Pharmaceuticals and Medical Devices Safety Information

No. 310 February 2014

Table of Contents

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

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Pharmaceuticals and Medical Devices Safety Information
No. 310 February 2014

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

[Outline of Information]

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

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

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

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

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

Abbreviations

3TC	Lamivudine
ABC	Abacavir
ACE	Angiotensin-converting enzyme
ADRs	Adverse drug reactions
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
APTT	Activated partial thromboplastin time
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
BAL	Bronchoalveolar lavage
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
C3	Complement 3
C4	Complement 4
CCr	Creatinine clearance
CD4	Cluster of differentiation 4
CH50	50% hemolytic unit of complement
CHDF	Continuous hemodiafiltration
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
ECOG PS	Eastern Cooperative Oncology Group Performance status
EFV	Efavirenz
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
FFP	Fresh frozen plasma
HAART	Highly active antiretroviral therapy
HbA1c	Hemoglobin A1c
HBc-Ab	Hepatitis B core antibody
HBe-Ab	Hepatitis B envelope antibody
HBe-Ag	Hepatitis B envelope antigen
HBs-Ab	Hepatitis B surface antibody
HBs-Ag	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus-Deoxyribonucleic acid
HCV-RNA	Hepatitis C virus-Ribonucleic acid
HHV-6	Human herpesvirus 6
HIV-1	Human immunodeficiency virus type 1
HPF	High power field
HR	Heart rate
IgA	Immunoglobulin A

IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IU	International unit
JCS	Japan Coma Scale
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LAD	Left anterior descending coronary artery
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
NAG	N-acetylglucosaminidase
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PLT	Platelet
PSL	Prednisolone
PT	Prothrombin Time
PT-INR	Prothrombin time - international normalized ratio
RA	Radial artery
RAHA	Rheumatoid arthritis hemagglutinatin
RBC	Red blood cell
RCC	Red cell concentrates
s-Cr	Serum creatinine
SP-D	Surfactant protein D
SpO2	Oxygen saturation
TBLB	Transbronchial lung biopsy
TDF	Tenofovir
WBC	White blood cell
β-2MG	β-2 microglobulin
γ-GTP	gamma-glutamyl transpeptidase

1

Thrombosis with YAZ Combination Tablets for Dysmenorrhea

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Drospirenone, ethinylestradiol betadex	YAZ Combination Tablets (Bayer Yakuhin, Ltd.)
Therapeutic Category	Mixed hormone preparations	
Indications	Dysmenorrhoea	

1. Introduction

YAZ Combination Tablets (hereinafter referred to as "YAZ"), which contain 3 mg of drospirenone, a synthetic progestogen, and 0.02 mg of ethinylestradiol, a synthetic estrogen, were approved in Japan for the indication of "Dysmenorrhoea" in July 2010. According to the marketing authorization holder (MAH), it is estimated to be used for approximately 187,000 Women-Year*.

Recently, thrombosis has been reported associated with administration of YAZ, leading to fatal outcome in some cases in Japan. As there was a possible lack of appropriate diagnosis and treatment despite the fact that the patients had symptoms suggestive of thrombosis, MHLW instructed the MAH to revise Precautions and distribute Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter) [1)]. The information is presented below.

*: Women-Year: Estimate number of users in case one woman uses 13 sheets of YAZ (28 tablets in one sheet) in one year.

2. Background

An alert has been provided about thrombosis associated with YAZ since the start of marketing as with other oral female hormone combination drugs (combinations of estrogen and progestogen, such as contraceptives and/or dysmenorrhoea drugs). In June 2013, however, the first fatal case (in a patient in her 20s) with thrombosis, of which causal relationship with YAZ cannot be ruled out, was reported in Japan. Accordingly, the MAH began to distribute materials for healthcare professionals in August 2013 in order to present the case and alert them of thrombosis.

Thereafter in September 2013, a fatal case (in a patient in her 10s) with thrombosis before June 2013, of which a causal relationship with YAZ cannot be ruled out, was reported in Japan, and the MAH therefore began to distribute materials for healthcare professionals in October 2013, as with the first case. In addition, after receiving the report of these 2 cases, the MAH distributed Patient Cards to ensure that a patient receiving YAZ would be examined and treated in consideration of thrombosis related to the product when she visits medical institutions other than obstetrics and gynecology.

Meanwhile, in January 2014, a fatal case (in a patient in her 40s) with thrombosis, of which a causal relationship with YAZ cannot be ruled out, has been reported. Based on the urgency of the situation, MHLW instructed the MAH of YAZ to revise Precautions, add a Warnings section on thrombosis, and distribute Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter) [1)] to ensure rapid communication of the alert on January 17, 2014 because: a) an alert has already been provided in the package insert about the risk of thrombosis associated with YAZ. However, 3 fatal cases, including this case, have been reported and a causal relationship with YAZ cannot be ruled out in

all the cases; b) in 2 of the 3 cases, the patients visited their prescribing physicians or other medical institutions for symptoms suggestive of thrombosis before they died, and their life could have been saved if they were appropriately diagnosed and treated; and c) 2 of the 3 patients were in their 20s or below and had no risk factors of thrombosis (e.g., smoking, obesity, past medical history, and family history).

3. Occurrence of thrombosis with YAZ

A total of 140 cases of serious thrombosis-related adverse reactions, including 3 fatal cases, were reported from November 2010, when YAZ was launched, to January 17, 2014. Two of the 3 fatal cases with thrombosis are presented below.

Case Summaries

No.	Patient		Description of components per sheet/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 20s	Dysmenorrhoea, acne, irregular menstruation (anaemia)	24 tablets of active drug: drospirenone 3 mg/ ethinylestradiol 0.02 mg; 4 tablets of placebo 7 days	**Intracranial venous sinus thrombosis** Body mass index (BMI), 17.3; Non-smoker; Family history, Grandfather Cerebral infarction; No prior medication; Nulliparity 10 days before prescription: The patient visited Hospital A for the first time. Hormone test showed normal level. Day of prescription: YAZ was prescribed at Hospital A. Day 1 of treatment: Treatment initiated (1 tablet/day). Day 3 of treatment: Headache occurred. Day 7 of prescription*: The patient visited an internal medicine department in Hospital B due to physical deconditioning. She complained of headache, nausea, and palpitations from the morning. Blood pressure was 105/68. Electrocardiogram and blood test showed normal. Anaemia was serious. Intravenous drip was administered. She was treated with domperidone, rebamipide, and biodiastase. No convulsion in lower extremities. No paralysis. Day 10 of prescription: The patient visited an internal medicine department in Hospital B again. She had headache. Blood pressure was 103/70. No abnormal findings. Clotiazepam was prescribed to be taken as needed. She was advised to visit gynecologist because of serious anaemia. The patient visited Hospital A again. She complained of feeling sick. She had nausea and impaired appetite. Vital signs were normal. Urine ketone body test showed negative. She complained of headache after fluid replacement was performed, therefore, the prescriber advised her to see a cerebral surgeon. (Total dose of YAZ was 7 tablets. Administration was immediately discontinued.) The patient visited a cerebral surgery department in Hospital C. At the time of visiting, no obvious

				symptoms such as paralysis were seen. The patient made an appointment for examination and went back home. She vomited and had difficulty in walking. Day 11 of prescription: Difficulty in movement occurred. Day 12 of prescription: In the morning, mother of the patient found her incontinent on the bed. The patient was transferred to Hospital D. Computed tomography (CT) and Magnetic resonance imaging (MRI) were conducted. She was immediately referred to Hospital E. On the way to Hospital E, level of consciousness was Japan Coma Scale (JSC) III-300 and convulsion was observed. Deep cerebral venous sinus thrombosis was diagnosed with CT findings. She was immediately admitted to Hospital E on the day, and started to receive treatment with heparin. Day 13 of prescription: Hydrocephalus was aggravated and respiratory failure occurred. Endotracheal intubation was performed. Antiphospholipid antibody: (-). Anti-Neutrophil Cytoplasmic Antibody: (-). Day 14 of prescription: The patient died. An autopsy was conducted on the same day. No marked traumatic injury was observed. There were no findings suggesting myocardial infarction or congenital anomaly.
	Concomitant medication: clotiazepam			

* Clinical course and therapeutic measures were described with "Day of prescription" instead of "Day of treatment" because Day of treatment was unknown.

Case Summaries

No.	Patient		Description of components per sheet/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 40s	Dysmenorrhoea (uterine myoma)	24 tablets of active drug: drospirenone 3 mg/ ethinylestradiol 0.02 mg; 4 tablets of placebo Ca. 1 year	**Pulmonary embolism, Deep vein thrombosis** BMI, 23.6; No Family history; Non-smoker; Para 2. No thrombus-related factor and history of thrombosis were identified with a medical interview (no measurement of fibrinolytic or coagulation system marker). No prior medication. Cervical cytology: Negative for intra epithelial lesion or malignancy. A myoma 4.5 cm in size was present. Prescriber proposed the patient about treatment of YAZ in case she has no anaemia by uterine myoma. Diclofenac sodium was prescribed. Day 1 of prescription*: No anaemia was found, then YAZ was prescribed for dysmenorrhoea (1 tablet/day). Diclofenac sodium and teprenone were prescribed. Day 47 of prescription: 3 sheets of YAZ were prescribed as no complaint was made by the patient about adverse event.

				Day 127 of prescription: 3 sheets of YAZ, diclofenac sodium and teprenone were prescribed. Day 208 of prescription: The patient complained of right leg cramps, but no tenderness when her leg was grasped by hand. Transvaginal ultrasound was performed as follow-up examination. The size of myoma was slightly increased to about 7 cm. Prescriber informed her that it was advisable to receive a treatment with surgery to improve the symptoms, but she was not so keen to have it. YAZ (3 sheets), diclofenac sodium and teprenone were prescribed. Solifenacin succinate was prescribed for pollakiuria. Day 223 of prescription: Solifenacin succinate was prescribed. Day 255 of prescription: Solifenacin succinate was prescribed. Day 295 of prescription: No increase of myoma was seen with transvaginal ultrasound. 3 sheets of YAZ were prescribed. 2 or 3 weeks before the day of withdrawal: The patient complained pain and swelling of her right leg and saw an orthopedist. Day 370 of prescription (withdrawal date): Difficulty of breathing developed and the patient was transferred to an emergency department. Depressed level of consciousness JCS: I-3, tachypnoea and difficulty of breathing were observed. Blood pressure, 94/74; heart rate (HR), 126; oxygen saturation (SpO_2), 100% under giving oxygen. When the patient was transferred into the ambulance, kinking of upper limbs, extension of lower limbs and ankylosis were observed. Cardio-respiratory arrest developed in the ambulance. After the ambulance reached the hospital, heart beating restarted. After this, 2 times of cardiac arrest occurred and she was resuscitated each time, but consciousness did not come back. Although body temperature decreased to 34 C-degrees by therapeutic hypothermia for protection of brain, bleeding developed remarkably so the therapy was stopped. Red cell concentrates (RCC): 7 units and fresh frozen plasma (FFP): 8 units were transfused. 1 day after withdrawal: RCC: 3 units were transfused. Contrast-enhanced CT revealed pulmonary embolism and deep vein thrombosis as well as pleural effusion. Treatment with heparin and warfarin was started. 6 days after withdrawal: Renal failure was gradually advanced. Urine output decrease was observed. Treatment with furosemide was made. 7 days after withdrawal: Continuous hemodiafiltration was initiated. Drainage of bilateral pleural effusion was made. 9 days after withdrawal:

				Pupils dilated and blood pressure rapidly increased appeared. Intracranial pressure increased caused by brain ischemia was considered and treatment with concentrated glycerin/fructose was made. 16 days after withdrawal: The patient was in a condition which can be judged as brain death without any discrepancy. 19 days after withdrawal: Cardiac arrest and respiratory arrest were observed. Mydriasis and pupillary light reflex lost were seen. It was confirmed that the patient died.
	Concomitant medications: diclofenac sodium, teprenone, solifenacin succinate			

* Clinical course and therapeutic measures were described with "Day of prescription" instead of "Day of treatment" because Day of treatment was unknown.

4. Precautions against thrombosis

Healthcare professionals should pay due attention to the following:

a) Thrombosis may occur with the use of the drug and it may have a fatal outcome. If any of the following symptoms appears, administration should be discontinued and appropriate measures taken immediately. Patients should also be instructed to stop taking the drug and visit an emergency medical institution immediately, if such symptom appears.

- Major symptoms of thrombosis that require emergency response
  Sudden severe pain/oedema of the lower limb, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance, etc.

b) Thrombosis may occur with the use of the drug irrespective of the existence of risk factor(s) such as age, smoking, obesity, and/or a family history of thrombosis. If the following symptoms and conditions appear, appropriate measures such as discontinuance of the drug should be taken.

- Symptoms of which thrombosis is suspected
  Swelling/pain/numbness/redness, hot feeling of the lower limb, headache, vomiting/ nausea, etc.
- Conditions of high risk of thrombosis
  Immobilized condition, remarkable elevation in blood pressure, dehydration, etc.

c) Patient Card[2)] should be provided to the patient, and the following explanation/instructions should be given to the patients taking this drug at the start and continuation of the use.

- Thrombosis may have a fatal outcome.
- Use of the drug should be stopped and consult a physician etc., immediately, if any symptom of which thrombosis is suspected appear and/or if at the condition of high risk of thrombosis, irrespective of the severity of the symptom/condition.
- Patient Card[2)] should be shown to a physician when patients visit the other medical institution suspecting thrombosis.

5. Closing comments

For the revisions to Precautions of the package insert, for which MHLW gave instruction to the MAH in addition to the distribution of Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter), please see page 35 of this document (4. Important Safety Information).

The risk of thrombosis is not limited to YAZ, and other oral female hormone combination drugs indicated for contraception or dysmenorrhoea are also known to have a risk. An alert has already been provided about this in the package inserts of such drugs. In the wake of the alert about YAZ, MHLW reviewed the risk of thrombosis associated with these oral female hormone combination drugs and concluded that these drugs might cause thrombosis like YAZ. Therefore, MHLW instructed to revise Precautions to add a further alert on thrombosis in February 2014. (Please see page 39 of this document.)

Healthcare professionals are encouraged to continuously cooperate for proper use of drugs by fully informing patients of the risk of thrombosis prior to use of oral female hormone combination drugs indicated for contraception or dysmenorrhoea, including YAZ, and promptly taking measures against any symptom suggestive of thrombosis.

<References>

1) Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue Letter): Thrombosis with YAZ COMBINATION TABLETS for Dysmenorrhea
http://www.pmda.go.jp/english/service/pdf/letter/140117-yaz.pdf
2) Patient Card for YAZ Combination Tablets
http://gynecology.bayer.jp/static/pdf/YAZ_patients_Card.pdf (Only available in Japanese language)

2

Rivaroxaban and Interstitial Pneumonia

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Rivaroxaban	Xarelto Tablets 10 mg, 15 mg (Bayer Yakuhin, Ltd.)
Therapeutic Category	Anticoagulants	
Indications	Reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.	

1. Introduction

Rivaroxaban (Xarelto Tablets) acts on the blood coagulation system and thereby reduce thrombus formation by selectively inhibiting the activated blood coagulation factor X. It was approved in Japan for the indication of "Reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation" in January 2012. Based on the number of tablets supplied in December 2013, the MAH estimates that the product is used in approximately 200,000 patients.

Because several cases of interstitial lung disease that developed after administration of rivaroxaban were recently reported in Japan, PMDA instructed the MAH to prepare and distribute materials for healthcare professionals about interstitial lung disease with Rivaroxaban, and MHLW instructed the MAH to revise Precautions of rivaroxaban on February 6, 2014.

The background and details are described below.

2. Background

In Japanese phase III clinical study of rivaroxaban in patients with nonvalvular atrial fibrillation, an adverse event of interstitial lung disease occurred in 2 patients (0.31%) in the rivaroxaban group (639 patients) and 4 patients (0.63%) in the control warfarin group (639 patients). Among these patients, a causal relationship with the study drug could not be ruled out in 1 patient in the rivaroxaban group.

Since its launch in April 2012, several cases of interstitial pneumonia that developed after administration of rivaroxaban have been reported in Japan, and cases with fatal outcome have also been reported. Therefore, PMDA started to review the need for providing an alert on interstitial pneumonia associated with rivaroxaban.

In the course of the review, it was found out that treatment with rivaroxaban was continued despite signs of interstitial pneumonia in some cases of interstitial pneumonia with fatal outcome, while treatment with rivaroxaban was discontinued at an early stage and measures including administration of corticosteroids were taken in cases of interstitial pneumonia that resolved. In light of the fact that the number of reports is growing as the number of patients using rivaroxaban increases, PMDA and MHLW considered that early detection of interstitial pneumonia and prompt measures at the time of onset of interstitial pneumonia were important. Therefore PMDA and MHLW instructed the MAH to prepare and distribute materials for healthcare professionals to promptly provide an alert on interstitial pneumonia on January 2014 and reviewed the revisions to the package insert.

As a result of the review at PMDA, 4 cases, of which causal relationship with rivaroxaban could not be ruled out, were identified (including 1 fatal case) among 13 cases of interstitial pneumonia reported from the launch of rivaroxaban (April 2012) to January 17, 2014. Because some of these cases involved bloody sputum and pulmonary alveolar haemorrhage and some other cases were likely to be lung disorder, rather than interstitial pneumonia, caused by pulmonary alveolar haemorrhage, MHLW

concluded that it was appropriate to provide an alert about these cases as interstitial lung disease and instructed the MAH to add the following descriptions in the package insert on February 2014:

Important Precautions	Patients should be instructed to immediately contact their physician if initial symptoms including cough, bloody sputum, dyspnoea, and/or pyrexia are observed.
Clinically Significant Adverse Reactions	If cough, bloody sputum, shortness of breath, dyspnoea, pyrexia, abnormal chest sound, etc. are observed, examinations including chest X-ray, chest CT scan, and/or serum marker test should be performed immediately and, if interstitial lung disease is suspected, administration of this drug should be discontinued and appropriate measures should be taken.

3. Occurrence of interstitial lung disease with rivaroxaban

Two of 4 cases of interstitial lung disease that developed after administration of rivaroxaban and of which causal relationship with rivaroxaban cannot be ruled out 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 80s	Atrial flutter (myocardial ischaemia) (dyslipidaemia)	10 mg for 28 days	**Interstitial lung disease** 1 day before administration: The patient experienced tachycardia and started treatment with verapamil at another Hospital A. Day 1 of administration: Administration of rivaroxaban (10 mg/day) was started. Day 7 of administration: The patient underwent ablation for atrial flutter at another Hospital B. After ablation, administration of verapamil was discontinued and administration of rivaroxaban was continued. Around Day 10 of administration: The patient had pyrexia (37.5°C level) and cough. Pyrexia occasionally appeared thereafter. Day 16 of administration: Minocycline, aldioxa, tranexamic acid, carbocysteine, and acetaminophen were administered at another Hospital C. Day 17 of administration: Extensive skin eruption accompanied by pruritus, with diameter of 1 cm, appeared on the lower thighs, etc. Day 20 of administration: Respiratory symptoms did not improve. The patient visited another Hospital D and chest X-ray showed infiltrative opacities. He was referred to this hospital without any additional prescription. Day 21 of administration: The patient visited this hospital. Administration of ceftriaxone was started for possible infectious pneumonia. Day 22 of administration: Findings upon hospitalization: 36.2°C; HR, 74;SPO_2, 96%; blood pressure, 125/73 mmHg; breath sounds, audible crackles. Blood test: C-reactive protein (CRP), 15.9; White blood cell

				count (WBC), 12,360; Eosino, 4.4%; Lactate dehydrogenase (LDH), 251; procalcitonin, 0.12; Rheumatoid arthritis hemagglutinatin (RAHA), 640; soluble Interleukin-2 receptor, 1,830; Immunoglobulin E radio-immunosorbent test, 5,000. Chest X-ray showed atrophy in the left lung and ground-glass to infiltrative opacities from the upper to the lower lung fields, predominantly at the lateral side of right and left lungs. CT scan further showed honeycomb lung in the lower lung field. Slight pleural effusion was noted at the left lung, without enlarged lymph nodes. Lung function test showed restrictive and mixed impairment, and diffusing capacity was relatively maintained. Day 24 of administration: The distance in 6-minute walk test was 370 m, and cardiopulmonary function was maintained with SPO_2 of 92%. Day 25 of administration: Administration of ceftriaxone was discontinued, and only tulobuterol patch 1 mg was applied for alleviation of symptoms. Day 27 of administration: Administration of codeine preparation was started at 4.5 mL. Pyrexia of 37.0°C and dry cough persisted, and eosinophil count increased to 1,185. Skin symptoms were alleviated. During the last few days, the infiltrative opacities in the lung seemed to be spreading and the left lung appeared to be decreasing in size. Day 28 of administration (day of discontinuation): Administration of prednisolone was started at 50 mg. Administration of rivaroxaban was discontinued. 6 days after discontinuation: Eosinophil count did not decrease, and respiratory failure was aggravated. High-dose steroid therapy (methylprednisolone 500 to 1,000 mg/day, drip infusion) was started. Chest CT showed irregularly enhanced interstitial opacities in both lungs. A small amount of pleural effusion was noted in the left thoracic cavity. No morbidly enlarged lymph nodes were found. 7 days after discontinuation: Although eosinophil count decreased to 0, respiratory failure advanced, and it did not improve despite noninvasive positive pressure ventilation. 10 days after discontinuation: The patient died of interstitial pneumonia.
	Concomitant medications: clopidogrel sulfate, sodium rabeprazole, pitavastatin calcium, carvedilol, verapamil hydrochloride			

Laboratory Examination

	Day 21 of administration	Day 24 of administration	Day 27 of administration	3 days after discontinuation	6 days after discontinuation
WBC (/mm^3)	12,360	–	12,100	19,810	23,720
CRP (mg/dL)	15.94	–	11.28	10.15	10.35
LDH (IU/L)	251	–	185	266	328
KL-6 (U/mL)	–	–	–	–	437
SP-D (ng/mL)	–	184	–	–	–

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 80s	Atrial fibrillation (hyperlipidaemia)	15 mg for 59 days	**Interstitial lung disease** Day 1 of administration: Warfarin was switched to rivaroxaban (15 mg/day). Day 52 of administration: The patient experienced cough at night. Day 55 of administration: Cough was aggravated, and bloody sputum appeared. Day 59 of administration (day of discontinuation): Bloody sputum was aggravated, and the patient visited the emergency outpatient department of this hospital. Chest X-ray showed ground-glass opacities in the bilateral upper lung field, and CT scan showed ground-glass and infiltrative opacities predominantly in the bilateral upper lobe with a marked decrease in volume. The patient was urgently admitted to the hospital. Drug-induced lung disorder and pulmonary alveolar haemorrhage developed. Administration of rivaroxaban was discontinued after that. 1 day after discontinuation: Administration of prednisolone (PSL) 50 mg/day was started. Oxygen 5 L was administered via mask. 4 days after discontinuation: The patient's condition was aggravated, requiring oxygen 15 L administered via reservoir mask. Steroid pulse therapy (methylprednisolone, 1 g for 3 days) was started. 6 days after discontinuation: Steroid pulse therapy was terminated. Administration of PSL 50 mg/day was continued. 7 days after discontinuation: Oxygen 7 L was administered via mask. 9 days after discontinuation: Oxygen 6 L was administered via mask. 12 days after discontinuation: Oxygen 4 L was administered intranasally. 16 days after discontinuation: Oxygen 1 L was administered intranasally. 18 days after discontinuation: Rehabilitation was started. 26 days after discontinuation: The dose of PSL was reduced from 50 mg to 40 mg. 28 days after discontinuation: CT scan showed an improvement of ground-glass opacities. Drug-induced lung disorder resolved. 30 days after discontinuation: Oxygen 3 L was administered intranasally only during exertion. 32 days after discontinuation: Administration of oxygen was discontinued. 40 days after discontinuation: The patient was discharged from the hospital. He was to be followed up on an outpatient basis.
	Concomitant medications: bisoprolol fumarate, pravastatin sodium			

Laboratory Examination

	Day 1 of administration	Day 59 of administration	29 days after discontinuation
WBC (/mm^3)	4,500	9,000	7,100
CRP (mg/dL)	0.1	13.9	0.0
LDH (IU/L)	200	346	240
KL-6 (U/mL)	−	495	1,610
SP-D (ng/mL)	−	−	83.4

4. Precautions against interstitial lung disease

As shown in **the table below**, precautions against interstitial lung disease were added in the sections of "Important Precautions" and "Clinically Significant Adverse Reactions" as a result of the revision of the package insert in February 2014. Healthcare professionals are encouraged to be aware of possible development of interstitial lung disease and the need for instructing patients and to take appropriate measures.

Table Precautions against interstitial lung disease in the package insert of rivaroxaban (February 2014)

Important Precautions	Interstitial lung disease may occur. Patients should be instructed to immediately contact their physician if symptoms including cough, bloody sputum, dyspnoea, and/or pyrexia occur.
Clinically Significant Adverse Reactions	Interstitial lung disease: Interstitial lung disease may occur, and it may be accompanied by bloody sputum and pulmonary alveolar haemorrhage in some cases. Patients should be carefully monitored, and if cough, bloody sputum, shortness of breath, dyspnoea, pyrexia, or abnormal chest sound, etc. are observed, examinations including chest X-ray, chest CT scan, and/or serum marker test should be performed immediately. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

Healthcare professionals are encouraged to take appropriate measures including prompt collaboration with a respiratory specialist for an immediate diagnosis if interstitial lung disease is suspected.

In addition, please be aware of the increased risk of pulmonary alveolar haemorrhage with rivaroxaban, although an alert on the increased risk of haemorrhage with combination of rivaroxaban and antiplatelet agents has been provided in the sections of Important Precautions and Interactions.

The alert on interstitial lung disease with rivaroxaban, distribution of which was started for healthcare professionals in the end of January 2014, is posted on the PMDA website, *Information on proper use of drugs from pharmaceutical companies* (provisionally translated title, http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201401_1.pdf) (Only available in Japanese language), to provide relevant information.

Healthcare professionals are encouraged to continuously cooperate for proper use of drugs.

3

Direct Patient Reporting System for Adverse Drug Reactions

1. Introduction

In March 2012, PMDA launched the pilot program for Direct Patient Reporting System for Adverse Drug Reactions. This web-based system allows patients/consumers or their families to report suspected adverse drug reactions.

The PMDSI No. 292 described the launch of the patient adverse drug reaction reporting system (http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-292.pdf). In this document, current situations of reports from the launch (March 26, 2012) to the end of March 2013 are presented.

2. Direct Patient Reporting System for Adverse Drug Reactions

The Direct Patient Reporting System for Adverse Drug Reactions (the System) is a program to collect information from patients/consumers who experienced adverse drug reaction or their families in the case that drug-induced adverse reactions are suspected. Collected information are to be used for the purpose of carrying forward safety measures for drugs such as identifying the trends in occurrences of adverse drug reactions.

Adverse drug reactions reports are received through the System on PMDA's Medical Product Information website (http://www.info.pmda.go.jp/fukusayou_houkoku/fukusayou_houkoku_attention.html) (Only available in Japanese language). To access this site, search for “患者副作用報告” (patient adverse drug reaction reporting) on a major internet search engine or access the Medical Product Information website (http://www.info.pmda.go.jp/index.html) and select “一般の皆様向け” (To the Public) – “患者副作用報告” (Direct Patient Reporting System for Adverse Drug Reactions).

3. Cases of patient adverse drug reaction reporting

A total of 184 reports were received from the launch of the System to the end of March 2013: 140 reports from patients/consumers and 44 reports from their families.

These reports include a total of 235 suspected drugs (222 ethical drugs and 13 over-the-counter drugs).

When the number of reports of adverse reactions is shown by therapeutic category, for reports from MAHs in accordance with the Pharmaceutical Affairs Law, the top three categories -(FY 2012) are "Antineoplastics-Miscellaneous," such as anticancer agents, "Miscellaneous metabolism agents-Miscellaneous," such as drugs for osteoporosis and immunosuppressants, and "Antivirals," such as anti-influenza agents. Meanwhile, for ethical drugs of reports from patients/consumers and their families, adverse reactions by psychiatric and neurological drugs are frequently reported, with psychotropics (39 events) being most frequent followed by antipyretics and analgesics, anti-inflammatory agents (23 events) and hypnotics and sedatives, anxiolytics (16 events). This tendency was similar to that observed in a pilot study of patient reporting by the "Research on System for Receiving Adverse Reaction Information from Patients" (chief researcher, Professor Mayumi Mochizuki, Faculty of Pharmacy, Keio University) supported by Health and Labour Sciences Research Grants, conducted before pilot operation of the System.

When the number of reports is compared using terms of adverse reactions, headache was most

frequent, followed by nausea and dizziness. In addition, 74% of the cases occurred in or after 2011. Many reports were submitted relatively soon after the occurrence of adverse drug reactions.

While the MHLW and PMDA are conducting safety measures for drugs mainly based on adverse reactions and other information reported by MAHs and healthcare professionals, PMDA's personnel also check adverse reactions reported through the System to review the need for taking further safety measures. If they consider that a received report is especially important for taking safety measures and further details are required, PMDA conducts a detailed investigation at the medical institution that saw the applicable patient. In this case, before starting the investigation, the reporter is informed that a survey of the medical institution is planned in order to give consent to it. Healthcare professionals are encouraged to be understanding and cooperative for detailed investigations.

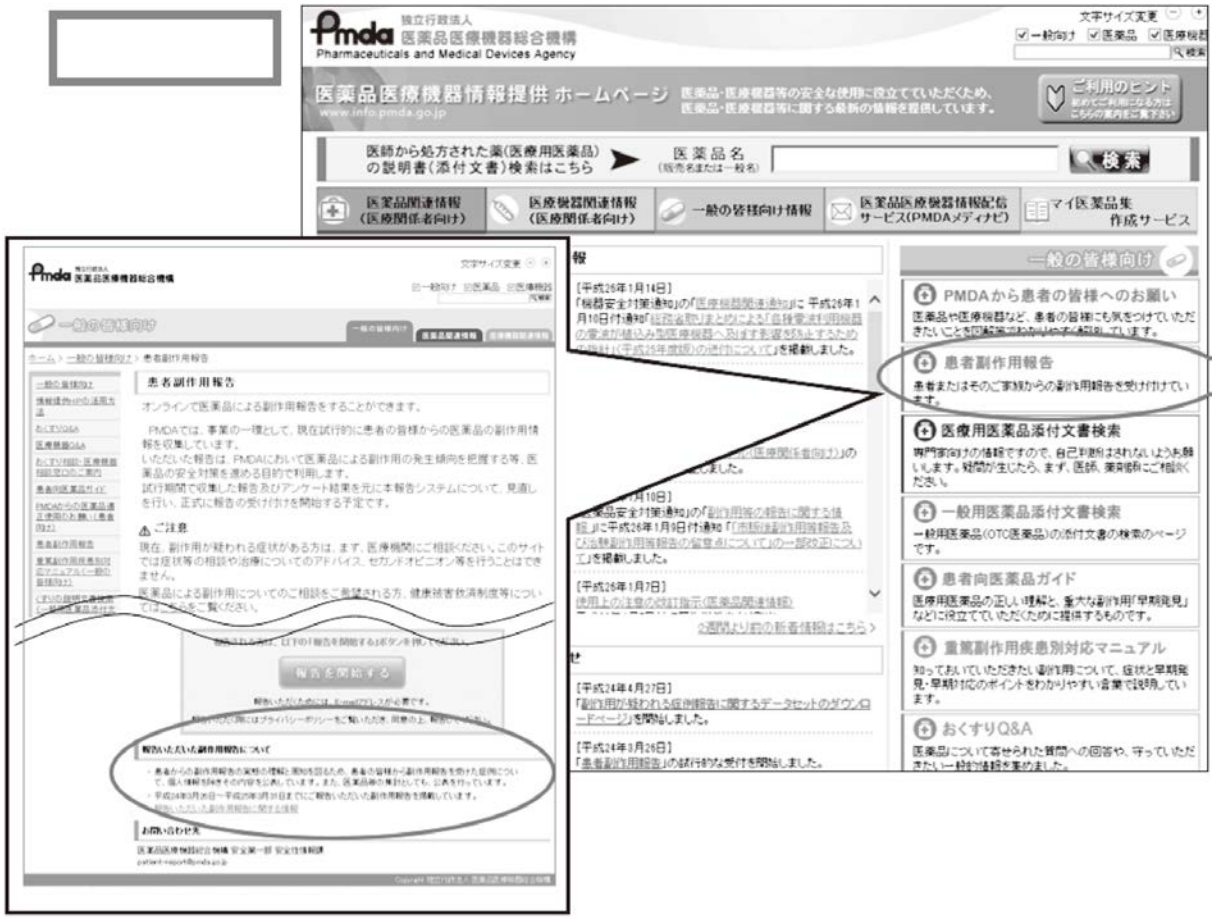
4. Publication of line listings of the System

Publication of two types of line listings (a report of adverse reaction from patients shown in each row) has been started for cases reported through the Direct Patient Reporting System for Adverse Drug Reactions. This publication is intended to inform the public of the types of drugs and related adverse reactions reported by patients. Please note that names of patients and medical institutions, date of onset of adverse reactions, and other details are not included in published information to protect the privacy of reporters, patients experiencing adverse reactions, and related healthcare professionals.

Line listings of the System are available on "報告いただいた副作用報告に関する情報" (Information on reported adverse reactions) on the System's website (see the figure in page 19 for the location). Two types of line listings are published on the website: one is a line listing of "患者副作用報告（症例ごと）" (Patient adverse drug reaction reporting [for each case)) that summarizes reports of adverse reactions for each patient and the other is a line listing of "患者副作用報告（医薬品ごと）" (Patient adverse drug reaction reporting [for each drug)) that summarizes reports of adverse reactions for each drug.

The line listing of "Patient adverse drug reaction reporting (for each case)" shows the time of report (every quarter of the year), time of onset of adverse reactions (every year), type of reporter (patients or their family), sex, age (age groups of 10 years), name of drugs, term of adverse reactions, and outcome (outcome of the most serious adverse reactions).

The line listing of "Patient adverse drug reaction reporting (for each drug)" shows the number of reports of each adverse reaction by name of the active ingredient of the drugs reported (by brand name for over-the-counter drugs). Cases reported from March 26, 2012 to March 31, 2013 are currently published. These line listings will be updated annually.



Line listing of "Patient adverse drug reaction reporting (for each case)" (example)
(reported from March 2012 to March 2013)

Time of report (quarter of the year)	Time of onset of adverse reactions	Reporter	Sex	Age	Name of drug	Term of adverse reaction	Outcome
Fourth/2011	2012	Patient	Male	60s	[Brand name]	Headache	Recovered

Line listing of "Patient adverse drug reaction reporting (for each drug)" (example)
(reported from March 2012 to March 2013)

Therapeutic category	Active ingredient	Term of adverse reaction (PT)	Summary
Hypnotics and sedatives, anxiolytics	[Nonproprietary name]	Skin eruption	1
		Hypoaesthesia	2

5. Closing comments

The Direct Patient Reporting System for Adverse Drug Reactions is now operated as a pilot program but will be officially launched after reviewing the reporting system and considering the operation and evaluation procedure, etc. based on the reports collected during the pilot period and the results of a questionnaire survey conducted among reporters.

The System is useful as information that does not come through the eyes of the MAHs and healthcare professionals, and is directly communicated to PMDA and MHLW as patients' opinions, possibly contributing to an understanding of any drug safety issue including a change in occurrence of adverse reactions.

In addition, publication of reports through the System will help communicate patients' opinion to many people. We hope many people make use of the System to carry further safety measures.

Healthcare professionals are continuously encouraged to report any suspected adverse drug reactions through the Drugs and Medical Devices Safety Information Reporting System (http://www.info.pmda.go.jp/info/houkoku.html) (Only available in Japanese language).

<References>

1) "Review on the Pharmaceutical Administration to Prevent Recurrence of Yakugai (Drug-induced suffering) (final proposal)" Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Recurrence of Yakugai Similar Sufferings, April 28, 2010
http://www.mhlw.go.jp/shingi/2010/04/s0428-8.html (Only available in Japanese language)

2) "Summary on System Reform of Pharmaceutical Affairs Law, etc." Subcommittee of Pharmaceutical System Reform of the Health Sciences Council, Ministry of Health, Labour and Welfare, January 24, 2012
http://www.mhlw.go.jp/stf/shingi/2r98520000020uxm.html (Only available in Japanese language)

4

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated January 7, January 17, and February 6, 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Atazanavir Sulfate

Brand Name (name of company)	REYATAZ CAPSULES 150 mg, 200 mg (Bristol-Myers K.K.)
Therapeutic Category	Antivirals
Indications	HIV-1 infection

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Tubulointerstitial nephritis: Tubulointerstitial nephritis may occur. Patients should be carefully monitored.
Cases of crystal deposition in the renal interstitium have been reported.

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 2010 to October 2013)

- Tubulointerstitial nephritis: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 2,470 (2012)
Launched in Japan: January 2004

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	HIV infection	Unknown for 5 years and 2 months	**Tubulointerstitial nephritis** 4 months before administration: The patient experienced cerebral toxoplasmosis, thereby revealing HIV infection. Urine analysis findings: Protein and occult blood were negative. After the treatment for cerebral toxoplasmosis, serum creatinine was stable at around 0.9 mg/dL. 2 months before administration: Highly active antiretroviral therapy (HAART) with zidovudine, lamivudine, and efavirenz was started. 1 month before administration: Urine analysis showed increased red blood cell count and white blood cell count, suggesting transient urinary tract infection. Day 1 of administration:

				Hallucination occurred as an adverse reaction to the above regimen of HAART therapy. HAART regimen was modified to use atazanavir sulfate/ritonavir, lamivudine, and tenofovir. At this point, serum creatinine was 0.9 mg/dL, and urine analysis showed that protein and occult blood were negative. After that, renal function gradually worsened. Creatinine clearance decreased from the 60 mL/min/1.73 m^2 level to the 30 mL/min/1.73 m^2 level; urine protein changed from - to 2+; urinary occult blood from 2+ to 3+. 3 years and 4 months after administration: Serum creatinine was 1.6 mg/dL. Nephrotoxicity due to tenofovir was suspected, and then tenofovir was changed to abacavir, but worsening of renal impairment progressed. 5 years after administration: Serum creatinine was 2.0 mg/dL. 5 years and 2 months after administration: The patient was admitted to hospital for a detailed examination. HAART therapy at hospital admission used atazanavir sulfate/ritonavir (300 mg/100 mg/day), lamivudine (150 mg/day), and abacavir (300 mg twice/day). Human immunodeficiency virus (HIV) viral load was undetectable (< 50 HIV RNA copies/mL) and cluster of differentiation 4 (CD4) T-cell count was 371/μL. Serum creatinine was 2.18 mg/dL, proteinuria ±, urinary occult blood ±, rod-like crystals detected in urinary sediment, urinary N-acetyl-glucosaminidase (NAG) 8.1 U/L, β2 microglobulin 25,295 μg/L, 24-hour creatinine clearance 48 mL/min/1.73 m^2, 24-hour urine protein 384 mg. Gallium scintigraphy: No accumulation in the kidneys. Kidney ultrasonography: Echogenicity was elevated in the kidney parenchyma, hyperechoic calculi were noted in bilateral renal pelvises, and the renal pelvises did not dilate. Kidney biopsy: The specimen included 43 glomeruli, global sclerosis was noted in 15 glomeruli (35%), and sclerosis with collapse and podocyte hyperplasia as seen in HIV-associated nephropathy were not noted. Severe interstitial fibrosis was noted in approximately 70% of the cortex and medulla, with diffuse inflammatory cell infiltration, mainly consisting of mononuclear cells and plasmacytes. Renal tubules became atrophic extensively. Needle crystals surrounded by multinucleated giant cells were noted in the tubulointerstitium. Many such crystal-associated granulomatous lesions were found in the whole specimen. Staining confirmed that crystals did not contain calcium. No findings of HIV-associated immune complex disease was noted. Pathological diagnosis: Diffuse tubulointerstitial nephritis with granuloma due to crystal formation
	Concomitant medications: tenofovir disoproxil fumarate, lamivudine, ritonavir, abacavir sulfate			

HARRT therapy

	4 months before administration	2 months before administration	Day 1 of administration	3 years and 4 months after administration	5 years after administration	5 years and 2 months after administration
AZT: zidovudine		AZT				
3TC: lamivudine		3TC				
EFV: efavirenz		EFV				
ATV/r: atazanavir/ritonavir			ATV/r			
TDF: tenofovir			TDF			
ABC: abacavir				ABC		

Laboratory Examination

	4 months before administration	2 months before administration	Day 1 of administration	3 years and 4 months after administration	5 years after administration	5 years and 2 months after administration
HIV test						
HIV viral load				Undetectable		Undetectable
CD4 T-cell count (μL)				200−300		371
Urine analysis						
Urine protein	−		−	2+		±
Urinary occult blood	−		−			±
pH						5.5
Nitrite						−
Urine sugar						−
RBC (HPF)						0−1
WBC (HPF)						5−9
Hyaline cast (HPF)						0−1
Rod-like crystal						+
NAG (U/L) (normal range ≤ 7.0 U/L)						8.1
β2MG (μg/L) (normal range ≤ 230 μg/L)						25,295
CCr (mL/min/1.73 m^2)						48
s-Cr (mg/dL)	0.9		0.9	1.6	2	2.18
Haemoglobin (g/dL)						13.5
WBC (/μL)						5,300
Lymphocyte count (/μL)						2,100
Eosinophil count (/μL)						0
Platelet count (/μL)						230,000
Total serum protein (g/dL)						7.8
Serum albumin (g/dL)						4.1
Serum sodium (mEq/L)						140
Serum potassium (mEq/L)						4.5
Serum chloride						107

(mEq/L)						
Serum calcium (mg/dL)						9.1
BUN (mg/dL)						25
HbA1c (%)						4.9
CRP (mg/dL)						0.06
Serum immunoglobulin						
IgG (mg/dL)						1,571
IgA (mg/dL)						299
IgM (mg/dL)						54
Serum complement factor						
C3 (mg/dL)						117
C4 (mg/dL)						22
CH50 (U/mL)						48.7
ACE (U/L)						5.6
Rheumatoid factor						–
Antinuclear antibody						–
Myeloperoxidase-antineutrophilic cytoplasmic antibody						–
Proteinase 3-antineutrophilic cytoplasmic antibody						–
HBs antigen						–
HCV antibody						–
Bacterial test						
Urine						–
Blood						-

2 Crizotinib

Brand Name (name of company)	XALKORI Capsules 200 mg, 250 mg (Pfizer Japan Inc.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	ALK fusion gene-positive, unresectable, advanced or relapsed non-small cell lung cancer

PRECAUTIONS (underlined parts are revised)

Warnings

Fulminant hepatitis or hepatic failure has been reported associated with administration of this drug, leading to fatal outcome in some cases. Patients should be carefully monitored through periodic liver function tests before and during the administration of this drug (especially, frequently during the initial treatment stage). If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Important Precautions

Fulminant hepatitis, hepatic failure, or hepatic dysfunction with elevations of ALT (GPT), AST (GOT), bilirubin, ALP, etc. may occur. Patients should be carefully monitored through periodic liver function tests before and during the administration of this drug (especially, frequently during the initial treatment

stage).
Prolonged QT interval or bradycardia may occur. Patients should be carefully monitored through periodic electrocardiography and electrolyte tests and measurements of pulse rate and blood pressure before and during the administration of this drug.

Adverse Reactions (clinically significant adverse reactions)

Fulminant hepatitis, hepatic failure, hepatic dysfunction: Fulminant hepatitis, hepatic failure, or hepatic dysfunction with elevations of ALT (GPT), AST (GOT), bilirubin, ALP, etc. may occur and fulminant hepatitis or hepatic failure leading to fatal outcome have been reported in some cases. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as drug suspension, dose reduction, and/or discontinuation of administration should be taken.

Prolonged QT interval, bradycardia: Prolonged QT interval or bradycardia (accompanying symptoms: hypotension, syncope, dizziness, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as drug suspension, dose reduction, and/or discontinuation of administration should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 5 months (May 2012 to October 2013)

- Fulminant hepatitis: 2 cases (1 fatal case)
- Serious bradycardia-associated cases †: 1 case (no fatal cases)

†: Cases corresponding to heart rate < 40 beats/min or Grade 3 or higher in the Common Terminology Criteria for Adverse Events version 4.0.

The number of patients using this drug per year estimated by MAHs:
Approximately 900 (May 2012 to May 2013)
Launched in Japan: May 2012

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Non-small cell lung cancer (dermatomyositis, metastasis to bone, metastasis to brain)	400 mg for 15 days 500 mg for 15 days	**Fulminant hepatitis** The patient had a history of surgery for a lesion of metastasis to brain (one month before administration of crizotinib) There was no metastasis to liver. Hepatitis C developed before was cured. Day 1 of administration: For anaplastic lymphoma kinase (ALK) fusion gene-positive non-small cell lung cancer, the patient started receiving crizotinib 200 mg twice daily in an inpatient setting as the first-line treatment. The general status (Eastern Cooperative Oncology Group [ECOG] performance status [PS]) at the start of administration was 2. Day 16 of administration: As there was no problem in the general status and laboratory test values, the dose of crizotinib was increased to 250 mg twice daily. Day 27 of administration: Impaired appetite occurred. Day 29 of administration: The patient was unable to take crizotinib in the morning, and vomited twice. The patient visited the emergency outpatient department. Blood test showed marked increased hepatic enzymes levels and substantially deteriorated coagulability, and then the patient was

				diagnosed with serious liver injury and urgently admitted to the hospital. Day 30 of administration (day of discontinuation): The patient was diagnosed with fulminant hepatitis, and plasma exchange and haemodialysis were started (everyday). Intravenous administration of methylprednisolone sodium succinate (100 mg/day) was performed. After that, the condition continued to worsen, and then administration of crizotinib was discontinued. Findings of dynamic contrast-enhanced CT; No obstructive hepatitis and gallstones were found. Periportal collar sign and pericholecystic oedema were observed. 1 day after discontinuation: Haemodiafiltration was started. 2 days after discontinuation: Continuous haemodiafiltration (CHDF) was started. Clonic convulsion occurred in the evening, and then fosphenytoin sodium hydrate was administered. 4 days after discontinuation: Concomitant pulmonary oedema occurred. Oxygenation improved by water removal by CHDF, but blood pressures fluctuated at low levels. Blood test showed no improvement of high hepatic enzymes levels and ammonia levels. The patient was in a coma. She was withdrawn from CHDF. 5 days after discontinuation: Convulsion lasted for several minutes. On the same day, considering that resuscitation was impossible, and the above treatment was discontinued. Continuous administration of midazolam was started. 6 days after discontinuation: Death was confirmed.
	Concomitant medications: domperidone, sodium rabeprazole, sitagliptin phosphate hydrate, prednisolone			

Laboratory Examination

	Before the start of administration	Day 29 of administration	Day 30 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	5 days after discontinuation
AST (IU/L)	17	3,236	–	783	175	140
ALT (IU/L)	11	5,201	–	1,164	261	179
Total bilirubin (mg/dL)	0.4	2.7	2.5	2.5	4.0	4.3
Direct bilirubin (mg/dL)	–	–	1.7	1.2	1.6	2.0
Albumin (g/dL)	4.3	4.0	3.2	3.5	3.4	2.7
Ammonia (μg/dL)	–	153	–	314	287	203
Cholinesterase (IU/L)	–	205	177	263	296	–
PT (%)	–	<10.0	11.4	31.7	30.7	22.0
APTT (%)	–	34.4	33.8	62.0	59.1	32.9
HBs-Ag	–	–	Negative	–	–	–
HBs-Ab	–	–	Negative	–	–	–
HBc-Ab	–	–	Negative	–	–	–
HBe-Ag	–	–	Negative	–	–	–
HBe-Ab	–	–	Negative	–	–	–

HBV-DNA (TaqMan PCR method)	–	–	<2.1	–	–	–
HCV-RNA (TaqMan PCR method)	–	–	<1.2	–	–	–

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 90s	Non-small cell lung cancer (diabetic nephropathy, metastasis to liver, metastasis to bone)	500 mg for 12 days	Bradycardia Day 1 of administration: For ALK fusion gene-positive non-small cell lung cancer, the patient started receiving crizotinib 250 mg twice daily in an inpatient setting as the first-line treatment. The general status (ECOG PS) at the start of administration was 1. Day 12 of administration (day of discontinuation): Bradycardia and delirium occurred, and administration of crizotinib was discontinued. Because of a depressed level of consciousness, electrocardiography was performed. Heart rate was 28 beats/min. Administration of *l*-isoprenaline hydrochloride 0.2 mg and physiological saline 100 mL was started. Intravenous administration of 2 ampoules of atropine was performed, but no improvement was seen. Pacing was explained to the patient's family, but it was decided that the patient would be followed up in a conservative manner. Administration of *l*-isoprenaline hydrochloride was started at 0.025 mg/hr. 1 day after discontinuation: Administration of precipitated calcium carbonate (for 4 days) and alfacalcidol (for 3 days) was started. 2 days after discontinuation: Bradycardia resolved. The dose of *l*-isoprenaline hydrochloride was gradually reduced, and it was completely discontinued on the same day. Administration of furosemide (for 5 days) was started. 4 days after discontinuation: Zopiclone and trazodone hydrochloride were administered. 5 days after discontinuation: Delirium resolved.
	Concomitant medications: naftopidil, amlodipine besilate, sitagliptin phosphate hydrate, oxycodone hydrochloride hydrate, prochlorperazine maleate, magnesium oxide			

Laboratory Examination

	Before the start of administration	Day 7 of administration	Day 12 of administration (day of discontinuation)			2 days after discontinuation
Heart rate (bpm)	62	48	28			69
QTc interval (ms)	–	450	410			–
BUN (mg/dL)	30.2	–	46.1	–	–	30.6
Cr (mg/dL)	1.64	–	2.75	–	–	1.64
eGFR	31	–	18	–	–	31
Na (mEq/L)	134	–	121	123	124	135
K (mEq/L)	5.5	–	6.5	5.5	5.9	6.3
Cl (mEq/L)	103	–	94	96	96	104
Ca (mg/dL)	8.5	–	6.6	6.7	6.7	7.0

3 Clopidogrel Sulfate-containing Products

[1] Clopidogrel Sulfate

Brand Name (name of company)	PLAVIX Tablets 25 mg, 75 mg (Sanofi K.K.)
Therapeutic Category	Blood and body fluid agents-Miscellaneous
Indications	Suppression of recurrent ischemic cerebrovascular disorder (excluding cardioembolic stroke) The following ischaemic heart diseases for which percutaneous coronary intervention (PCI) is indicated: Acute coronary syndrome (unstable angina, non ST elevation myocardial infarction, ST elevation myocardial infarction) Stable angina pectoris, old myocardial infarction Suppression of thrombus and embolus formation in patients with peripheral arterial disease

PRECAUTIONS (underlined parts are revised)

Important Precautions

Acquired haemophilia (prolonged activated partial thromboplastin time [APTT], decreased factor VIII activity, etc.) may occur. If prolonged APTT, etc. is observed, appropriate measures such as collaboration with a specialist should be taken, regardless of haemorrhage, in consideration of the possibility of acquired haemophilia.

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia, eosinophilic pneumonia: Interstitial pneumonia or eosinophilic pneumonia may occur. Patients should be carefully monitored. If cough, dyspnoea, pyrexia, abnormal chest sound, etc. are observed, examinations including chest X-ray and/or chest CT scan should be performed immediately. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

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

Acquired haemophilia: Acquired haemophilia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

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 2010 to November 2013)

- Acquired haemophilia-associated cases: 2 cases (no fatal cases)
- Eosinophilic pneumonia-associated cases: 2 cases (no fatal cases)
- Drug-induced hypersensitivity syndrome: 0 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 1.5 million (January 2012 to December 2012)
Launched in Japan: May 2006

[2] Clopidogrel Sulfate/Aspirin

Brand Name (name of company)	ComPlavin Combination Tablets (Sanofi K.K.)
Therapeutic Category	Blood and body fluid agents-Miscellaneous
Indications	The following ischaemic heart diseases for which percutaneous coronary intervention (PCI) is indicated: Acute coronary syndrome (unstable angina, non ST elevation myocardial infarction, ST elevation myocardial infarction) Stable angina pectoris, old myocardial infarction

PRECAUTIONS (underlined parts are revised)

Important Precautions

Acquired haemophilia (prolonged activated partial thromboplastin time [APTT], decreased factor VIII activity, etc.) may occur. If prolonged APTT, etc. is observed, appropriate measures such as collaboration with a specialist should be taken, regardless haemorrhage, in consideration of the possibility of acquired haemophilia.

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia, eosinophilic pneumonia: Interstitial pneumonia or eosinophilic pneumonia may occur. Patients should be carefully monitored. If cough, dyspnoea, pyrexia, abnormal chest sound, etc. are observed, examinations including chest X-ray and/or chest CT scan should be performed immediately. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

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

Acquired haemophilia: Acquired haemophilia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

Launched in Japan: December 2013

<Clopidogrel Sulfate> Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Angina pectoris (polymyalgia rheumatica, hypertension, dyslipidaemia, hyperlipidaemia)	75 mg for 7 days	**Acquired haemophilia** 12 days before administration: The patient visited this hospital with the chief complaint of exertional chest pain. Multidetector computed tomography showed severe stenosis of left anterior descending coronary artery (LAD). 1 day before administration: The patient visited the hospital again. Day 1 of administration:

				Oral administration of clopidogrel sulfate 75 mg/day, aspirin, and lansoprazole was started. Day 4 of administration: Subcutaneous haemorrhage was noted around the left eyelid and on the right upper limb. Day 7 of administration (day of discontinuation): The patient was admitted to this hospital for coronary angiography. Subcutaneous haemorrhage was noted around the left eyelid and on the right upper limb at the time of hospital admission. Coronary angiography was performed as scheduled (right radial artery [RA] approach). LAD #7 had 90% stenosis. After monitoring the lesion by intravascular ultrasonography, one drug-eluting stent (Nobori 3.5 - 14 mm) was placed. With favorable stent dilation, the procedure was completed. After PCI, new subcutaneous haemorrhage was noted on the right forearm, right thigh, left forearm, etc., but haemostasis at the puncture site was confirmed. 1 day after discontinuation: Haemostasis at the puncture site was confirmed, but generalized subcutaneous haemorrhage was not improved. As being a high responder to clopidogrel sulfate could not be ruled out, clopidogrel sulfate was changed to cilostazol, but no improvement was seen. The patient was discharged from the hospital. Phleborrhagia did not stop. At night, further increase in subcutaneous haemorrhage was noted and the patient visited the hospital again. The patient was re-admitted to the hospital for follow-up observation. Administration of cilostazol was discontinued. 3 days after discontinuation: FFP was administered but no improvement was seen. 5 days after discontinuation: As decreased factor VIII coagulation activity and increased factor VIII inhibitors were noted, the patient was diagnosed with acquired haemophilia (Cross mixing test was not performed.). The patient was transferred to another hospital, and underwent plasma exchange and steroid pulse therapy. Date unknown: Immunosuppressive agent, corticosteroid, and factor VIII were administered (Later, factor VIII product was switched to factor VII product.) The patient was transferred to the haematology department of another hospital for treatment. Subcutaneous haemorrhage disappeared by medical treatment, and the patient was discharged from the hospital. Aspirin was used alone as antiplatelet agent, but no cardiovascular events were observed until now.
	Concomitant medications: aspirin (the other suspected medication), lansoprazole (the other suspected medication), thiamine disulfide/B6/B12, adenosine triphosphate disodium hydrate, lorazepam, limaprost alfadex, methylprednisolone			

Laboratory Examination

	1 day before administration	2 days after discontinuation	3 days after discontinuation	5 days after discontinuation
APTT (sec)	–	72.4	–	–
PT·INR	–	0.92	–	–
PLT ($\times 10^4/mm^3$)	24.9	26.0	24.0	23.4

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Lacunar infarction (cardiac failure, arrhythmia, atrial fibrillation)	75 mg (for 371 days) ↓ Discontinued ↓ 75 mg (for 12 days)	**Eosinophilic pneumonia** Day 1 of administration: The patient had been found to have lacunar infarction on MRI and started receiving clopidogrel sulfate 75 mg /day. Day 251 of administration: For light-headedness, cerebrovascular disorder was suspected, and the patient started receiving cilostazol OD 200 mg/day at a local clinic. Day 316 of administration: For atrial fibrillation, administration of disopyramide 300 mg/day was started. Day 357 of administration: Chest x-ray showed slight reticular opacities in the left lower lung field. Day 371 of administration (day of discontinuation): Because bloody sputum was observed, administration of clopidogrel sulfate and cilostazol OD was discontinued. Pyrexia and sweaty at nighttime were also observed. 13 days after discontinuation: The symptoms improved at the time of the initial visit to the department of respiratory internal medicine. Day 1 of readministration: Administration of both drugs (clopidogrel sulfate 75 mg/day and cilostazol OD) was resumed as instructed by the physician of the local clinic. After that, pyrexia and sweaty at nighttime relapsed. Day 12 of readministration (day of discontinuation of readministration): The patient was urgently admitted to the hospital for suspected pneumonia. Treatment with ceftriaxone and azithromycin was performed and the administration of oral drugs was discontinued (administration of clopidogrel sulfate and disopyramide was discontinued). 2 days after discontinuation: The result of drug lymphocyte stimulation test (DLST) test was positive for clopidogrel sulfate (negative for cilostazol OD). 5 days after discontinuation: Bronchofiberscopy was performed, and bronchoalveolar lavage (BAL) was performed for the right upper lobe. BAL findings showed eosinophil-dominance and transbronchial lung biopsy (TBLB) showed infiltrations of lymphocytes and eosinophils (neutrophils 36%, eosinophils 24%, basophils 1.9%, lymphocytes 28.4%, monocytes 1.4%). 30 days after discontinuation: The pneumonia and symptoms promptly improved after discontinuation of both agents and administration of antibiotics (ceftriaxone and azithromycin). Outcome, improved. Date unknown: As the opacities improved without steroid treatment, the patient was discharged from the hospital.

	Concomitant medications: disopyramide (the other suspected medication), cilostazol (the other suspected medication), atenolol (the other suspected medication), verapamil hydrochloride (the other suspected medication), cefcapene pivoxil hydrochloride hydrate, cetirizine hydrochloride, epinastine hydrochloride

Laboratory Examination

	Day 36 of administration	Day 166 of administration	Day 357 of administration	5 days after discontinuation	Day 2 of readministration	30 days after discontinuation of readministration
WBC (/mm^3)	6,320	6,380	9,450	17,760	6,270	7,150
Lymphocytes (%)	41.1	47.5	-	16.0	35.6	42.4
Eosinophils (%)	10.1	10.3	-	0.8	4.3	12.2
Neutrophils (%)	38.5	30.9	-	77.0	48.3	33.0
Basophils (%)	0.6	1.1	-	0.2	1.1	0.8
CRP (mg/dL)	<0.25	<0.25	-	-	<0.25	-
IgE (IU/mL)	-	-	-	932	-	-

4 Sodium Valproate

Brand Name (name of company)	DEPAKENE Fine Granules 20%, 40%, DEPAKENE Tablets 100 mg, 200 mg, DEPAKENE-R Tablets 100 mg*, 200 mg*, DEPAKENE Syrup 5% (Kyowa Hakko Kirin Co., Ltd.) *The brand names were changed from DEPAKENE-R Tablets 100 and 200. SELENICA-R Granules 40%, SELENICA-R Tab. 200 mg, 400 mg (Kowa Company, Ltd.) and the others
Therapeutic Category	Antiepileptics
Indications	• Treatment of various types of epilepsy (petit mal, focal seizures, psychomotor seizures, and mixed seizures) and character and behaviour disorders associated with epilepsy (bad mood, irascible, etc.) • Treatment of mania and manic state in manic depressive illness • Suppression of development of migraine attack

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia, eosinophilic pneumonia: Interstitial pneumonia or eosinophilic pneumonia may occur. If cough, dyspnoea, pyrexia, etc. are observed, examinations including chest X-ray and/or chest CT scan should be performed immediately. If interstitial pneumonia or eosinophilic pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 7 months (April 2010 to October 2013)

- Interstitial pneumonia, eosinophilic pneumonia-associated cases: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 670,000 (January 2012 to December 2012)
Launched in Japan:
DEPAKENE Tablets 200 mg and DEPAKENE Syrup 5%: March 1975
DEPAKENE Tablets 100 mg: September 1981
DEPAKENE Fine Granules 40%: June 1984
DEPAKENE Fine Granules 20%: October 1987

DEPAKENE-R Tablets 100 mg, 200 mg*: January 1991
* The brand names were changed from DEPAKENE-R Tablets 100 and 200.
SELENICA-R Granules 40%: December 1991
SELENICA-R Tab. 200 mg: July 2004
SELENICA-R Tab. 400 mg: July 2006

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Adjustment disorder (Harada's disease)	200 mg for 72 days 100 mg for 2 days	**Interstitial pneumonia** During treatment with steroid treatment for Harada's disease at an ophthalmology department, the patient was referred to a psychiatry department due to sleep loss, trouble at home, etc. Day 1 of administration: The patient was diagnosed with adjustment disorder at the psychiatry department, and then started receiving sodium valproate 200 mg/day and other psychotropics. Day 51 of administration: Dry cough occurred. Day 57 of administration: At a visit to this hospital due to headache, chest CT showed bilateral diffuse interlobular septal thickening, ground-glass opacities, and reticular opacities. For suspected interstitial pneumonia, the patient was admitted to the hospital. Sialylated carbohydrate antigen KL-6 (KL-6) was 840 U/mL. Day 58 of administration: TBLB showed no marked change in lung tissues. Bronchoalveolar lavage fluid showed macrophage 54.5%, lymphocytes 32.0%, neutrophils 12.0%, eosinophils 1.5% (cell yield 490 × 10^3/mL), and both bacterial and viral test results were negative. After the end of the tests, oxygenation was poor, and then the patient was put under mechanical ventilation. Day 59 of administration: The result of blood culture was negative; the result of culture urine was negative. The patient extubated by herself. Day 61 of administration: On chest CT, the ground-glass opacities in both lungs were the same as in the last exam or partially shrank, and interlobular septal thickening was the same as in the last exam. Day 65 of administration: Respiratory failure progressed (arterial carbon dioxide partial pressure, 52 mmHg; arterial oxygen partial pressure, 63 mmHg), and oxygen 4 L/min was administered. Steroid half-pulse therapy was started (methylprednisolone 500 mg/day × 3 days). Day 68 of administration: Administration of prednisolone 40 mg/day was started. Day 69 of administration: Administration of loxoprofen sodium hydrate was started for headache.

				Day 71 of administration: Administration of sulfamethoxazole/trimethoprim was started to prevent infection. Day 72 of administration: The dose of sodium valproate was decreased to 100 mg/day. Day 74 of administration (day of discontinuation): Administration of sodium valproate was discontinued. DLST was not performed because the patient was still on corticosteroid treatment. KL-6 was 1582 U/mL. 1 day after discontinuation: Chest CT showed remarkable improvement of bilateral ground-glass opacities and interlobular septal thickening. Funicular opacities, atrophic changes, or mild ground-glass opacities, suggesting fibrillization, remained in some parts of the bilateral upper lobes and the right lower lobe. 27 days after discontinuation: KL-6 was 850 U/mL. 29 days after discontinuation: Interstitial pneumonia improved. At hospital discharge, the dose of prednisolone was gradually reduced to 20 mg/day, and was reduced by 5 mg/day every month. 76 days after discontinuation: KL-6 was 330 U/mL. 165 days after discontinuation: Administration of prednisolone was discontinued.
	Concomitant medications: lansoprazole, alendronate sodium hydrate, betamethasone sodium phosphate/fradiomycin sulfate (topical), zolpidem tartrate, haloperidol, lorazepam, lormetazepam, flunitrazepam, prednisolone			

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Epilepsy (none)	1200 mg for 50 days	**Eosinophilic pneumonia** Day 1 of administration: The patient started receiving sodium valproate based on the diagnosis of epilepsy. Around day 8 of administration: The patient noticed difficulty in breathing, the patient visited the previous hospital several times. Wheezing was heard by chest auscultation. The patient received intravenous treatment (corticosteroid) as having asthma. Day 36 of administration: Wheezing was considered to be caused by emphysema and asthma, periodic inhalation (corticosteroid) was started. Day 50 of administration (day of discontinuation): The symptoms were not improved, chest X-ray showed pneumonia, and then administration of sodium valproate was discontinued. 3 days after discontinuation: The patient was referred and admitted to this hospital. WBC was 15060/μL, CRP 4.41 mg/dL, and eosinophils 65.5%. Chest CT showed periphery-dominant non-segmental infiltration opacities. Drug-induced eosinophilic pneumonia due to sodium valproate was suspected and oral administration of prednisolone 40 mg was started. DLST result was negative.

				10 days after discontinuation: Wheezing disappeared and the pneumonia improved. WBC decreased to 10230/μL, CRP to 0.46 mg/dL, and eosinophils to 0.4%. The dose of prednisolone was reduced to 30 mg. 17 days after discontinuation: The symptoms were not found. WBC was 10690/μL, CRP 1.58 mg/dL, eosinophils 0.2%. The dose of prednisolone was reduced to 20 mg. 25 days after discontinuation: The symptoms were not found. WBC was 8380/μL, CRP 0.98 mg/dL, eosinophils 2.4%. The dose of prednisolone was reduced to 15 mg. Eosinophilic pneumonia resolved. 221 days after discontinuation: Administration of prednisolone was discontinued.
	Concomitant medications: none			

5 Drospirenone, Ethinylestradiol Betadex

Brand Name (name of company)	YAZ Combination Tablets (Bayer Yakuhin, Ltd.)
Therapeutic Category	Mixed hormone preparations
Indications	Dysmenorrhoea

PRECAUTIONS (underlined parts are revised)

Warnings

Thrombosis may occur with the use of the drug and it may have a fatal outcome. If any of the following symptoms appears and thrombosis is suspected, administration should be discontinued and appropriate measures taken immediately.

Symptoms of which thrombosis is suspected:

Sudden severe pain/oedema of the lower limbs, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance, etc.

Patients should be also instructed to stop taking this drug immediately and visit an emergency medical institution, if such symptoms appears.

(See "Contraindications," "Important Precautions," and "Clinically significant adverse reactions.")

Important Precautions

Thrombosis may occur with the use of the drug irrespective of the existence of risk factor(s) such as age (40 years old and over), smoking, obesity, and a family history of thrombosis. If any initial symptoms of which thrombosis is suspected appear, appropriate measures such as discontinuance of the drug should be taken.

Initial symptoms of which thrombosis is suspected

Vomiting/feeling nausea, headache, swelling/pain/numbness of the lower limbs, redness, hot feeling, etc.

If patients are at the condition of high risk of thrombosis (immobilized condition, remarkable elevation in blood pressure, dehydration, etc.), appropriate measures such as discontinuance of the drug should be taken.

The following explanation/instruction should be given to the patients taking this drug at the start and continuation of the use:

- Thrombosis may have a fatal outcome.
- Use of the drug should be stopped and consult physicians etc., immediately, if any initial symptom of which thrombosis is suspected appear and/or if at the condition of high risk of thrombosis, irrespective of the severity of the

symptom/condition.

- The use of the drug should be told to a physician at visit of other medical institution suspecting thrombosis so that the physician can consider possibility of thrombosis occurring with the use of the drug.

When a surgical operation becomes necessary during the treatment with the drug, due caution should be considered to prevent thrombosis. (See "Contraindications.")

Adverse Reactions (clinically significant adverse reactions)

Thrombosis: Since thrombosis (extremity, lungs, myocardium, brain, retina, etc.) may occur, women should carefully be monitored. If any symptoms such as sudden severe pain/oedema of the lower limbs, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance, etc., occur, administration should be discontinued immediately and appropriate measures taken.

Reference Information

The number of reported adverse reactions (fatal cases for which a causality to the drug could not be ruled out) for the past 3 years and 2 months (from initial marketing to January 2014)

- Thrombosis-associated cases: 3 cases

The number of patients using this drug per year estimated by MAHs:
Approximately 187,000 Women-Year* (from initial marketing to January 2014)

* Women-Year: Estimate number of users in case one woman uses 13 sheets of the drug (28 tablets in one sheet) in one year.

Launched in Japan: November 2010

6 Rivaroxaban

Brand Name (name of company)	Xarelto Tablets 10 mg, 15 mg (Bayer Yakuhin, Ltd.)
Therapeutic Category	Anticoagulants
Indications	Reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

PRECAUTIONS (underlined parts are revised)

Important Precautions

Interstitial lung disease may occur. Patients should be instructed to immediately contact their physician if symptoms including cough, bloody sputum, dyspnoea, and/or pyrexia occur.

Adverse Reactions (clinically significant adverse reactions)

Interstitial lung disease: Interstitial lung disease may occur, and it may be accompanied by bloody sputum and pulmonary alveolar haemorrhage in some cases. Patients should be carefully monitored, and if cough, bloody sputum, shortness of breath, dyspnoea, pyrexia, or abnormal chest sound, etc. are observed, examinations including chest X-ray, chest CT scan, and/or serum marker test should be performed immediately. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 10 months (from initial marketing to January 2014)

- Interstitial lung disease: 4 cases (1 fatal case)

The number of patients using this drug estimated by MAHs: Approximately 200,000 (estimated based on data in December 2013)
Launched in Japan: April 2012

5

Revision of Precautions (No. 253)

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 7, 2014 (excluding those presented in "4. Important Safety Information" of this Bulletin). This section also presents details of revisions to the Precautions section of package inserts and brand names of oral female hormone-containing preparations with the indication for contraception or dysmenorrhoea among drugs that have been revised according to the Notifications dated February 18, 2014.

1

Antiepileptics

Rufinamide

Brand Name	Inovelon Tablets 100 mg, 200 mg (Eisai Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome)**: Oculomucocutaneous syndrome may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, ocular hyperaemia, erythema, blister/erosion, and/or pharynx pain are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2

Hormones-Miscellaneous, Antidiabetic agents

(1) Lixisenatide
(2) Liraglutide (Genetical Recombination)
(3) Acarbose
(4) Anagliptin
(5) Alogliptin Benzoate
(6) Sitagliptin Phosphate Hydrate
(7) Pioglitazone Hydrochloride
(8) Miglitol
(9) Linagliptin

Brand Name

(1) Lyxumia Subcutaneous Injection 300 μg (Sanofi K.K.)
(2) ViCTOZA Subcutaneous Injection 18 mg (Novo Nordisk Pharma Ltd.)
(3) Glucobay Tablet 50 mg, 100 mg (Bayer Yakuhin, Ltd.) and the others
(4) SUINY Tab. 100 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
(5) NESINA Tablets 6.25 mg, 12.5 mg, 25 mg (Takeda Pharmaceutical Company Limited)
(6) JANUVIA Tablets 12.5 mg, 25 mg, 50 mg, 100 mg (MSD K.K.), GLACTIV Tablets 12.5 mg, 25 mg, 50 mg, 100 mg (Ono Pharmaceutical Co., Ltd.)
(7) ACTOS Tablets 15, 30, ACTOS OD Tablets 15, 30 (Takeda Pharmaceutical Company Limited) and the others
(8) SEIBULE Tab. 25 mg, 50 mg, 75 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
(9) Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)

Important Precautions	Hypoglycemic symptoms may occur. Attention should be paid when administering the drug to patients engaged in working at heights, driving, etc.

3 **Antidiabetic agents**

Alogliptin Benzoate/Pioglitazone Hydrochloride

Brand Name	LIOVEL Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
Important Precautions	Hypoglycemic symptoms may occur. Patients should be thoroughly informed of possible hypoglycemic symptoms and its treatment to raise awareness. Also, attention should be paid when administering the drug to patients engaged in working at heights, driving, etc.

4 **Antidiabetic agents**

Saxagliptin Hydrate

Brand Name	ONGLYZA Tablets 2.5 mg, 5 mg (Kyowa Hakko Kirin Co., Ltd.)
Important Precautions	Hypoglycemic symptoms or dizziness, etc. may occur. Patients should be cautioned against working at heights, operating dangerous machinery, driving, etc.

5 **Antidiabetic agents**

Voglibose (products with an indication to treat abnormal glucose tolerance)

Brand Name	BASEN Tablets 0.2, BASEN OD Tablets 0.2 (Takeda Pharmaceutical Company Limited)
Important Precautions	Hypoglycemic symptoms may occur. Patients with diabetes mellitus or abnormal glucose tolerance should be thoroughly informed of possible hypoglycemic symptoms and its treatment. Also, attention should be paid when administering the drug to patients with diabetes mellitus or abnormal glucose tolerance engaged in working at heights, driving, etc.

6 **Antidiabetic agents**

Voglibose (products without an indication to treat abnormal glucose tolerance)

Important Precautions	Hypoglycemic symptoms may occur. Patients should be thoroughly informed of possible hypoglycemic symptoms and its treatment. Also, attention should be paid when administering the drug to patients engaged in working at heights, driving, etc.

7 **Acting mainly on mold**

Amphotericin B (liposomal formulation)

Brand Name	AmBisome 50 mg for Intravenous Drip Infusion (Dainippon Sumitomo Pharma Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)	**Agranulocytosis, decreased white blood cell, decreased platelets**: Agranulocytosis, decreased white blood cell, or decreased platelets may occur. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

8 **Mixed hormone preparations**

(1) Chlormadinone Acetate/Mestranol
(2) Norethisterone/Ethinylestradiol (products with an indication to treat dysmenorrhoea)
(3) Norethisterone/Mestranol
(4) Norgestrel/Ethinylestradiol

Brand Name	(1) LUTEDION TABLETS (Aska Pharmaceutical Co., Ltd) (2) LUNABELL tablets, LUNABELL tablets LD, LUNABELL tablets ULD (Nobelpharma Co., Ltd.) (3) SOPHIA-A TABLETS, SOPHIA-C TABLETS (Aska Pharmaceutical Co., Ltd.) (4) PLANOVAR TABLETS (Aska Pharmaceutical Co., Ltd.)
Important Precautions	Thrombosis may occur with the use of the drug irrespective of the existence of risk factor(s) such as age, smoking, obesity, a family history of thrombosis. If any of the following symptoms appears, administration should be discontinued and appropriate measures taken immediately. Major symptoms of thrombosis that require emergency response Sudden severe pain/swelling of the lower limbs, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance, etc. Patients should be also instructed to stop taking this drug immediately and visit an emergency medical institution if such symptom appears. If any symptoms of which thrombosis is suspected appears during treatment with this drug, appropriate measures such as discontinuance of the drug should be taken. Symptoms of which thrombosis is suspected Pain/swelling/numbness/redness/hot feeling of the lower limbs, headache, nausea/vomiting, etc. If patients are at the condition of high risk of thrombosis (immobilized condition, remarkable elevation in blood pressure, dehydration, etc.), appropriate measures such as discontinuance of the drug should be taken. The following explanation/instruction should be given to the patients taking this drug at the start and continuation of the use: • Thrombosis may have a fatal outcome. • Use of the drug should be stopped and consult physicians etc., immediately, if any symptoms of which thrombosis is suspected appear and/or if at the condition of high risk of thrombosis, irrespective of the severity of the symptoms/condition. • The use of the drug should be told to a physician at visit of other medical institution suspecting thrombosis so that the physician can consider possibility of thrombosis occurring with the use of the drug. When a surgical operation becomes necessary during the treatment with the drug, due caution should be considered to prevent thrombosis.
Adverse Reactions (clinically significant adverse reactions)	**Thrombosis**: Since thrombosis (extremity, lungs, myocardium, brain, retina, etc.) may occur, women should carefully be monitored. If any symptoms such as sudden severe pain/oedema of the lower limbs, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual

disturbance etc., occur, administration should be discontinued immediately and appropriate measures taken.

9 **Contraceptives**

(1) Desogestrel/Ethinylestradiol
(2) Norethisterone/Ethinylestradiol (products with an indication for contraception)
(3) Levonorgestrel/Ethinylestradiol

Brand Name

(1) MARVELON 21, 28 (MSD K.K), Favoir tablets 21, 28 (Fuji Pharma Co., Ltd.)
(2) Synphase T28 Tablets (Kaken Pharmaceutical Co., Ltd.), ORTHO 777-21 Tablets, M-21 Tablets (Janssen Pharmaceutical K.K.)
(3) ANGE 21 TABLETS, 28 TABLETS (Aska Pharmaceutical Co., Ltd.), Triquilar Tablet 21, 28 (Bayer Yakuhin, Ltd.), Labellefille tablets 21, 28 (Fuji Pharma Co., Ltd.)

Important Precautions

Thrombosis may occur with the use of the drug irrespective of the existence of risk factor(s) such as age, smoking, obesity, and a family history of thrombosis. If any of the following symptoms appears, administration should be discontinued and appropriate measures taken immediately.

Major symptoms of thrombosis that require emergency response

Sudden severe pain/swelling of the lower limbs, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance, etc.

Patients should be also instructed to stop taking this drug immediately and visit an emergency medical institution if such symptom appears.

If any symptoms of which thrombosis is suspected appears during treatment with this drug, appropriate measures such as discontinuance of the drug should be taken.

Symptoms of which thrombosis is suspected

Pain/swelling/numbness/redness/hot feeling of the lower limbs, headache, nausea/vomiting, etc.

If patients are at the condition of high risk of thrombosis (immobilized condition, remarkable elevation in blood pressure, dehydration, etc.), appropriate measures such as discontinuance of the drug should be taken.

The following explanation/instruction should be given to the patients taking this drug at the start and continuation of the use:

- Thrombosis may have fatal outcome.
- Use of the drug should be stopped and consult physicians etc., immediately, if any symptoms of which thrombosis is suspected appear and/or if at the condition of high risk of thrombosis, irrespective of the severity of the symptoms/condition.
- The use of the drug should be told to a physician at visit of other medical institution suspecting thrombosis so that the physician can consider possibility of thrombosis occurring with the use of the drug.

When a surgical operation becomes necessary during the treatment with the drug, due caution should be considered to prevent thrombosis.

Adverse Reactions (clinically significant adverse reactions)

Thrombosis: Since thrombosis (extremity, lungs, myocardium, brain, retina, etc.) may occur, women should carefully be monitored. If any symptoms such as sudden severe pain/oedema of the lower limbs, sudden breath shortness, chest pain, severe headache, weakness/paralysis of extremities, dysarthria, acute visual disturbance etc., occur, administration should be discontinued immediately and appropriate measures taken.

6

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of February 1, 2014)

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

	Nonproprietary name / Brand name	Name of the marketing authorization holder	Date of EPPV initiate
◎	pH-4 Treated Acidic Normal Human Immunoglobulin (Subcutaneous injection) Hizentra 20% S.C. Injection 1 g/5 mL, 2 g/10 mL, 4 g/20 mL	CSL Behring K.K.	January 30, 2014
◎	Ioflupane (^{123}I) DaTSCAN Injectable	Nihon Medi-Physics Co., Ltd.	January 27, 2014
◎	Talaporfin Sodium LASERPHYRIN 100 mg FOR INJECTION*1	Meiji Seika Pharma Co., Ltd.	January 20, 2014
	Meropenem Hydrate (1) Meropen Vial for Intravenous Drip Infusion 0.25 g, 0.5 g (2) Meropen Kit for Intravenous Drip Infusion 0.5 g*2	Dainippon Sumitomo Pharma Co., Ltd.	December 20, 2013
	Methylphenidate Hydrochloride Concerta Tablets 18 mg, 27 mg*3	Janssen Pharmaceutical K.K.	December 20, 2013
	Laninamivir Octanoate Hydrate INAVIR DRY POWDER INHALER 20 mg*4	Daiichi Sankyo Company, Limited	December 20, 2013
	Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg*5	Janssen Pharmaceutical K.K.	December 20, 2013
	Vilanterol Trifenatate/Fluticasone Furoate Relvar 100 Ellipta 14 doses, Relvar 200 Ellipta 14 doses	GlaxoSmithKline K.K.	December 9, 2013
	Talc Unitalc Intrapleural 4 g	Nobelpharma Co., Ltd.	December 9, 2013
	Simeprevir Sodium SOVRIAD capsules 100 mg	Janssen Pharmaceutical K.K.	December 6, 2013
	Epinastine Hydrochloride ALESION Ophthalmic Solution 0.05%	Santen Pharmaceutical Co., Ltd.	November 25, 2013
	Acetaminophen acelio Intravenous Injection 1000 mg	Terumo Corporation	November 25, 2013
	Landiolol Hydrochloride ONOACT 50 for Injection*6	Ono Pharmaceutical Co., Ltd.	November 22, 2013

	Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL*[7], EYLEA solution for IVT inj. Kit 40 mg/mL*[7]	Bayer Yakuhin, Ltd.	November 22, 2013
	Topiramate TOPINA Tablets 25 mg, 50 mg, 100 mg*[8]	Kyowa Hakko Kirin Co., Ltd.	November 22, 2013
	Indacaterol Maleate/Glycopyrronium Bromide ultibro inhalation capsules	Novartis Pharma K.K.	November 20, 2013
	Tafamidis Meglumine Vyndaqel capsules 20 mg	Pfizer Japan Inc.	November 20, 2013
	Fluticasone Propionate/Formoterol Fumarate Hydrate Flutiform 50 Aerosol 56 puffs, 125 Aerosol 56 puffs	Kyorin Pharmaceutical Co., Ltd.	November 19, 2013
	Brinzolamide/Timolol Maleate AZORGA Combination Ophthalmic Suspension	Alcon Japan Ltd.	November 19, 2013
	Paliperidone Palmitate XEPLION Aqueous Suspension for IM Injection Syringe 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	Janssen Pharmaceutical K.K.	November 19, 2013
	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) Prevenar13 Suspension Liquid for Injection	Pfizer Japan Inc.	October 28, 2013
	Hydroxyethylated Starch 130000 VOLUVEN 6% solution for infusion	Fresenius Kabi Japan K.K.	October 25, 2013
	Fentanyl Citrate E-fen buccal tablet 50 μg, 100 μg, 200 μg, 400 μg, 600 μg, 800 μg	Teikoku Seiyaku Co., Ltd.	September 26, 2013
	Norethisterone/Ethinylestradiol LUNABELL tablets ULD	Nobelpharma Co., Ltd.	September 26, 2013
	Aminolevulinic Acid Hydrochloride ALAGLIO Oral 1.5 g	SBI Pharmaceuticals Co., Ltd.	September 26, 2013
	Aminolevulinic Acid Hydrochloride Alabel Oral 1.5 g	Nobelpharma Co., Ltd.	September 18, 2013
	Lixisenatide Lyxumia Subcutaneous Injection 300 μg	Sanofi K.K.	September 17, 2013
◎	Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 5 μg PLASTIC SYRING, 10 μg PLASTIC SYRING, 15μg 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*[9]	Kyowa Hakko Kirin Co., Ltd.	September 13, 2013
	Tolvaptan Samsca tablets 7.5 mg*[10]	Otsuka Pharmaceutical Co., Ltd.	September 13, 2013
	Eculizumab (Genetical Recombination) Soliris Drip Infusion 300 mg*[11]	Alexion Pharma G.K.	September 13, 2013
	Pertuzumab (Genetical Recombination) PERJETA Intravenous Infusion 420 mg/14 mL	Chugai Pharmaceutical Co., Ltd.	September 12, 2013
	Bisoprolol Bisono tape 4 mg, 8 mg	Toa Eiyo Ltd.	September 10, 2013
	Irbesartan/Trichlormethiazide Irtra Combination Tablets LD, HD	Shionogi & Co., Ltd.	September 4, 2013

	Topiroxostat (1) TOPILORIC Tablets 20 mg, 40 mg, 60 mg (2) URIADEC Tab. 20 mg, 40 mg, 60 mg	Fujiyakuhin Co., Ltd. Sanwa Kagaku Kenkyusho CO., LTD.	September 4, 2013
	Ibandronate Sodium Hydrate Bonviva IV Injection 1 mg Syringe	Chugai Pharmaceutical Co., Ltd.	August 29, 2013
	Abatacept (Genetical Recombination) ORENCIA SYRINGE FOR S.C. INJECTION 125 mg/1 mL	Bristol-Myers K.K.	August 27, 2013
	Hemin Normosang Infusion 250 mg	Orphan Pacific, Inc.	August 23, 2013
	Palivizumab (Genetical Recombination) Synagis for Intramuscular Injection 50 mg, 100 mg*12 Synagis Intramuscular Solution 50 mg, 100 mg*12	AbbVie G.K.	August 20, 2013
	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*13	Novartis Pharma K.K.	August 20, 2013
	Omalizumab (Genetical Recombination) Xolair for s.c. injection 150 mg, 75 mg*14	Novartis Pharma K.K.	August 20, 2013

*1 An additional indication for “the treatment of patients with primary malignant brain tumour (only in patients who undergo tumour resection)”

*2 An additional administration for “pyogenic meningitis”

*3 An additional administration for “patients aged 18 years or older”

*4 An additional indication for “the prophylaxis of influenza A or B virus infection”

*5 An additional indication for “the treatment of patients with the following symptoms cannot be managed by treatments with non-opioid analgesics and weak opioid analgesics (only in patients who switch from an opioid analgesic): moderate to severe chronic pain”

*6 An additional indication for “the treatment of tachyarrhythmia including atrial fibrillation and atrial flutter in patients with failed cardiac function”

*7 An additional indication for “the treatment of patients with macular oedema following central retinal vein occlusion”

*8 An additional administration for “pediatrics”

*9 An additional administration for “pediatrics”; EPPV was initiated in January 24, 2014 for NESP INJECTION 5 μg PLASTIC SYRING

*10 An additional indication for “the treatment of fluid retention in patients with hepatic cirrhosis which is not adequately responded to other diuretics such as loop diuretics”

*11 An additional indication for “the treatment of patients with atypical hemolytic uremic syndrome to inhibit thrombotic microangiopathy”

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

*13 An additional indication for “the treatment of patients with macular oedema following retinal vein occlusion or choroidal neovascularization following pathologic myopia”

*14 An additional administration for “pediatrics”