br>24 days after vaccination:<br>BT was 39°C. Headache was persistent. A blood test was performed at other hospital A (WBC 12 000/μL, CRP 0 mg/dL).<br>25 days after vaccination:<br>Pyrexia was persistent. The patient had neck pain, nuchal rigidity, and headache. Vomiting developed twice. Meningitis was suspected at other hospital A, and the patient was referred and admitted to the pediatric department of this hospital.<br>A cerebrospinal fluid examination showed increase in cell count. Based on the results of culture, etc., aseptic meningitis was diagnosed. Conservative treatment with rest and transfusion was started. Head CT showed no obvious abnormality. Due to severe headache, an analgesic drug and a concentrated glycerin/fructose were administered.<br>26 days after vaccination:<br>Head MRI showed no abnormal finding as well.<br>Blood test showed increased lipase. Treatment was continued similarly.<br>27 days after vaccination:<br>Pyrexia, headache, and abdominal pain were persistent. In another cerebrospinal fluid examination, the cell count further increased. Blood test showed increased amylase, and concomitant acute pancreatitis was diagnosed. The patient was transferred to other hospital B.<br>An electroencephalographic examination in the waking state showed no finding suggesting obvious deterioration in brain function. Aseptic meningitis and acute pancreatitis |

| | | | | |
|---|---|---|---|---|
| | | | | were diagnosed, and medical treatment with transfusion, fasting, and acid-reducing agents was performed.<br>33 days after vaccination:<br>The symptoms improved, and the patient was discharged from other hospital B.<br>41 days after vaccination:<br>The patient recovered.<br>Viral isolation (25 days after vaccination)<br>Mumps virus (vaccine strain) was detected from cerebrospinal fluid (polymerase chain reaction). |
| | Concomitant medications: acetaminophen | | | |

## Laboratory examination

| Laboratory parameter (unit) | 25 days after vaccination | 26 days after vaccination | 27 days after vaccination |
|---|---|---|---|
| Amylase (IU/L) | 115 | - | 199 |
| Lipase (IU/L) | - | 102.5 | 155.9 |

## 4 Levetiracetam

| | |
|---|---|
| **Brand name (name of company)** | (1) E Keppra Tablets 250 mg and 500 mg, and E Keppra Dry Syrup 50% (UCB Japan Co., Ltd.)<br>(2) E Keppra for I.V. infusion 500 mg (UCB Japan Co. Ltd.) |
| **Therapeutic category** | Antiepileptics |
| **Indications** | (1) Concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizure) in patients who fail to show a satisfactory response to other antiepileptic drugs<br>(2) As an alternative to levetiracetam oral tablets for the following treatment in patients who are not able to use the oral treatment temporarily:<br>Concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizure) in patients who fail to show a satisfactory response to other antiepileptic drugs |

### PRECAUTIONS (underlined parts are revised)

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

**Rhabdomyolysis:** Rhabdomyolysis may occur. Patients should be carefully monitored. If signs or symptoms including myalgia, feeling of weakness, increased creatine kinase (CK) (creatine phosphokinase), increased blood myoglobin, and increased urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be taken.

**Reference information**

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 7 months (April 2011 to October 2014)
Rhabdomyolysis: 7 cases (no fatal cases)
The number of patients using this drug per year estimated by MAHs:
Approximately 100 000 (November 2013 to October 2014)
Launched in Japan: Tablets, September 2010
Dry Syrup, August 2013
I.V. Infusion, not launched as of January 1, 2015

### Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 10s | Epilepsy (none) | 500 mg for 26 days<br>↓<br>2 000 mg for 30 days<br>↓<br>1 000 mg Continued | **Rhabdomyolysis**<br>Day 1 of administration:<br>The patient received levetiracetam 500 mg/day in addition to carbamazepine 300 mg/day.<br>Day 27 of administration:<br>The dose of levetiracetam was increased to 2 000 mg/day.<br>Day 55 of administration:<br>Myalgia occurred in the chest and upper limbs.<br>Day 56 of administration:<br>Blood test showed CK of 103 600 IU/L and myoglobinuria (+), and rhabdomyolysis was diagnosed. The patient was admitted to the hospital, and administration of fluid replacement was started. The dose of levetiracetam was decreased to 1 000 mg/day.<br>Day 60 of administration:<br>Symptoms such as myalgia were not found and since CK decreased to 6 510 IU/L, the patient was discharged from the hospital.<br>Day 73 of administration: |

| | | | | |
|---|---|---|---|---|
| | | | | CK was a normal level, the patient recovered from rhabdomyolysis. |
| | Concomitant medications: carbamazepine | | | |

## Laboratory examination

| | Day 29 of administration | Day 56 of administration | Day 58 of administration | Day 60 of administration | Day 73 of administration |
|---|---|---|---|---|---|
| WBC (/μL) | 5 400 | 6 000 | 5 200 | 6 100 | 7 400 |
| AST (IU/L) | 19 | 1 030 | 520 | 188 | 17 |
| ALT (IU/L) | 30 | 227 | 187 | 169 | 19 |
| LDH (IU/L) | 122 | 3 940 | 870 | 163 | 145 |
| CK (IU/L) | 97 | 103 600 | 40 700 | 6 510 | 113 |
| BUN (mg/dL) | 8.9 | 10 | 5 | 8 | 14 |
| Cr (mg/dL) | 0.82 | 0.88 | 0.75 | 0.77 | 0.83 |

## Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Female 20s | Epilepsy (mental retardation, motor developmental delay) | 500 mg for 16 days | **Rhabdomyolysis**<br>Day 1 of administration:<br>The patient received levetiracetam 500 mg/day in addition to carbamazepine 500 mg/day and phenobarbital 100 mg/day.<br>Day 15 of administration:<br>Because of astasia and poor oral intake, fluid replacement was administered. Blood test showed increase in CK to 2 723 IU/L (onset of rhabdomyolysis).<br>Day 16 of administration (day of discontinuation):<br>Because CK increased to 4 396 IU/L, administration of levetiracetam was discontinued.<br>3 days after discontinuation:<br>Maintaining a sitting position was possible.<br>10 days after discontinuation:<br>Walking with assistance was possible.<br>14 days after discontinuation:<br>Walking was possible.<br>16 days after discontinuation:<br>The patient recovered from rhabdomyolysis. |
| | The other suspected medications: carbamazepine<br>Concomitant medications: phenobarbital | | | |

## Laboratory examination

| | Day before administration | Day 15 of administration | Day 16 of administration (day of discontinuation) | 2 days after discontinuation | 9 days after discontinuation | 12 days after discontinuation |
|---|---|---|---|---|---|---|
| WBC (/μL) | 5 020 | 7 260 | 5 780 | 5 480 | 4 750 | 3 130 |
| AST (IU/L) | 28 | 67 | 105 | 75 | 23 | 25 |
| ALT (IU/L) | 12 | 17 | 30 | 36 | 23 | 30 |

| | | | | | | |
|---|---|---|---|---|---|---|
| LDH (IU/L) | 291 | 519 | 330 | 271 | 215 | 211 |
| CK (IU/L) | 34 | 2 723 | 4 396 | 2 019 | 189 | 75 |
| BUN (mg/dL) | 11.5 | 9.2 | 10.3 | 7.8 | 6.9 | 13.0 |
| Cr (mg/dL) | 0.44 | 0.36 | 0.43 | 0.35 | 0.36 | 0.44 |

## Case summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 3 | Female 20s | Epilepsy (none) | 1 000 mg for 5 days | **Rhabdomyolysis**<br>1 year and 5 months before administration<br>The patient started receiving sodium valproate (continued until 3 days before administration of levetiracetam).<br>2 days before administration:<br>Due to epileptic seizure, the patient was admitted to hospital, and phenytoin sodium was administered (for 2 days).<br>Day 1 of administration:<br>Administration of levetiracetam was started at 1 000 mg/day. Administration of sodium valproate was resumed at 800 mg.<br>1 day after administration:<br>Systemic myalgia and weakness of lower extremities occurred. CK was approximately 1 000 IU/L (onset of rhabdomyolysis).<br>Day 5 of administration (day of discontinuation):<br>CK was 2 410 IU/L. Administration of levetiracetam was discontinued.<br>28 day after discontinuation:<br>CK was 59 IU/L. The patient recovered from rhabdomyolysis. |
| | Concomitant medications: sodium valproate | | | |

## Laboratory examination

| | 2 days before administration | Day of discontinuation (Day 5 of administration) | 28 days after discontinuation |
|---|---|---|---|
| WBC (/μL) | 7 800 | 5 200 | − |
| AST (IU/L) | 15 | 26 | − |
| LDH (IU/L) | 150 | 175 | − |
| CK (IU/L) | 149 | 2 410 | 59 |
| BUN (mg/dL) | 6.8 | 9.8 | − |
| Cr (mg/dL) | 0.49 | 0.54 | − |

# 4

# Revision of Precautions (No. 262)

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 January 9, 2015.

## 1

**Antidiabetic agent**

## Linagliptin

**Brand name**

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

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

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

## 2

**Acting mainly on gram-positive and gram-negative bacteria, Antibiotics-Miscellaneous**

## (1) Amoxicillin Hydrate
## (2) Potassium Clavulanate/Amoxicillin Hydrate
## (3) Sodium Rabeprazole/Amoxicillin Hydrate/Clarithromycin
## (4) Sodium Rabeprazole/Amoxicillin Hydrate/Metronidazole
## (5) Lansoprazole/Amoxicillin Hydrate/Clarithromycin
## (6) Lansoprazole/Amoxicillin Hydrate/Metronidazole

**Brand name**

(1) Sawacillin Capsules 125 mg and 250 mg, Sawacillin Fine Granules 10%, Sawacillin Tablets 250 mg (Astellas Pharma Inc.), Pasetocin Capsules 125 mg and 250 mg, Pasetocin Fine Granules 10%, Pasetocin Tablets 250 mg (Kyowa Hakko Kirin Co., Ltd) and the others
(2) Augmentin Combination Tablets 125SS and 250RS, and Clavamox combination Dry Syrup for pediatric (GlaxoSmithKline K.K.)
(3) Rabecure PACK 400 mg and 800 mg (Eisai Co., Ltd.)
(4) Rabefine Pack (Eisai Co., Ltd.)
(5) Lansap 400 mg and 700 mg (Takeda Pharmaceutical Company Ltd.)
(6) Lampion Pack (Takeda Pharmaceutical Company Ltd.)

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

**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis, and erythroderma (dermatitis exfoliative):** TEN, oculomucocutaneous syndrome, erythema multiforme, acute generalised exanthematous pustulosis, and erythroderma (dermatitis exfoliative) may occur. Patients should be carefully monitored. If any abnormalities such as pyrexia, headache, arthralgia, erythaema/blister of the skin and mucous membranes, pustules, feeling tension/burning sensation/pain of skin are observed, administration of this drug should be discontinued and appropriate measures

should be taken.

**Meningitis aseptic:** Meningitis aseptic with symptoms including nuchal rigidity, pyrexia, headache, nausea/vomiting, or consciousness clouding may occur. If these symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

3 **Antivirals**

## Simeprevir Sodium

| | |
|---|---|
| **Brand name** | Sovriad Capsules 100 mg (Janssen Pharmaceutical K.K.) |
| **Adverse reactions (clinically significant adverse reactions)** | **Leukopenia, neutropenia:** Leukopenia and/or neutropenia may occur. Patients should be carefully monitored through periodic blood tests, etc. If the abnormality is severe, discontinuation of administration should be considered and appropriate measures should be taken. |

# 5

# List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting the adverse drug reaction (ADR) 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 ADR. EPPV is specified as a condition of approval.

(As of January 1, 2015)

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

| | Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | sirolimus<br>Rapalimus Tablets 1 mg | Nobelpharma Co., Ltd. | December 22, 2014 |
| ◎ | caspofungin acetate<br>Cancidas for Intravenous Drip Infusion 50 mg, 70 mg*1 | MSD K.K. | December 18, 2014 |
| ◎ | darbepoetin alfa (genetical recombination)<br>Nesp Injection 5 μg Plastic Syringe, 10 μg Plastic Syringe, 15 μg Plastic Syringe, 20 μg Plastic Syringe, 30 μg Plastic Syringe, 40 μg Plastic Syringe, 60 μg Plastic Syringe, 120 μg Plastic Syringe, 180 μg Plastic Syringe*2 | Kyowa Hakko Kirin Co., Ltd. | December 18, 2014 |
| ◎ | midazolam<br>Midafresa Injection 0.1% | Alfresa Pharma Corporation | December 17, 2014 |
| ◎ | rilpivirine hydrochloride/tenofovir disoproxil fumarate/emtricitabine<br>Complera Combination Tablets | Janssen Pharmaceutical K.K. | December 12, 2014 |
| ◎ | bosutinib hydrate<br>Bosulif Tablets 100 mg | Pfizer Japan Inc. | December 5, 2014 |
| ◎ | progesterone<br>Lutinus Vaginal Tablets 100 mg | Ferring Pharmaceuticals Co., Ltd. | December 5, 2014 |
| ◎ | ripasudil hydrochloride hydrate<br>Glanatec Ophthalmic Solution 0.4% | Kowa Company, Ltd. | December 2, 2014 |
| | anhydrous caffeine<br>Respia Injection or oral solution 60 mg | Nobelpharma Co., Ltd. | December 1, 2014 |
| | pegfilgrastim (genetical recombination)<br>G-lasta Subcutaneous Injection 3.6 mg | Kyowa Hakko Kirin Co., Ltd. | November 28, 2014 |
| | suvorexant<br>Belsomra Tablets 15 mg, 20 mg | MSD K.K. | November 26, 2014 |
| | vaniprevir<br>Vanihep Capsules 150 mg | MSD K.K. | November 25, 2014 |
| | anagrelide hydrochloride hydrate<br>Agrylin Capsules 0.5 mg | Shire Japan KK | November 25, 2014 |

| Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| tiotropium bromide hydrate<br>Spiriva 2.5 μg Respimat 60 puffs*[3] | Nippon Boehringer Ingelheim Co., Ltd. | November 18, 2014 |
| aflibercept (genetical recombination)<br>Eylea Solution Intravitreal Injections 40 mg/mL, Eylea Solution Intravitreal Injections Kit 40 mg/mL*[4] | Bayer Yakuhin, Ltd. | November 18, 2014 |
| Freeze-dried activated human blood coagulation factor VII concentrate containing factor X<br>Byclot for Intravenous Injection | The Chemo-Sero-Therapeutic Research Institute | November 11, 2014 |
| 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, 60 mg*[5] | Daiichi Sankyo Company, Limited | September 26, 2014 |
| voriconazole<br>Vfend Tablets 50 mg, 200 mg, Vfend for Intravenous Use 200 mg, Vfend Dry Syrup 2 800 mg*[6] | 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*[7] | 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%*[8] | 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*[9] | Bayer Yakuhin, Ltd. | September 19, 2014 |
| calcipotriol hydrate/betamethasone dipropionate<br>Dovobet Ointment | Leo Pharma K.K. | September 12, 2014 |
| 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 |

| Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| (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*10 | 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 |

*1 An additional administration for “pediatrics”

*2 An additional indication for “the treatment of patients with anaemia associated with myelodysplastic syndrome”

*3 An additional indication for “the remission of various symptoms associated with airway obstructive disorder in patients with the following diseases: bronchial asthma (to be used only in patients with severe and persistent disease)”

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

*5 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),” EPPV was initiated in December 8, 2014 for Lixiana 60 mg tablets.

*6 An additional administration for “pediatrics,” EPPV was initiated in December 5, 2014 for Vfend Dry Syrup 2 800 mg.

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

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

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

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

**List of corrections in the** Pharmaceuticals and Medical Devices Safety Information **No.318**

| Page | Revised | Original |
|---|---|---|
| 27 | References 1) | |
| | http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000063<u>4611</u>.pdf | http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000063<u>515</u>.pdf |