Pharmaceuticals and Medical Devices Safety Information

No. 313 May 2014

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

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This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 313 May 2014

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

[Outline of Information]

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1	**Fatal cases with XEPLION® Aqueous Suspension for IM injection**	*C* *P*	A total of 21 fatal cases have been reported following antipsychotic XEPLION administration since the launch of XEPLION on November 19, 2013 up to April 16, 2014 during Early Post-marketing Phase Vigilance. The MHLW/PMDA was aware of cases involving improper use of XEPLION, although the causes of death have not been established due to insufficient information. The MHLW required a marketing authorization holder of XEPLION to revise the Precautions section in the package insert and to circulate a Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue letter). Details are presented in this section.	4
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D: Distribution of Dear Healthcare Professional Letters *P*: Revision of Precautions *C*: Case Reports

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

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

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

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

Abbreviations

ADRs	Adverse drug reactions
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information

1

Fatal cases with XEPLION® Aqueous Suspension for IM injection

Active ingredient	Paliperidone palmitate
Brand Name (name of company)	XEPLION Aqueous Suspension for IM injection 25 mg, 50 mg, 75 mg, 100 mg, 150 mg (Janssen Pharmaceutical K.K.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

1. Introduction

XEPLION Aqueous Suspension for IM injection (XEPLION) containing paliperidone palmitate as an active ingredient is designed for once-a-month intramuscular injection. Paliperidone palmitate is hydrolyzed into paliperidone, an active metabolite, mainly by serine esterase at the injection site before entering into the circulation to exert its pharmacologic action. XEPLION was approved in the United States in July 2009 and in Europe in March 2012. In Asia, XEPLION has been approved in China, South Korea, Singapore, and Thailand. In Japan, XEPLION was approved for the indication of schizophrenia on September 20, 2013.

In the Early Post-marketing Phase Vigilance (EPPV) of XEPLION, which started after the launch on November 19, 2013, 21 fatal cases have been reported during the first 5 months (as of April 16, 2014; the number of users estimated by the marketing authorization holder [MAH] is approximately 10 900 patients). The causes of death in the reported fatal cases have not been established due to insufficient information and the causal relationship between death and XEPLION use is unknown. After the discussion among Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), and relevant specialist physicians at the first meeting of 2014 Subcommittee on Drug Safety of Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council on April 17, 2014 (hereinafter referred to as the Subcommittee on Drug Safety), the MHLW determined that it is necessary to further ensure proper use of XEPLION. The MHLW required the MAH of XEPLION to revise the Precautions section in the package insert and to circulate a Dear Healthcare Professionals Letter of Rapid Safety Communication (Blue Letter) on the same day. Details are described in the following sections.

2. Background

Since the launch of XEPLION on November 19, 2014, the MAH has conducted the EPPV and fatal cases where a causal relationship with XEPLION is unknown have been reported. The MAH provided information on 2 fatal cases included in an interim EPPV report and distributed a document to request proper use of XEPLION to medical institutions in February 2014.

But further fatal cases including sudden deaths were reported. In March, the MAH provided information on 7 fatal cases and a document to request for proper use of XEPLION and immediate reporting of adverse drug reactions (ADRs) to medical institutions under the instructions of PMDA. The MAH also voluntary changed the sentence from “Unexplained sudden deaths have been reported during the treatment with a similar drug” to “Unexplained sudden deaths have been reported during the treatment with XEPLION” in the Other Precautions section of the package insert under the instructions of PMDA.

After the number of XEPLION-related fatal cases reached 17 on April 4, the PMDA/MHLW instructed the MAH to provide specific information on the fatal cases and precautions to be used based on the characteristics of the 4-week sustained-release injection to healthcare professionals, although the causal relationship between death and XEPLION use was unknown. The MHLW discussed the safety measures of XEPLION at the Subcommittee on Drug Safety on April 17.

At the Subcommittee on Drug Safety, 20 fatal cases excluding 1 case reported on the previous day were reviewed by MHLW, PMDA, and relevant specialist physicians. Possible cause of death and clinical course varied among the cases, information on clinical course to death was unknown in many cases, and the causal relationship between death and XEPLION use is unknown. However, the MHLW/PMDA was aware of cases involving improper use of XEPLION and determined that revision of the Precautions was necessary. Distribution of a Blue Letter was also scheduled to further ensure proper use of XEPLION.

3. Fatal cases during the use of XEPLION Aqueous Suspension for IM injection

Details of 3 of the fatal cases reviewed for the preparation of precautions to ensure proper use of XEPLION are shown below. Some specific situations or concomitant drugs are underlined because they should have been taken into consideration in the treatment with XEPLION and the proper use is specifically requested in the Blue Letter.

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Schizophrenia (hepatitis C, hypertension, hepatic function abnormal)	75 mg (twice)	The male patient had a medium height/weight and consumed alcohol (amount unknown, presumably a heavy drinker). Systolic blood pressure of more than 200 mmHg had persisted at one time in the past. Considering that schizophrenia relapsed many times and that the treatment of complications required a number of medications, <u>the general condition of the patient had been poor and the underlying disorder had been unstable.</u> Blood pressure would increase sometimes when the oral medication was discontinued. Approximately 12 years and 6 months before administration: The patient was diagnosed with schizophrenia. He was repeatedly admitted to and discharged from hospital for schizophrenia. The treatment had been switched to risperidone sustained-release suspension for injection several years earlier because the patient might have had poor compliance with oral antipsychotics after the patient finished group therapy and started to live alone. Approximately 1 month and a half before administration: Risperidone sustained-release suspension for injection 37.5 mg was administered 14 days before administration: The dose of risperidone sustained-release suspension for injection was reduced to 25 mg (last dose of risperidone sustained-release suspension for injection). Date unknown: <u>Aggravation of underlying disorder</u> (talkativeness) was noted.

				Day 1 of administration: Due to the symptom aggravation after the dose reduction of risperidone sustained-release suspension for injection, treatment with XEPLION 75 mg, which is equivalent to risperidone sustained-release suspension for injection 37.5 mg (higher dose), was started. Day 32 of administration: XEPLION 75 mg was injected (second dose). Both first and second injections were given to the deltoid muscle. After the second injection, the patient did not visit the hospital before his death. Day 40 of administration (day of onset): The patient was found dead in his home by his family. No further information is available.
	Concomitant medications: zotepine, ursodeoxycholic acid, atenolol, candesartan cilexetil, valsartan, sodium valproate, kallidinogenase, trichlormethiazide			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Schizophrenia (hypotension, arrhythmia)	150 mg (twice)	The patient had been admitted to hospital 4 times before she started to use risperidone sustained-release suspension for injection. Yearly the patient had received health check-ups at another clinic and the check-ups had found no abnormality. Date unknown: The patient started receiving midodrine hydrochloride 4 mg/day, olanzapine 17.5 mg/day, and quetiapine fumarate 400 mg/day. Approximately 3 years and 4 months before administration: Treatment with risperidone sustained-release suspension for injection 50 mg/2 weeks was started. The patient had not been admitted to hospital after starting risperidone sustained-release suspension for injection. Approximately 3 years before administration: A health check-up found suspected arrhythmia. A detailed examination was performed at an internal medicine department in the nearby hospital, results showed no abnormality, and no treatment was given. 14 days before administration: Risperidone sustained-release suspension for injection 50 mg was administered (the last dose before switching to XEPLION). Day 1 of administration: Treatment with XEPLION 150 mg was started. Injection site was deltoid muscle. No abnormality was noted before or after injection. Day 28 of administration: XEPLION 150 mg was administered. Injection site was deltoid muscle. The dose of olanzapine was reduced to 15 mg. Day 34 of administration (day of onset): Myocardial infarction developed. The patient was found in cardio-respiratory arrest in the bathroom. She died of myocardial infarction.
	Concomitant medications: midodrine hydrochloride, olanzapine, quetiapine fumarate, clonazepam, sodium valproate, sennoside, levomepromazine maleate, promethazine hydrochloride, pantethine, senna leaf/senna fruit, magnesium oxide, daikenchuto, mosapride citrate hydrate, biperiden hydrochloride, distigmine bromide			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 50s	Schizophrenia (hypertension, obesity, diabetes mellitus, extrapyramidal symptom)	150 mg (once) 100 mg (once) 150 mg (once)	Body mass index was 41.2. The patient lived with his family. Treatment adherence was relatively good. Overall, persecutory delusion (ex. his mind is read by others, someone is watching him), extrapyramidal symptoms (tremble), and psychiatric symptoms were stable. The patient had been admitted to this hospital 3 times. Approximately 30 years before administration: The patient visited this hospital for the first time. The patient was initially diagnosed as depression but later as schizophrenia. Approximately 9 years and 7 months before administration: Treatment with risperidone tablet 6 mg was started. Approximately 1 year and 9 months before administration: The dose of risperidone was increased to 12 mg. Treatment with paliperidone extended-release tablet 6 mg was started. Approximately 1 year and 8 months before administration: The dose of risperidone was reduced to 9 mg. The dose of paliperidone extended-release tablet was increased to 12 mg. Day 1 of administration: Treatment with XEPLION 150 mg was started (initial dose; administration site, deltoid muscle) 7 days after administration: XEPLION 100 mg was administered (second dose; administration site, deltoid muscle) The dose of risperidone was reduced to 6 mg. 35 days after administration: During the visit, he complained of auditory hallucinations (clicking sounds). XEPLION 150 mg was administered (third dose; administration site, right deltoid muscle) because the extrapyramidal symptoms (tremble) had improved. The dose of risperidone was reduced to 5 mg. The patient did not have other complaints. Date unknown: Symptom of “having shortness of breath when walking” was found. Date unknown: The patient visited an internal medicine department in another hospital for the above symptom. Electrocardiogram and X-ray showed no abnormality. The patient went home. 42 days after administration: The patient visited this hospital and talked about the above symptom during the interview. 43 days after administration (day of onset): The patient was found in cardio-respiratory arrest by his family. In the morning, emergency services notified that the patient had been found in cardio-respiratory arrest and was

				transporting to hospital by ambulance. An hour and a half later, it had been reported that the patient was transported to another hospital but died.
	Concomitant medications: paliperidone extended-release tablet, risperidone tablet, lithium carbonate, biperiden hydrochloride, mequitazine, lorazepam, triazolam, eszopiclone, sodium picosulfate hydrate, yokukansan, sennoside, telmisartan, allopurinol, fenofibrate, metformin hydrochloride, extended-release tolterodine tartrate			

4. Proper use of XEPLION Aqueous Suspension for IM injection

The Subcommittee on Drug Safety found the following facts in the reported 20 fatal cases: (1) use of XEPLION in patients with unstable physical conditions, (2) suspected XEPLION overdose after switching from risperidone sustained-release suspension for injection (a similar drug), and (3) concomitant use of XEPLION with other antipsychotics from the start of administration despite its rapid increase of blood concentration. Please pay attention to the following points to further ensure proper use of XEPLION.

(1) XEPLION should not be administered in patients who are rapidly agitated, or in unstable patients that are likely to require concomitant use of many types of antipsychotics.
Sustained-release antipsychotics are generally used to manage relapsing of psychotic symptoms. Once XEPLION is injected, it is not possible to eliminate the drug immediately from the body. Therefore, somatic symptoms of patients should be checked and the necessity of treatment with XEPLION should be fully assessed before starting treatment with XEPLION, and due attention should be paid to the prevention and treatment of adverse reactions and overdose, etc.

(2) The main active metabolite of both XEPLION and risperidone is paliperidone (9-hydroxy risperidone).
Caution should be exercised in dosage and administration to avoid overdose when switching from risperidone sustained-release suspension for injection (Risperdal Consta® Intramuscular Injection) to XEPLION.
The following administration methods are estimated to maintain approximately as the same active metabolite levels as in steady state of Risperdal Consta Intramuscular Injection.

Risperdal Consta	→	XEPLION
25 mg every 2 weeks	→	50 mg every 4 weeks
50 mg every 2 weeks	→	100 mg every 4 weeks

(3) For patients who have never been treated with paliperidone or risperidone, stability of symptoms with oral paliperidone or oral risperidone for a certain period should be established prior to initiating treatment with XEPLION. XEPLION treatment should be started without concomitant use of oral paliperidone or oral risperidone.
Risperdal Consta Intramuscular Injection, which has the same active ingredients as XEPLION, takes 3 weeks or more from first administration to have significant release of medication with efficacy continuing for 2 weeks. During the first three weeks, therefore, oral antipsychotics are concomitantly used.
However, since XEPLION increases its plasma concentrations from first administration, concomitant use of other antipsychotics should be avoided during XEPLION treatment.

5. Closing comments

For the revision to Precautions of the package insert, for which MHLW gave instruction to the MAH in addition to the distribution of Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter), please see page 10 of this document (2. Important Safety Information).

Many of the reported fatal cases provide no information on the clinical course to death; in some cases unexplained sudden death was reported while in some others the patient was found dead. Therefore, the causal relationship between death and XEPLION use is unknown at the moment. Healthcare professionals should thoroughly understand the prolonged-action of XEPLION prior to use of this drug, use XEPLION only in patients with relatively stable symptoms, monitor the patient carefully after using XEPLION, promptly take measure against any abnormalities, and instruct the patient, family and/or caretaker to visit a medical institution immediately if any abnormalities are observed. Healthcare professionals are encouraged to continuously cooperate for proper use of drugs.

<Reference>

Materials for Subcommittee on Drug Safety of Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the first meeting in 2014)
http://www.mhlw.go.jp/stf/shingi/0000043934.html (only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated April 17, 2014, the contents of important revisions are provided in this section.

1 Paliperidone Palmitate

Brand Name (name of company)	XEPLION Aqueous Suspension for IM injection 25 mg, 50mg, 75 mg, 100 mg, and 150 mg (Janssen Pharmaceutical K.K.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

PRECAUTIONS (underlined parts are revised)

Precautions for Dosage and Administration

For patients who have never been treated with paliperidone or risperidone, response to therapy and tolerability with oral paliperidone or oral risperidone should be established for a certain period prior to initiating treatment with this drug. This drug should be started without concomitant use of oral paliperidone or oral risperidone.

When switching from another prolong-acting injectable antipsychotic to this drug, due attention should be paid for the timing and dosage with consideration for pharmacokinetics of drugs, and patients should be carefully monitored for their symptoms.

The main active metabolite of both this drug and risperidone is paliperidone. Caution should be exercised in dosage and administration to avoid overdose when switching from risperidone sustained-release suspension for injection to this drug.

The following administration methods are estimated to maintain approximately as the same active metabolite levels as in steady state of risperidon sustained-release suspension for injection. (See "PHARMACOKINETICS")

- Administering paliperidone sustained-release suspension for injection 50 mg at 4-week intervals after two weeks from the last dose of risperidone sustained-release suspension for injection 25 mg to a patient who was treated with risperidone sustained-release suspension for injection 25 mg at 2-week intervals
- Administering paliperidone sustained-release suspension for injection 100 mg at 4-week intervals after two weeks from the last dose of risperidone sustained-release suspension for injection 50 mg to a patient who was treated with risperidone sustained-release suspension for injection 50 mg at 2-week intervals

Important Precautions

Since sustained-release antipsychotics are generally used to manage relapsing psychiatric symptoms. This drug should not be administered in patients who are rapidly agitated, or in unstable patients that are likely to require concomitant use of many types of antipsychotics. Once this drug is injected, it is not possible to eliminate the drug immediately from the body. Therefore, the necessity of treatment with this drug should be fully assessed before starting treatment with this drug, and due attention should be paid to the prevention and treatment of adverse reactions, and overdose, etc. [See "Precautions for Dosage and Administration", "Adverse Reactions", and "Overdose."]

Reference Information

Launched in Japan: November 2013

3

Revision of Precautions (No. 256)

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 April 23, 2014.

1

Antiprotozoans

Pentamidine Isetionate

Brand Name	Benambax 300 mg for Injection (Sanofi K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Hypotension, prolonged QT, ventricular arrhythmia, and/or severe bradycardia**: Serious hypotension, prolonged QT, and/or ventricular arrhythmia (including torsades de pointes) may occur. If these symptoms are observed, administration of this drug should be discontinued immediately and permanently. Severe bradycardia may also occur. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of May 1, 2014)

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

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Trastuzumab Emtansine (Genetical Recombination) KADCYLA Intravenous Infusion 100 mg, 160 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2014
◎	Riociguat Adempas tablets 0.5 mg, 1.0 mg, 2.5 mg	Bayer Yakuhin, Ltd.	April 18, 2014
◎	Levocetirizine Hydrochloride Xyzal Syrup 0.05%	GlaxoSmithKline K.K.	April 17, 2014
◎	Dolutegravir Sodium Tivicay Tablets 50 mg	ViiV Healthcare K.K.	April 17, 2014
◎	Brentuximab Vedotin (Genetical Recombinatin) ADCetris for Intravenous Infusion 50 mg	Takeda Pharmaceutical Company Limited	April 17, 2014
◎	Ipragliflozin L-Proline Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	April 17, 2014
◎	Tadalafil Zalutia Tablets 2.5 mg, 5 mg	Eli Lilly Japan K.K.	April 17, 2014
	Tolvaptan Samsca tablets 7.5 mg, 15 mg*1	Otsuka Pharmaceutical Co., Ltd.	March 24, 2014
	Fluticasone Furoate Allermist 27.5μg 56 metered Nasal Spray*2	GlaxoSmithKline K.K.	March 17, 2014
	Pazopanib Hydrochloride Votrient Tablets 200 mg*3	GlaxoSmithKline K.K.	March 17, 2014
	Mogamulizumab (Genetical Recombination) POTELIGEO Injection 20 mg*4	Kyowa Hakko Kirin Co., Ltd.	March 17, 2014
	Cinacalcet Hydrochloride REGPARA TABLETS 25 mg, 75 mg*5	Kyowa Hakko Kirin Co., Ltd.	February 21, 2014
	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*6	Novartis Pharma K.K.	February 21, 2014

	pH-4 Treated Acid Normal Human Immunoglobulin (Subcutaneous injection) Hizentra 20% S.C. Injection 1 g/5 mL, 2 g/10 mL, 4 g/20 mL	CSL Behring K.K.	January 30, 2014
	Ioflupane (^{123}I) DaTSCAN Injectable	Nihon Medi-Physics Co., Ltd.	January 27, 2014
	Talaporfin Sodium LASERPHYRIN 100 mg FOR INJECTION*[7]	Meiji Seika Pharma Co., Ltd.	January 20, 2014
	Meropenem Hydrate (1) Meropen Vial for Intravenous Drip Infusion 0.25 g, 0.5 g (2) Meropen Kit for Intravenous Drip Infusion 0.5 g*[8]	Dainippon Sumitomo Pharma Co., Ltd.	December 20, 2013
	Methylphenidate Hydrochloride Concerta Tablets 18 mg, 27 mg*[9]	Janssen Pharmaceutical K.K.	December 20, 2013
	Laninamivir Octanoate Hydrate INAVIR DRY POWDER INHALER 20 mg*[10]	Daiichi Sankyo Company, Limited	December 20, 2013
	Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg*[11]	Janssen Pharmaceutical K.K.	December 20, 2013
	Fentanyl Citrate Abstral Sublingual Tablets 100 μg, 200 μg, 400 μg	Kyowa Hakko Kirin Co., Ltd.	December 12, 2013
	Vilanterol Trifenatate/Fluticasone Furoate Relvar 100 Ellipta 14 doses, Relvar 200 Ellipta 14 doses	GlaxoSmithKline K.K.	December 9, 2013
	Talc Unitalc Intrapleural 4 g	Nobelpharma Co., Ltd.	December 9, 2013
	Simeprevir Sodium SOVRIAD capsules 100 mg	Janssen Pharmaceutical K.K.	December 6, 2013
	Epinastine Hydrochloride ALESION Ophthalmic Solution 0.05%	Santen Pharmaceutical Co., Ltd.	November 25, 2013
	Acetaminophen acelio Intravenous Injection 1000 mg	Terumo Corporation	November 25, 2013
	Landiolol Hydrochloride ONOACT 50 for Injection*[12]	Ono Pharmaceutical Co., Ltd.	November 22, 2013
	Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL*[13], EYLEA solution for IVT inj. Kit 40 mg/mL*[13]	Bayer Yakuhin, Ltd.	November 22, 2013
	Topiramate TOPINA Tablets 25 mg, 50 mg, 100 mg*[14]	Kyowa Hakko Kirin Co., Ltd.	November 22, 2013
	Indacaterol Maleate/Glycopyrronium Bromide ultibro inhalation capsules	Novartis Pharma K.K.	November 20, 2013
	Tafamidis Meglumine Vyndaqel capsules 20 mg	Pfizer Japan Inc.	November 20, 2013
	Fluticasone Propionate/Formoterol Fumarate Hydrate Flutiform 50 Aerosol 56 puffs, 125 Aerosol 56 puffs	Kyorin Pharmaceutical Co., Ltd.	November 19, 2013
	Brinzolamide/Timolol Maleate AZORGA Combination Ophthalmic	Alcon Japan Ltd.	November 19, 2013

	Suspension		
	Paliperidone Palmitate	Janssen Pharmaceutical K.K.	November 19, 2013
	XEPLION Aqueous Suspension for IM Injection Syringe 25 mg, 50 mg, 75 mg, 100 mg, 150 mg		
	Darbepoetin Alfa (Genetical Recombination)	Kyowa Hakko Kirin Co., Ltd.	September 13, 2013
	NESP INJECTION 5 μg PLASTIC SYRING, 10 μg PLASTIC SYRING, 15μg PLASTIC SYRINGE, 20 μg PLASTIC SYRINGE, 30 μg PLASTIC SYRINGE, 40 μg PLASTIC SYRINGE, 60 μg PLASTIC SYRINGE, 120 μg PLASTIC SYRINGE, 180 μg PLASTIC SYRINGE*15		

*1 An additional indication for "the control of disease progression in patients with autosomal dominant polycystic kidney who already had increased kidney volume and whose kidney volume was further rapidly increasing"

*2 An additional administration for "pediatrics"

*3 An additional indication for "the treatment of patients with radically unresectable or metastatic renal cell carcinoma"

*4 An additional indication for "the treatment of patients with relapsed or refractory CCR4-positive peripheral T-cell lymphoma, and patients with relapsed or refractory CCR4-positive cutaneous T-cell lymphoma"

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

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

*7 An additional indication for "the treatment of patients with primary malignant brain tumour (only in patients who undergo tumourectomy)"

*8 An additional administration for "pyogenic meningitis"

*9 An additional administration for "patients aged 18 years or older"

*10 An additional indication for "the prophylaxis of influenza A or B virus infection"

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

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

*13 An additional indication for "the treatment of patients with macular oedema following central retinal vein occlusion"

*14 An additional administration for "pediatrics"

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

List of corrections in the Pharmaceuticals and Medical Devices Safety Information No.312

Page	10
Original	TAXOL INJECTION 30 mg, 100 mg (Bristol-Myers K.K.)
Revised	TAXOL INJECTION 30 mg, 100 mg (Bristol-Myers K.K.) and the others