Pharmaceuticals and Medical Devices Safety Information

No. 321 March 2015

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

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Pharmaceuticals and Medical Devices Safety Information

No. 321 March 2015

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Lamotrigine and Serious Skin Disorders**	*R* *P* *C*	During the last 4 months, 4 cases of serious skin disorders leading to death, in which causality between the serious skin disorders and Lamictal (lamotrigine) Tablets could not be ruled out, have been reported in patients treated with lamotrigine in Japan. In all 4 cases, treatment with lamotrigine did not comply with the recommended dosage and frequency of administration as stated in the package insert. The MHLW instructed the marketing authorization holder of lamotrigine to revise the Precautions section in the package insert and to raise caution by a Dear Healthcare Professionals Letter of Rapid Safety Communication on February 4, 2015. Details are provided in this section.	5
2	**Abiraterone Acetate and Hypokalaemia**	*P* *C*	Cases of serious hypokalaemia have been reported in patients treated with Zytiga (abiraterone acetate) Tablets. The MHLW instructed the marketing authorization holder of abiraterone acetate to revise the Precautions section in the package insert on February 2, 2015. Details are provided in this section.	14
3	**The MIHARI Project**		The PMDA has been conducting the MIHARI project and developing a system to utilize electronic medical records or other databases for safety measures. Details are provided in this section.	20
4	**Important Safety Information**	*P* *C*	**Abiraterone acetate (and 3 others):** Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated February 2,, February 4, and February 17, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.	23
5	**Revision of Precautions (No. 263)**		Montelukast Sodium (and 1 other)	34
6	**List of Products Subject to Early Post-marketing Phase Vigilance**		List products subject to Early Post-marketing Phase Vigilance as of March 1, 2015.	35
Reference	**The Drug and Medical Devices Safety Information Reporting System –Reporting via e-Gov was closed**		Reporting of ADRs, infections, and malfunctions via e-Gov was closed. Healthcare providers are encouraged to report serious ADRs, infections, and malfunctions by mail, fax, or e-mail.	38

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications *R*: Distribution of Dear Healthcare Professional Letters of Rapid Communications *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.pmda.go.jp/safety/info-services/medi-navi/0007.html

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

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

Abbreviations

ADR	Adverse drug reaction
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BE	Base excess
BEact	Base excess at actual oxygen saturation
BUN	Blood urea nitrogen
$cHCO_3$	Corrected bicarbonate
CK (CPK)	Creatine kinase (Creatine phosphokinase)
Cl	Chloride
Cr (CRE)	Creatinine
CRP	C-reactive protein
CT	Computed tomography
ctO2	Total oxygen
CYP17	Cytochrome P450 C17
D-Bil	Direct bilirubin
DIHS	Drug-induced hypersensitivity syndrome
EHR	Electronic health record
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
GPC	Gram-positive cocci
Hb	Hemoglobin
JCS	Japan Coma Scale
K	Potassium
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
LH-RH	Luteinizing hormone-releasing hormone
MAB	Maximal androgen blockade
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Na	Sodium
O_2	Oxygen
PE	Plasma exchange
PLT	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PCO_2	Carbon dioxide partial pressure
PO_2	Oxygen partial pressure
PS	Performance status
PSA	Prostate-specific antigen
RBC	Red blood cell count
SpO_2	Oxygen saturation
T-Bil	Total bilirubin
TEN	Toxic epidermal necrolysis
tHb	Total-hemoglobin
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Lamotrigine and Serious Skin Disorders

Active ingredient	Lamotrigine
Brand name (name of company)	Lamictal Tablets for Pediatrics 2 mg, 5 mg, Lamictal Tablets 25 mg, 100 mg (GlaxoSmithKline K.K.)
Therapeutic category	Antiepileptics, psychotropics
Indications	1. Monotherapy for the following types of seizures in epileptic patients: Partial seizures (including secondary generalized seizures) Tonic-clonic seizures 2. Concomitant therapy with antiepileptics for the following types of seizure in epileptic patients who have not sufficiently respond to other antiepileptics: Partial seizures (including secondary generalized seizures) Tonic-clonic seizures Generalized seizures of Lennox-Gastaut syndrome 3. Suppression of recurrent/relapsed mood episodes in patients with bipolar disorder

1. Introduction

Lamotrigine was approved for indications of combination therapy with antiepileptic drugs for partial seizures (including secondary generalized seizures), tonic-clonic seizures and generalized seizures of Lennox-Gastaut syndrome in epileptic patients who do not sufficiently responded to other antiepileptics in October 2008. Thereafter, it was also approved for indications of the suppression of recurrent/relapsed mood episodes in patients with bipolar disorder in July 2011, and monotherapy for partial seizures (including secondary generalized seizures) and tonic-clonic seizures in epileptic patients in August 2014. The marketing authorization holder (MAH) estimated that lamotrigine was used in approximately 376 000 patients since the launch (December 12, 2008) until December 31, 2014.

In Japan, 4 cases of serious skin disorders leading to death, in which causality between the serious skin disorders and lamotrigine could not be ruled out, have been reported during approximately 4 months from September to December 2014. In all 4 cases, treatment with lamotrigine did not comply with the recommended dosage and frequency of administration as stated in the package insert, and treatment with lamotrigine was not discontinued until the symptoms became serious after the onset of skin disorders. Consequently, the Ministry of Health, Labour and Welfare (MHLW) instructed the MAH to revise the Precautions and to distribute a Dear Healthcare Professionals Letter of Rapid Safety Communication (blue letter)[1)] on February 4, 2015. Their details are introduced below.

2. Background

Precaution has been provided to serious skin disorders associated with lamotrigine in the "`Warnings," as well as "Precautions of Dosage and Administration," "Important Precautions," and "Clinically significant adverse reactions" sections since the launch on December 2008. In addition, a precaution has been provided since the launch of lamotrigine that the incidence of skin disorders such as rash increases when lamotrigine is administered at an excessive dose. Therefore, the recommended dosage and frequency of administration at treatment initiation, recommended dosage and frequency of administration during a dose titration period until the establishment of a maintenance dose, and recommended dose titration intervals are stipulated in detail for each concomitant medication.

Of the cases of serious skin disorders reported after marketing of lamotrigine, the recommended dosage and frequency of administration were not complied with in many cases. However, information on proper use has been periodically provided from the MAH and relevant academic societies. In January 2012, a document titled "Compliance with Dosage and Administration and Ensuring Early Detection for Lamictal Tablets (lamotrigine)-induced Serious Skin Disorders[2)]" was posted on the PMDA website as "a PMDA Alert for Proper Use of Drugs" to present information on the proper use of lamotrigine.

During a period of approximately 6 years and 1 month from the launch on December 2008 to January 2015, however, a total of 16 cases* of serious skin disorders leading to death were reported. Particularly, during approximately 4 months from September to December 2014, they were intensively reported. A total of 4 cases of the reported fatal cases during these approximately 4 months were serious skin disorders for which causality between the serious skin disorders and lamotrigine could not be ruled out. In all the cases, the treatment was not complied with, for example, the dose was excessive at the start of treatment, lamotrigine was administered every day in combination with sodium valproate at treatment initiation, and the dose was titrated earlier than that specified. Furthermore, in these 4 fatal cases, administration of lamotrigine was not discontinued, or the instruction on treatment discontinuation was not adhered to until the symptoms became serious after the onset of adverse reactions. Hence, it was determined to be important to detect adverse reactions as soon as possible and to ensure to start appropriate treatment. In addition, serious skin disorders that occurred in the fatal cases included not only toxic epidermal necrolysis (TEN) and oculomucocutaneous syndrome (Stevens-Johnson syndrome) mentioned in the Warnings section but also cases for which causality to drug-induced hypersensitivity syndrome (DIHS) could not be ruled out; thus, it was found to be necessary to also thoroughly notify the development of DIHS. Based on this, the MHLW took the urgency into consideration and instructed the MAH of lamotrigine to revise the Precautions on February 4, 2015, to add necessary cautions into the Warnings section, and to distribute a Dear Healthcare Professionals Letter of Rapid Safety Communication (blue letter)[1)] to promptly inform healthcare professionals of the details of precautions.

* Of these, 1 case (a case for which a causal relationship could not be assessed due to a lack of information as of February 4) was found to have not received lamotrigine as a results of a subsequent investigation.

3. The fatal cases related to serious skin disorders caused by lamotrigine

The clinical course of the 3 fatal cases related to serious skin disorders is introduced below.

Case 1 TEN/DIHS

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
1	Male 50s	Epilepsy (Traumatic intracranial haemorrhage, paresis, aphasia, disorientation, osteoporosis, hepatitis alcoholic, pseudarthrosis, pleural effusion, hepatic atrophy)	25 mg/day Consecutive 8-day treatment ↓ 50 mg/day for 38 days	Sodium valproate 1 200 mg/day had been administered for treatment of symptomatic epilepsy. Day 1 of administration: The patient visited to the emergency outpatient department because of epileptic seizure. Administration of lamotrigine 25 mg/day was started (concomitant use with sodium valproate) for treatment of epilepsy. 8 days after start of administration: The dose of lamotrigine was increased to 50 mg/day. 20 days after start of administration: The patient visited to the emergency outpatient department because of a fall arising from dizziness. At that time, pyrexia and systemic smooth-surfaced papules were noted, accompanied by enlargement of the preauricular lymph nodes at a glance, thus, rubella was suspected. 36 days after start of administration: During the visit to the outpatient neurology department, the patient did not complain of skin eruption. 43days after start of administration:

				During the visit to the outpatient orthopedics department, the orthopedic surgeon found skin eruption and consulted a dermatologist, advising the patient to visit the dermatology department. When examined at the dermatology clinic, an adverse reaction associated with lamotrigine was suspected. However, since oral mucosal eruption was not found and laboratory test data were free of abnormalities, the patient would be followed-up with an anti-allergic drug and topical corticosteroid. The dermatologist instructed the patient to visit the clinic again. 46 days after start of administration: Discontinuation of lamotrigine was decided by discussion between the dermatologist and the attending physician. The patient was informed of the decision. 49 days after start of administration: During subsequent follow-up at the dermatology clinic, skin eruption tended to subside. 53 days after start of administration: Skin eruption disappeared. The outcome of the eruption was "improved." 64 days after start of administration: At the time of visit to the attending physician, exacerbated skin eruption and pyrexia were noted. Interview of the patient revealed failure of the patients to comply with the instructions on discontinuation of lamotrigine. Administration of lamotrigine was discontinued and the patient was admitted to hospital. 3 days after discontinuation: At the dermatology department, immunoglobulin therapy (2 500 mg/day) and steroid mini-pulse therapy (prednisolone 500 mg/day) were administered for 3 days for DIHS (TENS type). 7 days after discontinuation: Sepsis occurred. Administration of meropenem (1.5 g/day) and thrombomodulin alfa (25 600 U/day) was started. Sputum culture showed gram-positive cocci (GPC) 4+ and blood culture showed GPC+. 10 days after discontinuation: The regimen was switched to prednisolone 100 mg/day. 12 days after discontinuation: The regimen was switched to cefazolin 6 g/day. Methicillin-sensitive *Staphylococcus aureus* bacteraemia triggered by skin eruption was definitely diagnosed. 13 days after discontinuation: Plasma exchange (PE) was performed (until 16 days after discontinuation of medication). 16 days after discontinuation: Skin eruption tended to improve. 21 days after discontinuation: Blood pressure decreased due to septic shock during cefazolin treatment. Vancomycin (1 g/day), meropenem (3 g/day), and thrombomodulin alfa (25 600 U/day) were administered. The patient was admitted to the intensive care unit. Poor response to calling and dark black skin occurred. 22 days after discontinuation: Administration of intravenous injection of human antithrombin III was started (until 24 days after discontinuation of medication). 24 days after discontinuation: *Pseudomonas aeruginosa* was detected from blood culture. 26 days after discontinuation The dose of prednisolone was reduced to 80 mg/day. Skin eruption tended to improve, and the patient was transferred to an

				ordinary ward. 33 days after discontinuation: The dose of prednisolone was reduced to 70 mg/day. Circulation did not stabilize, and the general condition was aggravated. 35 days after discontinuation: Despite continued treatment, hepatic failure developed, leading to death.
	Concomitant drugs (suspected drugs): minodronic acid hydrate, sodium valproate			

Laboratory examination

Parameter	90 days before administration	Day 1 of administration:	20 days after of administration	64 days after of administration	3 days after discontinuation	7 days after discontinuation	25 days after discontinuation	26 days after discontinuation	29 days after discontinuation	33 days after discontinuation
ALT (IU/L)	—	11	—	14	17	16	28	27	24	12
AST (IU/L)	—	36	—	52	29	38	71	63	57	51
T-Bil (mg/dL)	1.78	1.93	1.87	1.85	2.67	2.51	7.67	8.96	22.64	29.78
D-Bil (mg/dL)	—	—	—	—	—	—	—	5.46	18.82	24.48
ALP (IU/L)	326	473	—	243	166	191	653	532	596	510
LDH (IU/L)	243	253	—	483	433	514	254	224	339	359
γ-GTP (IU/L)	16	26	—	27	24	36	—	—	58	43
WBC ($\times 10^3/\mu L$)	6.9	6.9	4.5	10.5	—	8.4	—	—	—	3.2
CRP (mg/dL)	—	0.20	0.59	2.90	—	14.18	—	—	—	8.85
PLT ($\times 10^4\mu L$)	6.1	7.4	4.5	4.9	—	6.4	—	—	—	4.7
Cr (mg/dL)	0.66	0.82	0.83	0.67	—	0.69	—	—	—	2.71

Case 2 DIHS

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
2	Female 60s	Bipolar disorder (depression, suicidal ideation, depressive symptom aggravated)	50 mg/day for 25 days	61 days before administration: The patient was admitted to another hospital. Condition stabilized in response to treatment with fluvoxamine maleate 75 mg, flunitrazepam 2 mg, and levomepromazine maleate. 23 days before administration: The patient was discharged from the hospital. Day 1 of administration: The patient had strong suicidal ideation. Administration of lamotrigine (50 mg/day) was started. Day 2 of administration: Olanzapine 5 mg was added. The dose of fluvoxamine maleate was increased to 150 mg. Day 8 of administration: Clomipramine hydrochloride 75 mg was added. Day 19 of administration: The patient mentally stabilized. Date unknown: Suspected Stevens-Johnson syndrome and increased liver function test developed. Day 24 of administration: Pyrexia (40°C) and systemic erythema occurred. Multiple organ failure (hepatic failure, renal failure) and DIHS developed. Day 25 of administration: Disturbed consciousness (Japan Coma Scale [JCS] II-30) was found and neuroleptic malignant syndrome was suspected, the patient was transported to this hospital. Hepatic failure, renal failure, sepsis, thyroid dysfunction, generalized erythema, and disturbed consciousness (alanine aminotransferase [AST], 20 323 IU/L; alanine aminotransferase [ALT], 7 382 IU/L; creatinine [Cr], 3.22 mg/dL; blood urea nitrogen [BUN], 37.4 mg/dL; creatine kinase [CK], 3 299 IU/L) were noted and the

				patient was urgently admitted to the hospital. Administration of lamotrigine was discontinued. 1 day after discontinuation: Steroid pulse therapy (continued until 3 days after discontinuation), continuous hemodiafiltration/hemodialysis were started. PE for 8 sessions was performed (until 48 days after discontinuation). 4 days after discontinuation: The regimen was switched to water-soluble prednisolone 60 mg drip infusion, with dose level later reduced (continued until 48 days after discontinuation). 36 day after discontinuation: β-D-glucan increased, and pyrexia (38°C) and aggravation of disturbed consciousness were noted again. 42 day after discontinuation: Candida positive at the tip of the central vein catheter was found. General condition exacerbated due to sepsis. 48 day after discontinuation: The patient died. Cause of death: Multiple organ failure, fulminant hepatic failure, DIHS, and renal failure Skin biopsy findings: Epidermal keratinocyte necrosis and lymphocyte infiltration into the epidermis seen (1 day after discontinuation). Post-mortem liver and kidney biopsy: Strong signs of drug-induced liver disorder
	Concomitant drugs: clomipramine hydrochloride, fluvoxamine maleate, flunitrazepam, levomepromazine maleate, paroxetine hydrochloride hydrate, mirtazapine, alprazolam, zolpidem tartrate, duloxetine hydrochloride, olanzapine.			

Laboratory examination

Parameter	59 days before administration	34 days before administration	Day 1 of administration	Day 23 of administration	Day of discontinuation	21 days after discontinuation
ALT (IU/L)	25	17	43	467	7 382	56
AST (IU/L)	20	13	32	408	20 323	61
T-Bil (mg/dL)	0.5	0.6	0.7	0.3	2.3	—
ALP (IU/L)	243	240	255	651	—	—
γ-GTP (IU/L)	15	15	15	120	—	—
LDH (IU/L)	147	139	154	501	18 742	—
CK (IU/L)	—	—	—	—	3 299	—
WBC (/μL)	5 400	6 000	3 800	—	15 120	15 240

Case 3 Toxic epidermal necrolysis syndrome/Stevens-Johnson syndrome

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
3	Male 80s	Epilepsy (metastatic brain tumor, lung cancer, altered state of consciousness, atrial fibrillation, cerebral haemorrhage, hypertension, delirium,	25 mg/day for 9 days ↓ 50 mg/day for 22 days	Before administration: The patient was treated for lung cancer and metastatic brain tumor. Activities of daily living were almost possible without assistance. Day 1 of administration: The patient was taken to the hospital by ambulance because of disturbed consciousness (JCS II-10) associated with seizure. Symptomatic epilepsy was diagnosed and the patient was admitted to the hospital. Administration of lamotrigine (25 mg/day) was started. Magnetic resonance imaging revealed a new metastatic brain tumor. Day 9 of administration: The dose of lamotrigine was changed to 50 mg/day.

		insomnia)		Date unknown: Oedema developed after gamma-knife treatment for metastatic brain tumor. Corticosteroid treatment was started. Day 28 of administration: Skin eruption (on back) occurred. Day 29 of administration: Stomatitis occurred. Day 30 of administration: Erythema multiforme (trunk) and erosion (buttocks, scrotum, extremities, lips, and oral cavity) developed. Administration of prednisolone 10 mg was started. Topical application of ethyl aminobenzoate and betamethasone butyrate propionate was started. *Escherichia coli* were detected from a blood culture. Sepsis occurred. Administration of lamotrigine was discontinued. 1 day after discontinuation: Erosion (trunk, forehead) developed. Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome were diagnosed. The dose of prednisolone was increased to 15 mg. Administration of gentamicin sulfate and ceftriaxone sodium injection was started for treatment of sepsis. 6 days after discontinuation: Skin exfoliation (systemic) developed. 7 days after discontinuation Despite high-dose gamma-globulin therapy and steroid pulse therapy (3 days), the patient's condition failed to improve. 11 days after discontinuation: Pyrexia relapsed and *Enterococcus* was detected from a blood culture. Sepsis was treated simultaneously. 19 days after discontinuation: The patient died. Cause of death: End-stage cancer, rash, TEN, skin eruption, erythema multiforme, skin erosion, scrotum erosion, stomatitis, lip erosion, mouth ulcer, skin exfoliation, and Stevens-Johnson syndrome
	Concomitant drugs: clemastine fumarate, nitrazepam, lansoprazole, risperidone			

Laboratory examination

Parameter	Day 1 of administration	14 days after administration	29 days after administration	1 day after discontinuation	4 days after discontinuation	5 days after discontinuation	6 days after discontinuation	11 days after discontinuation	12 days after discontinuation
ALT (IU/L)	39	26	26	40	92	—	76	52	—
AST (IU/L)	29	24	26	35	63	—	64	53	—
LDH (IU/L)	271	278	279	263	416	—	299	335	—
γ-GTP (IU/L)	—	19	—	24	—	—	67	62	—
CPK (IU/L)	207	239	—	142	—	—	125	52	—
Cr (mg/dL)	0.93	1.07	1.20	0.85	0.82	—	0.84	0.70	—
BUN (mg/dL)	14.9	21.9	29.0	18.1	17.6	—	24.6	35.4	—
WBC (/μL)	5,500	6,900	13,400	2,200	1,900	1,900	2,400	2,400	2,300
CRP (mg/dL)	—	2.32	5.29	—	17.43	—	19.40	28.35	—

4. Precautions for serious skin disorders

Cases of serious skin disorders leading to death, for which causality to lamotrigine could not be ruled out, were reported. Healthcare professionals should pay due attention to the following:

(1) Symptoms such as pyrexia (higher than 38°C), ocular hyperaemia, lip/oral mucosa erosion, pharyngodynia, general malaise, and lymphadenopathy in addition to rash might indicate the development of a serious skin disorders. Administration of this drug should be discontinued immediately.

(2) Delay in the treatment of skin disorders might lead to a serious outcome. Healthcare professionals should consult with a dermatologist at an early stage, and appropriate measures should be taken.

(3) Patients and their family should be advised to see a doctor immediately if a rash and/or the symptoms described in the above item (1) occurred.

5. Compliance with the dosage and administration of lamotrigine

The incidence of skin disorders increased when lamotrigine was administered at doses higher than the recommended dosage and frequency of administration. Healthcare professionals should check the recommended dosage and frequency of administration of lamotrigine and pay special attention to the following:

- ✓ During the initial phase of treatment, this drug should not be used at doses higher than the recommended dosage and frequency of administration.
- ✓ When used concomitantly with sodium valproate, this drug should be administered on alternate days for the first 2 weeks (only for adult patients).
- ✓ This drug should not be used at doses higher than recommended dosage and frequency of administration during dose titration before establishing the maintenance dose.
- ✓ A dose increase should not be attempted earlier than the specified timing.

[Dosage and Administration of lamotrigine]

For patients with epilepsy (adults)

	Concomitant use of sodium valproate	No concomitant use of sodium valproate[Note 1)]			Lamotrigine alone
		Patients receiving drug(s) for which the effect of glucuronidation of lamotrigine is unclear	(1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 2)]	(2) Concomitant use of other antiepileptic(s)[Note 3)]	
Weeks 1-2	25 mg on alternate-days administration		50 mg/day (once daily)	25 mg/day (once daily)	
Weeks 3-4	25 mg/day (once daily)		100 mg/day (twice daily in divided doses)	50 mg/day (once daily)	
Week 5 or later	Gradually increased by 25-50 mg/day every 1 or 2 weeks		Gradually increased by ≤100 mg/day every 1 or 2 weeks	At Week 5, 100 mg/day (once daily or twice daily in divided doses) Thereafter, gradually increased by ≤100 mg/day every 1 or 2 weeks	
Maintenance dose	100-200 mg/day (twice daily in divided doses)		200-400 mg/day (twice daily in divided doses)	100-200 mg/day (up to 400 mg/day) (once daily or twice daily in divided doses) (dose increase by ≤100 mg/day at an interval of 1 week or longer)	

Concomitant use of antiepileptics in epileptic patients (children)

	Concomitant use of sodium valproate		No concomitant use of sodium valproate[Note 1)]		
	Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 2)]	No concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 2)]	Patients receiving drug(s) for which the effect of glucuronidation of lamotrigine is unclear	(2) Concomitant use of other antiepileptic(s) [Note 3)]	(1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 2)]
Weeks 1-2	0.15 mg/kg/day (once daily)				0.6 mg/kg/day (twice daily in divided doses)
Weeks 3-4	0.3 mg/kg/day (once daily)				1.2 mg/kg/day (twice daily in divided doses)
Week 5 or later	Gradually increased by ≤0.3 mg/kg/day every 1 or 2 weeks				Gradually increased by ≤1.2 mg/kg/day every 1 or 2 weeks
Maintenance dose	1-5 mg/kg/day (up to 200 mg/day) (twice daily in divided doses)	1-3 mg/kg/day (up to 200 mg/day) (twice daily in divided doses)			5-15 mg/kg/day (up to 400 mg/day) (twice daily in divided doses)

For suppression of recurrent/relapsed mood episodes in patients with bipolar disorder (adults)

	Concomitant use of sodium valproate	For patients not taking sodium valproate[Note 1)]			Lamotrigine alone
		Patients receiving drug(s) for which the effect of glucuronidation of lamotrigine is unclear	(1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 2)]	(2) Concomitant use of other antiepileptic(s)[Note 4)]	
Weeks 1-2	25 mg on alternate-days administration		50 mg/day (once daily)	25 mg/day (once daily)	
Weeks 3-4	25 mg/day (once daily)		100 mg/day (twice daily in divided doses)	50 mg/day (once daily or twice daily in divided doses)	
Week 5 or later	50 mg/day (once daily or twice daily in divided doses)		200 mg/ day (twice daily in divided doses)	100 mg/day (once daily or twice daily in divided doses)	
Week 6 or later	100 mg/day (up to 200 mg/day) (once daily or twice daily in divided doses) (dose increase by ≤50 mg/day at an interval of 1 week or longer)		At Week 6, 300 mg/day Week 7 or later, 300-400 mg/day (up to 400 mg/day) (twice daily in divided doses) (dose increase by ≤100 mg/day at an interval of 1 week or longer)	200 mg/ day (up to 400 mg/day) (once daily or twice daily in divided doses) (dose increase by ≤100 mg/day at an interval of 1 week or longer)	

Note 1) Patients receiving drug(s) for which the effect of the glucuronidation of lamotrigine is unclear should follow the dosage and administration of lamotrigine used concomitantly sodium valproate.
Note 2) Drugs that induces glucuronidation of lamotrigine, including phenytoin, carbamazepine, phenobarbital, and primidone
Note 3) Drugs that do not affect the glucuronidation of lamotrigine, including zonisamide, gabapentine, topiramate, levetiracetam
Note 4) Drugs that do not affect the glucuronidation of lamotrigine, including lithium, olanzapine, aripiprazole

Pharmacists at the pharmacy department in hospitals or pharmacies should pay attention to the doses, frequency of administration and concomitant medications when dispensing lamotrigine. In addition, pharmacists should collaborate in thoroughly complying with the recommended dosage and frequency of administration of lamotrigine such as making inquiries to prescribing physicians as necessary.

Documents to fully notify specific example handling of this problem were issued on February 4, 2015 from the Japanese Society of Hospital Pharmacists and on February 6, 2015 from the Japan Pharmaceutical Association to each of their members. Please therefore refer to them as well[3), 4)].

6. Closing comments

For the revision of the packages insert, please see "4. Important safety Information" on page 23 of this document.

When using lamotrigine, healthcare professionals are encouraged to comply with the recommended dosage and frequency of administration, to make efforts for early detection, and to continuously cooperate for proper use of the drug.

<References> (including provisionally translated titles)

1) Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue letter), Serious skin disorders suggestively caused by Lamictal (lamotrigine) Tablets
http://www.pmda.go.jp/files/000198527.pdf
PMDA Investigation Result
http://www.pmda.go.jp/files/000199152.pdf

2) Compliance with Dosage and Administration and Ensuring Early Detection for Lamictal Tablets (lamotrigine) induced Serious Skin Disorders
http://www.pmda.go.jp/files/000153788.pdf

3) Actions for Dear Healthcare Professionals Letter of Rapid Safety Communication (blue letter) on serious skin disorders suggestively caused by Lamictal Tablets
(JSHP Document No. 26-250 dated February 4, 2015 for Japanese Society of Hospital Pharmacists members)
http://www.jshp.or.jp/cont/15/0205-1.html (only available in Japanese language)

4) Dispatch of references on the proper use of lamotrigine (brand name: Lamictal Tablets)
(JPA Document No. 94 from the President of the Prefectural Pharmaceutical Associations dated February 6, 2015, Document to officers of medical safety measures, JPA)
http://nichiyaku.info/member/minfo15/pdf/20150206.pdf (only available in Japanese language)
* The document issued by the Japan Pharmaceutical Association is posted only on the website for its members.

2

Abiraterone Acetate and Hypokalaemia

Active ingredient	Abiraterone acetate
Brand name (name of company)	Zytiga Tablets 250 mg (Janssen Pharmaceutical K.K.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Castration-resistant prostate cancer

1. Introduction

Abiraterone acetate (Zytiga Tablets 250 mg) is an antineoplastic that is assumed to inhibit the activity of 17.20-hydroxylase/C17,20-lyase (cytochrome P450 C17 [CYP17]), an androgen synthesis enzyme, and reduce the contents of testosterone and dihydrotestosterone in a tumor, thereby preventing tumor proliferation. In Japan, it was approved in July 2014 for the indication "castration-resistant prostate cancer." In addition, alerts against hypokalaemia associated with abiraterone acetate have been provided in the package insert and other relevant documents since the time of its approval.

After the launch of abiraterone acetate to the market in September 2014, multiple cases of serious hypokalaemia for which a causality to abiraterone acetate could not be ruled out were reported. In consideration of this, on February 2, 2015, the MHLW instructed the MAH to revise the Precautions for abiraterone acetate. On the same day, the MAH started to provide information using information materials. Its details are introduced below.

2. Background

Hypokalaemia caused by abiraterone acetate is assumed to be attributable to excess mineralocorticoid states associated with the CYP17 inhibitory activity. In Japanese and overseas clinical studies submitted at the time of approval review, the development of hypokalaemia was reduced when administered in combination with low-dose glucocorticoid (prednisolone in the Japanese clinical studies), and hypokalaemia did not lead to treatment discontinuation in any of the subjects. Based on this, concomitant use with prednisolone was stipulated to be an approved dosage and administration. In addition, cautions against hypokalaemia were included in the Important precautions section and other relevant sections of the package insert while taking account of the occurrence of hypokalaemia when abiraterone acetate was administered in combination with prednisolone in the clinical studies.

Since the launch of abiraterone acetate (September 2, 2014) until December 31, 2014, abiraterone acetate has been used in approximately 4 000 patients and serious hypokalaemia has been reported in 6 cases, including 1 fatal case (causal relationship could not be ruled out in 4 cases [including 1 fatal case]) by January 9, 2015. In light of these circumstances, the MHLW instructed the MAH to revise the Precautions for abiraterone acetate on February 2, 2015. On the same day, the MAH prepared an information material for healthcare professionals (Information on Proper Use of Drugs)[1)] under instructions from the PMDA and started to provide the information to medical institutions.

3. The occurrence of hypokalaemia associated with abiraterone acetate

Since the launch of abiraterone acetate until January 9, 2015, serious hypokalaemia has been reported in 6 cases, including 1 case of arrhythmia, which was attributable to hypokalaemia and led to death (**Table 1**). A causal relationship to abiraterone acetate could not be ruled out in 4 cases.

Table 1 Serious hypokalaemia reported in 6 cases after marketing in Japan

No.	Term of adverse reaction	Outcome	Serum potassium level (mEq/L)		Symptoms noted after the development of hypokalaemia	Time to onset of event after the start of abiraterone acetate treatment
			Before abiraterone acetate treatment	Nadir		
1	Hypokalaemia	Improved	4.5	2.1	Convulsion, muscular weakness	2 weeks
2	Electrolyte imbalance	Recovered	4.7	3.0	No	2 weeks
3	Hypokalaemia	Recovered	3.2	1.7	Numbness, muscular weakness	4 weeks
4	Hypokalaemia	Recovered	3.4	2.5	Ventricular tachycardia, ventricular fibrillation, disturbed consciousness, syncope	18 days
5	Hypokalaemia	Recovered	4.2	2.2	No	4 weeks
6	Hypokalaemia	Death	2.9	1.5	Ventricular tachycardia	11 weeks

* Case No. 1, 3, 5 and 6 were assessed as the events for which a causal relationship to abiraterone acetate could not be ruled out.

Of serious cases for which a causal relationship to abiraterone acetate could not be ruled out, 2 cases are introduced below.

[Case summaries]

Case No. 1

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
Male 70s	Castration-resistant prostate cancer (Hypertension, peripheral oedema)	1 000 mg (for 16 days)	**Hypokalaemia, convulsion, hypotension** Date unknown: The patient started receiving trichlormethiazide and furosemide. Approximately 8 years before administration: Tumor-node-metastasis classification was T3aN0M0. Retropubic radical prostatectomy and external-beam radiotherapy were performed, and maximal androgen blockade (MAB) (luteinizing hormone-releasing hormone [LH-RH] agonist and nonsteroidal antiandrogen) therapy was started. Approximately 5 years and 7 months before administration: Administration of a study drug for the treatment of prostate cancer and dexamethasone (1 mg/day) was started because the value of prostate-specific antigen (PSA) did not improve. Approximately 3 years and 7 months before administration: Administration of docetaxel hydrate was started. Approximately 2 years and 3 months before administration: Docetaxel hydrate was changed to another study drug for the treatment of prostate cancer. A corticosteroid type was changed to treatment with prednisolone (10 mg/day). Approximately 2 years and 1 month before administration: Administration of the other study drug for the treatment of prostate cancer was discontinued and the study drug was changed to cabazitaxel acetonate. Approximately 2 months before administration: Cabazitaxel acetonate was changed to enzalutamide. Administration of prednisolone was terminated. 3 weeks before administration: Administration of enzalutamide was discontinued due to anorexia and marked malaise. Day 1 of administration:

			Administration of abiraterone acetate (1 000 mg/day) and prednisolone (10 mg/day) was started. Potassium (K) was 4.5 mEq/L. Day 16 of administration (day of onset/day of discontinuation): The patient was urgently admitted to hospital due to convulsion, muscular weakness, and hypokalaemia. Administration of abiraterone acetate was discontinued. Hematological findings on admission: Sodium (Na), 135 mEq/L; K, 2.1 mEq/L; Chloride (Cl), 95 mEq/L; and cortisol, 4.0 μg/dL. After admission, treatment such as vasopressors, potassium correction, and prednisolone was continued, but the blood pressure was not stabilized. The hemodynamics was stabilized after an increase in the dose of prednisolone. 1 day after discontinuation: After potassium correction, the K level increased to 4.5 mEq/L. The blood pressure tended to increase after treatment with dopamine hydrochloride. The patient recovered from convulsion. Hypotension and hypokalaemia improved. 7 days after discontinuation: K was 5.0 mEq/L. 13 days after discontinuation: The patient was discharged from the hospital. K was 4.8mEq/L. Hydrocortisone sodium phosphate100 mg was administered.
	The other suspected medications: trichlormethiazide, furosemide and prednisolone Concomitant medications: sennoside, calcium carbonate precipitated/cholecalciferol/magnesium carbonate, ursodeoxycholic acid, tamsulosin hydrochloride, denosumab (genetical recombination), hydrocortisone, hydrocortisone sodium phosphate		

Laboratory examination

	3 weeks before administration	Day 1 of administration	Day 12 of administration	Day 16 of administration (day of onset/day of discontinuation)	1 day after discontinuation	7 days after discontinuation	13 days after discontinuation	25 days after discontinuation
K (mEq/L)	4.7	4.5	4.6	2.1	4.5	5.0	4.8	5.1
Na (mEq/L)	—	—	—	135	—	—	—	—
Cl (mEq/L)	—	—	—	95	—	—	—	—

Case No. 3

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
Male 60s	Castration-resistant prostate cancer (diabetes mellitus, asthenia, hepatic function abnormal, peripheral oedema)	1 000 mg (for 29 days)	**Hypokalaemia, hepatic impairments** Date unknown: The patient started receiving trichlormethiazide and furosemide. Approximately 2 years and 6 months before administration: ABCD rating (Jewett staging system) was D2. MAB (LH-RH agonist and nonsteroidal antiandrogen) therapy and administration of denosumab were started. Approximately 1 year and 2 months before administration: Administration of docetaxel hydrate (60 mg/m^2) and dexamethasone (1 mg/day) was started. Approximately 2 months before administration: Docetaxel hydrate (14 doses in total) was changed to enzalutamide. Administration of dexamethasone was continued. Approximately 1 month and a half before administration: Hepatic **impairments**, asthenia, and lower limb oedema occurred. 14 days before administration:

			K was 3.2 mEq/L. Day 1 of administration: Enzalutamide was changed to abiraterone acetate (1 000 mg/day). A corticosteroid type was changed from dexamethasone (1 mg/day) to prednisolone (10 mg/day). Day 15 of administration: K was 3.0 mEq/L. Day 23 of administration: The dose of prednisolone was increased to 15 mg/day. Cortisol was 4.0 μg/dL. Day 25 of administration: The dose of prednisolone was increased to 20 mg/day. Cortisol was 3.0 μg/dL. Day 29 of administration (day of onset/day of discontinuation): The patient was urgently admitted to hospital because hypokalaemia, numbness-like symptoms, extreme muscular weakness, and hepatic **impairments** occurred. Administration of abiraterone acetate was discontinued. Hematological findings on admission: K, 1.7 mEq/L; cortisol, 6.6 μg/dL; AST (glutamate oxaloacetate transaminase [GOT]), 114 IU/L; ALT (glutamate pyruvate transaminase [GPT]), 117 IU/L; lactate dehydrogenase (LDH), 349 IU/L and total bilirubin (T-Bil), 1.5 mg/dL After admission, supplementation of potassium was performed. 9 days after discontinuation: The patient was discharged from the hospital. K was3.7mEq/L. 1 month after discontinuation: K was 4.2 mEq/L. Approximately 2 months after discontinuation: K was 5.0 mEq/L. Hypokalaemia improved and outcome of hepatic **impairments** was unknown.
	The other suspected medications: trichlormethiazide, furosemide, prednisolone Concomitant medications: ursodeoxycholic acid, leuprorelin acetate, insulin lispro (genetical recombination), alprazolam		

Laboratory examination

	14 days before administration	Day 1 of administration	Day 15 of administration	Day 29 of administration (day of onset/day of discontinuation)	2 days after discontinuation	4 days after discontinuation	9 days after discontinuation	1 month after discontinuation	2 months after discontinuation
K (mEq/L)	3.2	—	3.0	1.7	2.0	2.6	3.7	4.2	5.0
Na (mEq/L)	—	—	—	130	—	—	—	—	—
Cl (mEq/L)	—	—	—	73	—	—	—	—	—

4. Precautions for hypokalaemia

(1) Development of hypokalaemia during treatment with abiraterone acetate

For hypokalaemia associated with abiraterone acetatet, hypokalaemia has been included in the Other adverse reactions section, and caution that periodic blood test, etc., should be performed during the treatment with abiraterone acetate included in the Important precautions section of the package insert since the marketing authorization.

After the market launch, cases of serious hypokalaemia with clinical symptoms occurred in association with abiraterone acetate treatment. Consequently, hypokalaemia was added to the Clinically significant adverse reactions section of the package insert, and the following statements were added: Hypokalaemia accompanied by symptoms such as convulsion and/or muscular weakness may occur; cases leading to arrhythmia have been reported; and patients should be carefully monitored through periodic measurements of serum electrolyte levels such as serum potassium during treatment with abiraterone acetate. Precaution was to be also provided using an information material for healthcare professionals[1)].

During treatment with abiraterone acetate, healthcare professionals are encouraged to ensure periodic patient's monitoring of serum electrolyte levels such as serum potassium. Also, healthcare professionals are encouraged to ensure careful observation for symptoms related to hypokalaemia such as convulsion and/or muscular weakness.

(2) Serum potassium correction before the start of treatment with abiraterone acetate

In clinical studies submitted for approval review, a serum potassium level of ≥3.5 mEq/L was defined as one of the inclusion criteria.

In the patients who experienced serious hypokalaemia after the market launch, serum potassium levels had been low before the start of treatment with abiraterone acetate, and multiple patients experienced serious hypokalaemia with clinical symptoms after abiraterone acetate treatment. Hence, it was to be added to the Important precautions section of the package insert that "Serum potassium levels should be measured before the start of treatment with this drug. If hypokalaemia is observed, serum potassium level should be corrected before starting therapy," and precaution was to be provided using an information material for healthcare professionals[1)] as well.

When using abiraterone acetate, healthcare professionals should measure serum electrolyte levels such as serum potassium before starting administration. Also, if hypokalaemia is observed before treatment initiation, administration of abiraterone acetate should be started after correcting the serum potassium level.

(3) Patients requiring special attention to the development of hypokalaemia

With regard to patients requiring special attention during treatment with abiraterone acetate, as common applicable subjects of adverse reactions (hypertension, fluid retention, and hypokalaemia) likely to be attributable to increases in mineralocorticoid levels caused by the CYP17 inhibitory activity, "patients with a current or past history of cardiovascular disease" have been mentioned in the Careful administration section to raise caution since the marketing authorization.

In patients who experienced serious hypokalaemia after marketing, a number of patients with hypokalaemia at the start of treatment with abiraterone acetate, patients with complications such as diabetes mellitus, and patients who had been concomitantly on diuretics or other drugs possibly inducing hypokalaemia were noted.

Consequently, as patients requiring special attention to the development of hypokalaemia, "patients with hypokalaemia or risk of hypokalaemia due to factors of complications or concomitant drugs" were to be added to the Careful administration section of the package insert, and precaution was to be also provided using an information material for healthcare professionals[1)].

During treatment with abiraterone acetate, healthcare professionals are encouraged to check whether or not patients have a current or past history of cardiovascular disease, hypokalaemia, or diseases possibly causing hypokalaemia, or are on concomitant medications. When abiraterone acetate is to be administered to patients requiring special attention, this drug should be administered with care as frequently measuring serum potassium levels and monitoring symptoms related to hypokalaemia with special attention.

(4) Measures when identifying hypokalaemia during treatment with abiraterone acetate

With regard to measures for hypokalaemia, precaution has been provided in the Important Precautions section that appropriate measures such as potassium supplementation since the marketing authorization.

After the market launch, in some patients who experienced serious hypokalaemia caused by abiraterone acetate treatment, supplement of potassium was not performed at the onset of hypokalaemia. In consideration of this, it was to be also added in the Clinically significant adverse reactions section that appropriate measures such as potassium supplementation and cessation of abiraterone acetate should be taken, and precaution was to be provided using an information material for healthcare professionals[1)] as well.

If hypokalaemia is observed during treatment with abiraterone acetate, actions should be considered to include the measures such as potassium supplementation (oral or drip infusion) and cessation of abiraterone acetate, and appropriate measures should be taken.

5. Information on hypokalaemia described in the Precautions section

Alert against hypokalaemia in the latest package insert including the present revision of the Precautions are provided in the Careful administration, Important precautions, and Clinically significant adverse reactions sections as shown in the table below (See "4. Important Safety Information" of this document [page 23] for the precaution revised on February 2, 2015.).

Table.

Careful administration	Patients with a current or past history of cardiovascular disease [Increases in mineralocorticoid concentrations associated with the 17 α-hydroxylase/C17,20-lyase (CYP17) inhibitory activity of this drug may cause hypertension, hypokalaemia, and fluid retention.] Patients with hypokalaemia or risks of hypokalaemia due to factors of complications or concomitant drugs [Hypokalaemia may occur or be exacerbated.]
Important precautions	Increased blood pressure, hypokalaemia, and/or fluid retention may occur. Cautions should be paid to the following: (1) Serum electrolyte levels such as serum potassium should be measured before the start of treatment with this drug. If hypokalaemia is observed, serum potassium level should be corrected before starting therapy. (2) Patients should be carefully monitored through periodic blood pressure measurements, blood test, and body weigh measurement, etc. during treatment with this drug. Appropriate measures including treatment with an antihypertensive or supplementation of potassium as necessary should be taken.
Clinically significant adverse reactions	Hypokalaemia (8.4%): Hypokalaemia with symptoms including convulsion and/or muscular weakness may occur, and arrhythmia has been reported in some cases. Patients should be carefully monitored through periodic measurements of serum electrolyte levels such as serum potassium. If any abnormalities are observed, appropriate measures such as supplementation of potassium and cessation of this drug should be taken.

Healthcare professionals should thoroughly read the package insert of abiraterone acetate and newly prepared/distributed information material ("Information on Proper Use of Drugs")[1)] and to take appropriate actions for hypokalaemia associated with abiraterone acetate.

During the use of abiraterone acetate, not only hypokalaemia but also various adverse reactions may occur. Healthcare professionals are encouraged to cooperate the proper use of abiraterone acetate based on a thorough understanding of its safety profile.

<Reference>

1) Information on proper use of drugs from Market Authorization Holder, Hypokalaemia associated with Zytiga Tablets 250 mg (abiraterone acetate)
http://www.pmda.go.jp/files/000198350.pdf (only available in Japanese language)

3

The MIHARI Project

1. Introduction

The PMDA has been conducting the MIHARI Project as one of the activities for reinforcement and enhancement of the system for safety information collection and evaluation of medical products, and established a system for the use of electronic health records (EHRs), etc. for safety measures.

In recent years, the availability of electronic EHRs such as claim data and electronic medical record data has received much attention in post-marketing safety measures for drugs in Japan. In order to promote greater understanding of the use of EHRs for safety measures, a summary of the MIHARI Project is introduced below.

2. The MIHARI Project

The PMDA has evaluated the safety of drugs primarily relying on the information such as existing spontaneous adverse drug reaction (ADR) reports or post-marketing surveillance results, etc. However, only with these sources of information, there are limitations such as the frequency of ADR being unknown, difficulty in comparing with similar drugs, and some adverse events that are unlikely to be reported. Consequently, for further reinforcement and enhancement of safety measures, the PMDA has launched the MIHARI Project in the second mid-term plan (Fiscal year [FY] 2009 to FY 2013) aiming at building a framework of quantitative evaluation by pharmacoepidemiological methods using EHRs (**Figure 1**). PMDA has conducted some pilot studies in the last five years of the MIHARI Project for ensuring access to EHR data, data characterization, and assessment of the feasibility of applying the pharmacoepidemiological methods to drug-safety evaluation with the Japanese EHR data, and established the framework enabling quantitative evaluation of the risk of adverse events after prescription of drugs, assessment of the effect of regulatory action, and survey on drug utilization.

In the third mid-term plan (FY 2014 to FY 2018), the PMDA intends to apply this framework into a real situation of risk management of drug safety. In addition, the PMDA will work to establish access to another database and to review and implement novel pharmacoepidemiological methods using EHR database.

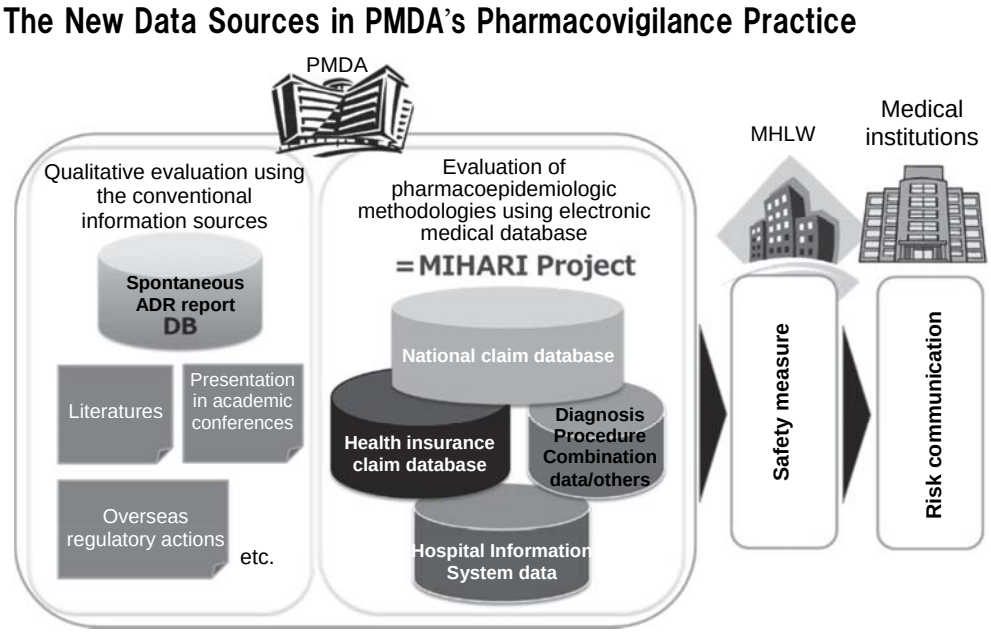

Figure 1. Goal of the MIHARI Project

3. MIHARI Communication

The reports of the results of studies carried out in the MIHARI Project have been posted on the PMDA website as needed. Since FY 2014, the PMDA has started to release the "MIHARI Communication" as a new communication tool so that healthcare professionals who don't have expert knowledge of pharmacoepidemiology can easily understand the contents of study reports. The MIHARI Communication summarizes the objectives, design and data interpretation of a study by using figures and tables and by avoiding technical terms to the extent possible.

As of March 16, 2015, the MIHARI Communication, which is posted, is as listed in Table 1.

Table 1. List of currently available investigation reports for MIHARI Communication (as of March 16, 2015)

No	Title
1	Drug utilization assessment of biguanides antidiabetic agent
2	Interferon products and the risk of depressive symptoms
3	Olanzapine and the risk of hyperlipidemia
4	Nonsteroidal anti-inflammatory drugs and the risk of acute asthmatic attack
5	Drug utilization assessment of antimicrobial agents during the perioperative period in children
6	Drug utilization assessment of doxorubicin
7	Validity of the definition to identify the new incidence of diabetes mellitus, hyperlipidemia, and hyperthyroidism using electronic medical records
8	Validity of the definition to identify the new incidence of acute renal failure using electronic medical records
9	Antipsychotics and the risk of glucose metabolism disorder
10	Antipsychotics and the risk of parkinsonism

4. The materials related to the MIHARI Project

On the webpage of the MIHARI Project in the PMDA website, the reports of studies conducted in the MIHARI Project, MIHARI Communication, and relevant information such as presentations at academic conferences and literature are summarized and provided. For details, information is available at the following site.

MIHARI website
http://www.pmda.go.jp/safety/surveillance-analysis/0011.html
(only available in Japanese language)

5. Closing Comments

Information on the MIHARI Project will be posted as it becomes available. Please utilize it to collect information on the use of EHRs for safety measures for drugs.

4

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated February 2 (1), February 4 (2) and February 17 (3, 4), 2015, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Abiraterone Acetate

Brand name (name of company)	Zytiga Tablets 250 mg (Janssen Pharmaceutical K.K.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Castration-resistant prostate cancer

PRECAUTIONS (underlined parts are revised)

Careful administration

Patients with hypokalaemia or risks of hypokalaemia due to factors of complications or concomitant drugs.

Important precautions

Increased blood pressure, hypokalaemia, and/or fluid retention may occur. Caution should be paid to the following:

(1) Serum electrolyte levels such as serum potassium should be measured before the start of treatment with this drug. If hypokalaemia is observed, serum potassium level should be corrected before starting therapy.

(2) Patient should be carefully monitored through periodic blood pressure measurements, blood test, and body weight measurement, etc. during treatment with this drug. Appropriate measures including treatment with an antihypertensive or supplementation of potassium as necessary should be taken.

Adverse reactions (clinically significant adverse reactions)

Hypokalaemia: Hypokalaemia with symptoms including convulsion and muscular weakness may occur, and arrhythmia has been reported in some cases. Patients should be carefully monitored through periodic measurements of serum electrolyte levels such as serum potassium. If any abnormalities are observed, appropriate measures such as supplementation of potassium and cessation of this drug should be taken.

Thrombocytopenia: Thrombocytopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Rhabdomyolysis: Rhabdomyolysis may occur. Attention should be paid to muscular weakness, myalgia, increased creatine kinase (creatine phosphokinase), and increased blood and urine myoglobin. If these symptoms 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 4 months (from initial marketing to January 2015)

Case of adverse events suggestive of hypokalaemia: 4 cases (1 fatal case)
Case of adverse events suggestive of thrombocytopenia: 4 cases (no fatal case)
Case of adverse events suggestive of rhabdomyolysis: 0 case

The number of patients using this drug per year estimated by MAH: 4 000 (from initial marketing to December 2014)

Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Castration-resistant prostate cancer (diabetes mellitus, hypertension, angina pectoris, metastases to bone)	1 000 mg (for 19 days) ↓ Discontinuation ↓ 500 mg (for 5 days) ↓ Discontinuation ↓ 500 mg (1-week treatment followed by 1-week rest period, for 33 days) ↓ 1 000 mg (1-week treatment followed by 1-week rest period, for 16 days)	**Thrombocytopenia** Metastases were noted in the right ilium and pubis. History of chemotherapy: None Approximately 4 years before administration: The patient visited this hospital for the first time. Unexplained low platelet (PLT) counts were observed from the initial visit. Approximately 6 months before administration: Estramustine phosphate sodium was administered for castration-resistant prostate cancer (for 8 days). Adverse reactions such as itching and wheals occurred. Before administration: Performance status (PS) for progression of primary disease was 1. 8 days before administration: PLT count was 120 000/mm^3. Day 1 of administration: The patient was admitted to hospital and administration of abiraterone acetate (1 000 mg/day) and prednisolone (10 mg/day) was started. Day 10 of administration: PLT was 125 000/mm^3. Day 11 of administration: No abnormalities including laboratory test values were found. Day 19 of administration (day of discontinuation): Administration of abiraterone acetate was discontinued. 1 day after discontinuation (day of onset): Because PLT markedly decreased to 28 000/mm^3, the patient was urgently admitted to the hospital. No hemolytic crisis developed. Symptoms at the onset of thrombocytopenia included petechiae and purpura. Treatment and blood transfusion for thrombocytopenia were not performed. Steroid therapy was not performed. Disseminated intravascular coagulation was not found. 4 days after discontinuation: PS for progression of primary disease was 2. 9 days after discontinuation: PLT was 52 000/mm^3. 10 days after discontinuation (Day 1 of re-administration): PLT was 149 000/mm^3. Thrombocytopenia improved. Administration of abiraterone acetate was resumed at 500 mg/day. Day 2 of re-administration (day of onset): PLT was 108 000/mm^3. Thrombocytopenia developed. The patient was discharged from the hospital. Day 4 of readministration: PLT was 74 000/mm^3. Day 5 of readministration (day of discontinuation of re-administration): Administration of abiraterone acetate was discontinued. 4 days after discontinuation of re-administration: PLT was 100 000/mm^3. Thrombocytopenia improved. 7 days after discontinuation of re-administration (Day 1 of re-

				readministration): Administration of abiraterone acetate was resumed at 500 mg/day (1-week administration followed by 1-week rest period). Day 34 of re-readministration: Because PSA increased to 58 ng/mL, the dose of abiraterone acetate was increased to 1 000 mg/day (1-week administration followed by 1-week rest period). Day 49 of re-readministration: Administration of abiraterone acetate was completed. No thrombocytopenia due to re-readministration developed.
	Concomitant medications: prednisolone, aspirin, bisoprolol fumarate, nicorandil, calcium L-aspartate hydrate, alfacalcidol, goserelin acetate, insulin aspart (genetical recombination)			

Laboratory examination

	8 days before administration	Day 10 of administration	1 day after discontinuation	4 days after discontinuation	9 days after discontinuation	Day 2 of re-administration	Day 4 of re-administration	4 days after discontinuation of re-administration
PLT ($\times 10^4/mm^3$)	12.0	12.5	2.8	5.2	14.9	10.8	7.4	10.0
Hb (g/dL)	14.7	14.3	12.5	—	12.2	13.8	—	—
RBC ($\times 10^4/mm^3$)	433	406	407	—	400	449	—	—
WBC ($\times 10^3/mm^3$)	5.4	3.9	3.2	—	5.1	5.3	—	—

2 Lamotrigine

Brand name (name of company)	Lamictal Tablets for pediatrics 2 mg, 5 mg, Lamictal Tablets 25 mg, 100 mg (GlaxoSmithKline K.K.)
Therapeutic category	Antiepileptics
Indications	1. Monotherapy for the following types of seizures in epileptic patients: Partial seizures (including secondary generalized seizures) Tonic-clonic seizures 2. Concomitant therapy with antiepileptics for the following types of seizures in epileptic patients who have not sufficiently respond to other antiepileptics: Partial seizures (including secondary generalized seizures) Tonic-clonic seizures Generalized seizures of Lennox-Gastaut syndrome 3. Suppression of recurrent/relapsed mood episodes in patients with bipolar disorder

PRECAUTIONS (underlined parts are revised)

Warnings

Serious skin disorders with general symptoms such as toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens‐Johnson syndrome), and drug-induced hypersensitivity syndrome may occur in patients treated with this drug, and result in fatal outcomes in some cases. Attention should be paid to the following items:

1. Dosage and frequency of administration in the package insert of this drug should be followed because the incidence of skin disorders is increased when this drug is administered at doses higher than recommended dosage and frequency of administration.
   (1) During the initial phase of treatment, this drug should not be used at doses higher than recommended dosage and frequency of administration. When used concomitantly with sodium valproate, this drug should be administered on alternate days for the first 2 weeks (only for adult patients).
   (2) This drug should not be used at doses higher than recommended dosage and frequency of administration during dose titration before establishing the maintenance dose. A dose increase should not be attempted earlier than the specified timing.
2. If a rash occurs, healthcare professionals should consult with a dermatologist in an early stage, and appropriate measures should be taken. The following symptoms in addition to a rash might indicate a serious skin disorder; therefore, administration of this drug should be discontinued immediately:
   Pyrexia (higher than 38°C), ocular hyperaemia, lips/oral mucosa erosion, pharyngodynia, general malaise, lymphadenopathy, etc.
3. Careful attention should be paid to pediatric patients because an increased incidence of serious skin disorders has been reported in pediatric patients.
4. Patients or their families should be advised to see their doctor immediately when a rash and/or the above symptoms occur.

Reference information

The number of reported adverse reactions resulting in death (for which a causality between the adverse reactions and the drug could not be ruled out) for the past 4 months (September to December 2014)
Serious skin disorders: 4 fatal cases
The number of patients using this drug per year estimated by MAH (from initial marketing to December 2014): Approximately 376 000
Launched in Japan: December 2008

Case summary

See the case summaries in “1. Lamotrigine and Serious Skin Disorders” on page 6 of this document.

3 Apixaban

Brand name (name of company)	Eliquis Tablets 2.5 mg, 5 mg (Bristol-Myers K.K.)
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)

Adverse reactions (clinically significant adverse reactions)

Interstitial lung disease: Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities such as cough, blood sputum, shortness of breath, dyspnoea, pyrexia, and/or abnormal chest sound are observed, examinations including chest X-ray, chest CT scan, and 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 corticosteroid 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 11 months (from initial marketing to January 2015)

Case of adverse events suggestive of interstitial lung disease: 7 cases (no fatal case)

The number of patients using this drug estimated by MAH (from initial marketing to January 2015): Approximately 222 000

Launched in Japan: February 2013

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Prophylaxis of thromboembolism (atrial fibrillation)	5 mg for 240 days	**Interstitial lung disease, acute respiratory distress syndrome** Past treatment/Medical history: Cardiac ablation, cardiac tamponade, atrial flutter 66 days before administration: The patient started receiving warfarin potassium. 17 days before administration Computed tomography (CT) was performed. A change after chronic inflammation was noted in the middle lobe of the right lung. 16 days before administration: Ablation was performed. Cardiac tamponade was observed, and heparin was used. Day 1 of administration: For prophylaxis of thromboembolism, heparin was switched to apixaban (5 mg/day) at the time of hospital discharge. Day 81 of administration: Bloody sputum occurred, and the patient visited the hospital. CT was performed. A macular opacity was found in the middle lobe of the right lung. It was already found on CT performed 17 days before administration. It tended to increase somewhat. Day 97 of administration: With referral by Hospital A, the patient visited the respiratory medicine department of this hospital. Day 99 of administration: Bronchoscopy was performed. The result of acid-fast bacteria test was negative. Approximately 7 months of administration:

				Cough and sputum were noted. Day 222 of administration: The patient visited the outpatient department of this hospital. CT was performed, but no abnormality was noted. Day 237 of administration: Pyrexia and difficulty in breathing developed. Pneumonia was suspected, and the patient was admitted to Hospital A. Medical treatment was performed with meropenem hydrate and garenoxacin mesilate hydrate. Day 240 of administration (day of discontinuation): With referral to the respiratory medicine department, the patient visited the emergency department. Chest X-ray images and chest CT showed ground-glass opacities. Acute respiratory distress syndrome was diagnosed. After drip infusion of meropenem hydrate 0.5 g in the emergency unit, the patient was admitted to the respiratory medicine department. Physical findings at hospital admission: Oxygen saturation (SpO_2), 90% (Room air); 94% (O_2 5L/min) Rales were heard in bilateral lower dorsal regions. Examination findings at hospital admission: White blood cell count (WBC) 11 400, C-reactive protein (CRP) 14.605, LDH 414 Legionella urinary antigen (-), pneumococcus urinary antigen (-) (1) Chest X-ray images: Reticular opacities were noted in bilateral middle/lower lung fields (2) Chest CT: Ground-glass opacities and interlobular septal thickening images were noted in bilateral upper lobes. Crazy paving appearance was found. In bilateral lower lobes, dense opacities were mainly seen. Traction bronchiectatic image and mediastinal emphysema were observed, without pleural effusion. After hospital admission, administration of apixaban was discontinued. Treatment was started with meropenem hydrate 1.5 g/day + azithromycin hydrate 500 mg/day. Considering the possibility of acute interstitial pneumonia, sivelestat sodium hydrate and steroid pulse therapy with methylprednisolone 1g/day was administered for 3days. 3 days after discontinuation: After pulse therapy, administration of sivelestat sodium hydrate + methylprednisolone sodium succinate 40 mg/day were started. No marked change was noted in hematological findings, but as poor oxygenation was seen, nasal high flow (30 L/min, O_2 60%) was started. After that, oxygen was gradually reduced according to oxygenation. The respiratory status and opacities tended to improve. Steroid reaction was judged to be relatively favorable. Pulse therapy was performed twice. Steroid maintenance therapy at 1 mg/kg was started. The dose was gradually tapered by 1 tablet/2 weeks. Antibiotics were terminated after administration for a total of 10 days. Date unknown: D-dimer level was high. Leg vein echography showed deep vein thrombosis. The condition was adjusted with administration of warfarin potassium. Date unknown: Mediastinal emphysema resolved spontaneously. Date unknown:

				With oxygen free, SpO_2 was 98%. The activities of daily living tended to improve, and the patient was discharged from the hospital. Outpatient follow-up was started. At the time of hospital discharge, warfarin potassium tablets at 1 mg/day were prescribed.
	Concomitant medications: tipepidine hibenzate, amezinium metilsulfate, zolpidem tartrate			

Laboratory examination

	13 days before administration	Day 240 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	9 days after discontinuation	10 days after discontinuation	38 days after discontinuation
WBC (/mm^3)	—	11 400	—	—	—	—	—	—
LDH (IU/L)	—	414	—	—	—	—	—	—
CRP (mg/dL)	—	14.605	—	—	—	—	—	—
tHb (g/dL)	9.2	10.8	12.7	—	11.5	—	11.0	—
sO_2 (%)	98.6	95.5	94.9	—	98.0	—	98.4	—
ctO_2 (mL/dL)	12.7	14.1	16.7	—	15.7	—	14.9	—
$cHCO_3$ (mmol/L)	29.0	23.6	20.5	—	27.1	—	27.4	—
pH	7.448	7.481	7.399	—	7.502	—	7.422	—
pCO_2 (mmHg)	44.6	32.1	34.0	—	34.8	—	42.8	—
pO_2 (mmHg)	120.8	68.5	72.9	—	125.0	—	77.5	—
BEact (mmol/L)	6.2	1.0	-3.1	—	4.3	—	3.1	—
BE (mmol/L)	5.6	0.5	-3.5	—	3.9	—	3.2	—
SpO_2 (%)	—	92	94	—	—	—	—	—
Legionella antigen	—	Negative	—	—	—	—	—	—
β-D-glucan (pg/mL)	—	<6	—	—	—	—	—	—
KL-6 (U/mL)	—	—	—	1 771	—	2 224	—	1 053

4 Memantine Hydrochloride

Brand name (name of company)	Memary Tablets 5 mg, 10 mg, and 20 mg, Memary OD Tablets 5 mg, 10 mg, and 20 mg (Daiichi Sankyo Company, Limited)
Therapeutic category	Central nervous system agents-Miscellaneous
Indications	Prevent progression of dementia symptoms in patients with moderate to severe Alzheimer's type dementia

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Hepatic function disorder and jaundice: Hepatic function disorder and/or jaundice with elevations of AST (GOT), ALT (GPT), Al-P, bilirubin etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 6 months (from initial marketing to November 2014)

Case of adverse events suggestive of hepatic function disorder/jaundice: 3 cases (1 fatal case)

The number of patients using this drug per year estimated by MAH (2014): Approximately 300 000

Launched in Japan: June 2011

Case summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Dementia Alzheimer's type (diabetes mellitus, constipation)	5 mg for 7 days ↓ 10 mg for 7 days ↓ 15 mg for 4 days	**Hepatic function abnormal** Day 1 of administration: The patient had unrest due to dementia. She bit off many things. Administration of memantine hydrochloride at 5 mg/day through gastric fistula was started. Day 8 of administration: The dose of memantine hydrochloride was increased to 10 mg/day. Day 15 of administration: The dose of memantine hydrochloride was increased to 15 mg/day. Day 18 of administration (day of onset) (day of discontinuation): With a body temperature of 37.7°C, the patient was active, but with somnolence to a certain degree. The results of in-hospital blood sampling, which was periodically performed, were AST 1 053 IU/L, ALT 1 000 IU/L, alkaline phosphatase (ALP) 1 684 IU/L, LDH 900 IU/L, and ammonia 82 μg/dL. Hepatic function disorder occurred suddenly. Abdominal CT scan revealed no abnormal findings. Disturbed consciousness and jaundice were not observed. Administration of all oral medications was discontinued and eating was stopped. Fluid replacement 1 500 ml/day was performed. An insulin sliding scale was performed. 4 days after discontinuation: Hepatic function disorder tended to improve. Drip infusion was terminated. Tube feeding was restarted. 11 days after discontinuation: Administration of sitagliptin phosphate hydrate and voglibose was resumed. 21 days after discontinuation:

				AST decreased to 16 IU/L, ALT to 13 IU/L, ALP to 345 IU/L, and LDH to 157 IU/L. After that, the events did not relapse.
	Concomitant medications: sitagliptin phosphate hydrate, voglibose, magnesium oxide			

Laboratory examination

	112 days before administration	97 days before administration	82 days before administration	59 days before administration	31 days before administration	6 days before administration
ALT (IU/L)	13	11	10	—	13	14
AST (IU/L)	16	15	14	—	17	16
ALP (IU/L)	312	299	311	—	318	341
T-Bil (mg/dL)	0.2	0.3	0.4	—	0.3	0.3
CPK (IU/L)	—	18	23	—	—	—
CRE (mg/dL)	0.27	0.34	0.38	0.31	0.32	0.36
LDH (IU/L)	137	143	137	—	146	163
BUN (mg/dL)	22.8	23.1	24.1	—	18.4	19.9

	Day 18 of administration (day of onset) (day of discontinuation)	1 day after discontinuation	4 days after discontinuation	7 days after discontinuation	16 days after discontinuation	21 days after discontinuation
ALT (IU/L)	1 000	620	156	67	—	13
AST (IU/L)	1 053	349	25	19	—	16
ALP (IU/L)	1 684	1 400	820	614	—	345
T-Bil (mg/dL)	1.0	1.4	0.8	0.5	—	0.4
CPK (IU/L)	55	46	44	43	—	—
CRE (mg/dL)	0.30	0.30	0.20	0.20	0.37	—
LDH (IU/L)	900	206	131	138	—	157
BUN (mg/dL)	20.4	19.6	8.3	10.5	—	—

Case summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Dementia	5 mg for 7 days ↓ 10 mg for 70 days ↓ 15 mg for 7 days ↓ 20 mg for 108 days ↓ 10 mg for 63 days	**Hepatic function disorder, jaundice, general malaise** The start time of use was unknown, but the patient took many kinds of supplements (details unknown). The patient was smoker. History of alcohol consumption. 958 days before administration: The patient started receiving donepezil hydrochloride 5 mg for Alzheimer's type dementia. 278 days before administration: Administration of fursultiamine hydrochloride 75 mg was started at a nearby hospital. 144 days before administration: Administration of sarpogrelate hydrochloride 300 mg was started at a nearby hospital. Day 1 of administration: Concomitant use of memantine hydrochloride 5 mg was started. Day 8 of administration: The dose of memantine hydrochloride was increased to 10 mg. Day 15 of administration: The dose of memantine hydrochloride was increased to 15 mg. Day 22 of administration: The dose of memantine hydrochloride was increased to 20 mg. Day 130 of administration: General malaise was observed, and the dose of memantine hydrochloride was reduced to 10 mg. Day 178 of administration:

				Due to the patient being transferred to another hospital, administration of donepezil hydrochloride was terminated. Day 185 of administration (day of onset): The patient visited a nearby hospital due to anorexia. Blood test showed T-BiI 11.4 mg/dL, AST 1 608 IU/L, ALT 652 IU/L, ALP 558 IU/L, and γ-GTP 284 IU/L and jaundice and hepatic function disorder were noted. Day 187 of administration: The patient visited the reporting medical institution. The condition was judged to have no urgency, and the patient made a reservation for hospital admission on Day 190 of administration, and returned home. Day 190 of administration: The patient was admitted to the hospital. From the results of blood sampling, echography, CT, and magnetic resonance cholangiopancreatography, drug-induced haptic function disorder was suspected. Administration of fursultiamine and sarpogrelate hydrochloride was discontinued. Oral administration of ursodeoxycholic acid was started. Intravenous administration of glycyrrhizin/glycine/L-cysteine was started. Day 192 of administration (day of discontinuation): Administration of memantine hydrochloride was discontinued. 4 days after discontinuation: The hepatic function did not improve sufficiently, and oral administration of prednisolone (30 mg/day) was started. 5 days after discontinuation: When drug lymphocyte stimulation test was performed for memantine hydrochloride for which the regimen was modified just recently, the result was positive. 11 days after discontinuation: Oral administration of prednisolone was discontinued. Intravenous infusion of prednisolone acetate (50 mg/day) was started. 15 days after discontinuation: The dose of prednisolone acetate for intravenous infusion was reduced to 40 mg/day. 16 days after discontinuation The dose of ursodeoxycholic acid was increased to 600 mg/day. 20 days after discontinuation: The dose of prednisolone acetate for intravenous infusion was reduced to 30 mg/day. 21 days after discontinuation: The dose of ursodeoxycholic acid was increased to 900 mg/day. 22days/23days after discontinuation: The hepatic function did not improve sufficiently. Bilirubin adsorption was performed, but the function still did not improve sufficiently. 25 days after discontinuation: The patient died (no autopsy).
	Concomitant medications: sarpogrelate hydrochloride, donepezil hydrochloride, fursultiamine hydrochloride			

Laboratory examination

	Day 38 of administration	Day 152 of administration	Day 185 of administration (day of onset)	Day 190 of administration	Day 191 of administration	1 day after discontinuation
ALT (IU/L)	14	24	652	318	211	184
AST (IU/L)	26	40	1 608	212	131	124
ALP (IU/L)	276	—	558	547	432	483
T-Bil (mg/dL)	2.3	—	11.4	20.8	17.0	20.8
CRE (mg/dL)	0.72	0.81	—	—	0.77	0.79
LDH (IU/L)	227	308	—	453	327	333
BUN (mg/dL)	7.5	5.1	—	8.8	9.8	11.4
γ-GTP (IU/L)	47	143	284	193	139	129

	3 days after discontinuation	5 days after discontinuation	7 days after discontinuation	10 days after discontinuation	12 days after discontinuation	14 days after discontinuation
ALT (IU/L)	154	130	139	130	145	152
AST (IU/L)	122	129	123	110	120	116
ALP (IU/L)	—	447	460	434	450	477
T-Bil (mg/dL)	21.3	20.5	21.9	18.3	18.7	19.0
CRE (mg/dL)	0.88	0.90	0.85	0.86	0.90	0.96
LDH (IU/L)	—	332	327	283	294	295
BUN (mg/dL)	9.1	14.2	13.6	15.3	16.9	21.7
γ-GTP (IU/L)	—	100	114	94	94	90

	17 days after discontinuation	21 days after discontinuation	23 days after discontinuation (First)	23 days after discontinuation (Second)	24 days after discontinuation
ALT (IU/L)	157	159	162	133	179
AST (IU/L)	109	106	106	88	135
ALP (IU/L)	512	527	471	—	—
T-Bil (mg/dL)	20.1	21.2	20.4	11.4	19.6
CRE (mg/dL)	0.81	0.99	1.73	—	1.55
LDH (IU/L)	342	370	356	—	—
BUN (mg/dL)	22.2	22.9	38.9	—	38.2
γ-GTP (IU/L)	90	85	62	—	—

5

Revision of Precautions (No. 263)

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 February 17, 2015.

1 Allergic agents-Miscellaneous

Montelukast Sodium

Brand name	Singulair Tablets 5 mg, 10 mg, Singulair Chewable Tablets 5 mg, Singulair Fine Granules 4 mg (MSD K.K.), Kipres Tablets 5 mg, 10 mg, Kipres Chewable Tablets 5 mg, Kipres Fine Granules 4 mg (Kyorin Pharmaceutical Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Thrombocytopenia**: Thrombocytopenia may occur (initial signs and symptoms are bleeding tendency including purpura, epistaxis, and gingival bleeding). If these symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2 Antivirals

Telaprevir

Brand name	Telavic Tablets 250 mg (Mitsubishi Tanabe Pharma Corporation)
Precautions for dosage and administration	A reduced initial dose should be considered in geriatrics or in patients with renal impairment, hypertension, or diabetes mellitus because a risk of serious renal impairment may be increased in these patients. It should be noted that the reduced dose may lower the response rate of hepatitis C virus ribonucleic acid turning undetectable. The balance of risks and benefits should be carefully considered.

List of corrections in the Pharmaceuticals and Medical Devices Safety Information No.320

Page	33
Original	[Brand name] (5) LANSAP 400, 700 (Takeda Pharmaceutical Company Limited)
Revised	[Brand name] (5) LANSAP 400, 800 (Takeda Pharmaceutical Company Limited)

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 a new drug. It is imposed that its MAH is responsible for collecting the ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of March 1, 2015)

◎: Products for which EPPV was initiated after January 2, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	secukinumab (genetical recombination) Cosentyx for S.C. Injection 150 mg Syringe, Cosentyx for S.C. Injection 150 mg	Novartis Pharma K.K.	February 27, 2015
◎	vonoprazan fumarate Takecab Tablets 10 mg, 20 mg	Takeda Pharmaceutical Company Limited	February 26, 2015
◎	vemurafenib Zelboraf Tablets 240 mg	Chugai Pharmaceutical Co., Ltd.	February 26, 2015
◎	rabeprazole sodium Pariet Tablets 5 mg, 10 mg*1	Eisai Co., Ltd.	February 26, 2015
◎	empagliflozin Jardiance Tablets 10 mg, 25 mg	Nippon Boehringer Ingelheim Co., Ltd.	February 24, 2015
◎	streptozocin Zanosar IV Infusion 1 g	Nobelpharma Co., Ltd.	February 23, 2015
◎	fexofenadine hydrochloride Allegra 5% Dry Syrup	Sanofi K.K.	January 19, 2015
◎	alemtuzumab (genetical recombination) MabCampath 30 mg I.V. Infusion	Sanofi K.K.	January 15, 2015
	sirolimus Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	December 22, 2014
	caspofungin acetate Cancidas for Intravenous Drip Infusion 50 mg, 70 mg*2	MSD K.K.	December 18, 2014
	darbepoetin alfa (genetical recombination) Nesp Injection 5 μg Plastic Syringe, 10 μg Plastic Syringe, 15 μg Plastic Syringe, 20 μg Plastic Syringe, 30 μg Plastic Syringe, 40 μg Plastic Syringe, 60 μg Plastic Syringe, 120 μg Plastic Syringe, 180 μg Plastic Syringe*3	Kyowa Hakko Kirin Co., Ltd.	December 18, 2014
	midazolam Midafresa Injection 0.1%	Alfresa Pharma Corporation	December 17, 2014

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
rilpivirine hydrochloride/tenofovir disoproxil fumarate/emtricitabine Complera Combination Tablets	Janssen Pharmaceutical K.K.	December 12, 2014
bosutinib hydrate Bosulif Tablets 100 mg	Pfizer Japan Inc.	December 5, 2014
progesterone Lutinus Vaginal Tablets 100 mg	Ferring Pharmaceuticals Co., Ltd.	December 5, 2014
ripasudil hydrochloride hydrate Glanatec Ophthalmic Solution 0.4%	Kowa Company, Ltd.	December 2, 2014
anhydrous caffeine Respia Injection or oral solution 60 mg	Nobelpharma Co., Ltd.	December 1, 2014
pegfilgrastim (genetical recombination) G-lasta Subcutaneous Injection 3.6 mg	Kyowa Hakko Kirin Co., Ltd.	November 28, 2014
suvorexant Belsomra Tablets 15 mg, 20 mg	MSD K.K.	November 26, 2014
vaniprevir Vanihep Capsules 150 mg	MSD K.K.	November 25, 2014
anagrelide hydrochloride hydrate Agrylin Capsules 0.5 mg	Shire Japan KK	November 25, 2014
tiotropium bromide hydrate Spiriva 2.5 μg Respimat 60 puffs*[4]	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2014
aflibercept (genetical recombination) Eylea Solution Intravitreal Injections 40 mg/mL, Eylea Solution Intravitreal Injections Kit 40 mg/mL*[5]	Bayer Yakuhin, Ltd.	November 18, 2014
Freeze-dried activated human blood coagulation factor VII concentrate containing factor X Byclot for Intravenous Injection	The Chemo-Sero-Therapeutic Research Institute	November 11, 2014
standardized Japanese cedar pollen extract original solution Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL bottle, 2 000 JAU/mL bottle, 2 000 JAU/mL pack	Torii Pharmaceutical Co., Ltd.	October 8, 2014
bimatoprost GlashVista Cutaneous Solution 0.03% 5 mL	Allergan Japan K.K.	September 29, 2014
edoxaban tosilate hydrate Lixiana Tablets 15 mg, 30 mg, 60 mg*[6]	Daiichi Sankyo Company, Limited	September 26, 2014
voriconazole Vfend Tablets 50 mg, 200 mg, Vfend for Intravenous Use 200 mg, Vfend Dry Syrup 2 800 mg*[7]	Pfizer Japan Inc.	September 26, 2014
metronidazole Anaemetro Intravenous Infusion 500 mg	Pfizer Japan Inc.	September 26, 2014
delamanid Deltyba Tablets 50 mg	Otsuka Pharmaceutical Co., Ltd.	September 26, 2014
treprostinil Treprost 20 mg for Injection, 50 mg for Injection, 100 mg for Injection, 200 mg for Injection	Mochida Pharmaceutical Co., Ltd.	September 26, 2014
anti-human thymocyte immunoglobulin, rabbit Thymoglobuline for Intravenous Infusions 25 mg*[8]	Sanofi K.K.	September 19, 2014

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
donepezil hydrochloride Aricept Tablets 3 mg, 5 mg, 10 mg, Aricept D Tablets 3 mg, 5 mg, 10 mg, Aricept Fine Granules 0.5%, Aricept Oral Jelly 3mg, 5mg, 10 mg, Aricept Dry Syrup 1%*9	Eisai Co., Ltd.	September 19, 2014
aflibercept (genetical recombination) Eylea Solution for IVT inj. 40mg/mL, Eylea Solution for IVT inj. Kit 40 mg/mL*10	Bayer Yakuhin, Ltd.	September 19, 2014
calcipotriol hydrate/betamethasone dipropionate Dovobet Ointment	Leo Pharma K.K.	September 12, 2014
eftrenonacog alfa (genetical recombination) Alprolix Intravenous 500, 1000, 2000, 3000	Biogen Idec Japan Ltd.	September 8, 2014
alectinib hydrochloride Alecensa Capsules 20 mg, 40 mg	Chugai Pharmaceutical Co., Ltd.	September 5, 2014
cabazitaxel acetonate Jevtana 60 mg I.V. Infusion	Sanofi K.K.	September 4, 2014
umeclidinium bromide/vilanterol trifenatate Anoro Ellipta 7 doses	GlaxoSmithKline K.K.	September 4, 2014
(1) daclatasvir hydrochloride (2) asunaprevir (1) Daklinza Tablets 60 mg (2) Sunvepra Capsules 100 mg	Bristol-Myers K.K.	September 3, 2014
cysteamine bitartrate Nicystagon Capsules 50 mg, 150 mg	Mylan Seiyaku Ltd.	September 3, 2014
canagliflozin hydrate Canaglu Tablets 100 mg	Mitsubishi Tanabe Pharma Corporation	September 3, 2014
nivolumab (genetical recombination) Opdivo Intravenous Infusion 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	September 2, 2014
ruxolitinib phosphate Jakavi Tablets 5 mg	Novartis Pharma K.K.	September 2, 2014
velaglucerase alfa (genetical recombination) Vpriv Intravenous Injection 400 U	Shire Japan KK	September 2, 2014
abiraterone acetate Zytiga Tablets 250 mg	Janssen Pharmaceutical K.K.	September 2, 2014
efinaconazole Clenafin Topical Solution 10% for Nail	Kaken Pharmaceutical Co., Ltd.	September 2, 2014

*1 An additional indication for "the treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low-doses aspirin"

*2 An additional administration for "pediatrics"

*3 An additional indication for "the treatment of patients with anaemia associated with myelodysplastic syndrome"

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

*5 An additional indication for "the treatment of patients with diabetic macular oedema"

*6 An additional indication for "the reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and the treatment and suppression of relapse for venous thromboembolisms (deep vein thrombosis and pulmonary thromboembolism)," EPPV was initiated in December 8, 2014 for Lixiana 60 mg tablets.

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

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

*9 An additional indication for "the suppression of progression of dimentia symptoms in patients with Lewy body dementia"

*10 An additional indication for "the treatment of choroidal neovascularization in pathologic myopia"

The Drug and Medical Devices Safety Information Reporting System – Reporting via e-Gov was closed

Regarding reports of AR, infections, and malfunctions ((hereinafter referred to as AR reports) for drugs, medical devices, or regenerative medicinal products (hereinafter referred to as pharmaceuticals) based on the provisions of Article 68-10, Paragraph 2 of the Act on Securing Quality, Efficacy, and Safety of Pharmaceuticals, Gene Therapy Products, and Cosmetics (Act No. 145, 1960; hereinafter referred to as Act), we are grateful to you for your continuous understanding and cooperation.

AR reports have been received via postal mail, FAX, e-Gov for electronic application, and e-mail, but in light of the recent use status (there have been no uses of e-Gov since FY 2009), the reception of reports via e-Gov was closed on March 31, 2015 (Tuesday).

Accordingly, the "Precautions for Reporting," etc. in the report form has partially changed. (It will be inserted at the end of the April issue and thereafter).

Medical and pharmaceutical providers are encouraged to report serious AR, infections, and malfunctions they have found in their daily practice by postal mail, fax, or e-mail.

✓ Handling of Personal Information

Regarding handling of personal information when medical and pharmaceutical providers cooperate for collection of information (Article 68-2, Paragraph 2 of the Act) when reports of AR are made under the Drugs and Medical Devices Safety Information Reporting System or when reports of AR are made by MAHs, etc., limitations depending on intended uses and limitations of provisions to third parties under the Act on the Personal Information Protection (Act No. 57, 2003) will not apply as cases under the Act. We appreciate your proactive cooperation.

[References] PMDA website

✓ Reports by healthcare professionals (request for ADR/adverse reaction/infections/malfunction reporting)
http://www.pmda.go.jp/safety/reports/hcp/0001.html (only available in Japanese language)

✓ How to report and report form
http://www.pmda.go.jp/safety/reports/hcp/pmd-act/0002.html (only available in Japanese language)

Contact information for reporting pharmaceutical and medical device safety information

Address to	Safety Information Division, Office of Safety I, PMDA
Mail	Shin-Kasumigaseki Bldg. 3□3□2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013
FAX	0120–395–390 (Toll free in Japan)
E-mail	anzensei-hokoku@pmda.go.jp

Notice

The Pharmaceuticals and Medical Devices Agency has (PMDA) completely redesigned its website. The URL of the top page after the complete redesign is as follows.
http://www.pmda.go.jp/

Please cooperate for the Relief Systems for Sufferers!

Relief System for Sufferers from AR

- This system is a public system based on the Act on the Pharmaceuticals and Medical Devices Agency.
- If adverse health effects including AR leading to hospital admission despite properly using drugs, relief benefits such as medical expenses, medical benefits, a disability pension, and a bereaved family pension will be provided.
- If AR were reported, healthcare professionals should provide information regarding the Relief Systems to the patient (or bereaved family) and also cooperate for preparing a medical certificate, etc. to be attached to the written request.

Relief System for Sufferers from Disease Infected from Biological Products

- This system is a public system based on the Act on the Pharmaceuticals and Medical Devices Agency.
- If adverse health effects including disease caused by infections leading to hospital admission despite properly using biological product on or after April 1, 2004, relief benefits such as medical expenses, medical benefits, a disability pension, and a bereaved family pension will be provided.
- If infection, etc. that seems to have been caused by a biological product were reported, healthcare professionals should provide information regarding the Relief Systems to the patient (or bereaved family) and also cooperate for preparing a medical certificate, etc. to be attached to the written request.

We will send you a leaflet that describes the mechanism of the system and the request form at no charge. (Only available in Japanese language)

Pharmaceuticals and Medical Devices Agency

Shin-Kasumigaseki Bldg. 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013

0120-149-931 (Toll free in Japan)

http://www.pmda.go.jp/

E-mail:kyufu@pmda.go.jp

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