Pharmaceuticals and Medical Devices Safety Information

No. 287 January 2012

rev.1*

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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) website (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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*Correction to the list in "3. List of Products Subject to Early Post-marketing Phase Vigilance."

Pharmaceuticals and Medical Devices Safety Information
No. 287 January 2012

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

[Outline of Information]

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

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

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

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

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

Abbreviations

ADRs	Adverse drug reactions
CPAP	Continuous positive airway pressure
DLST	Drug lymphocyte stimulation test
EM major	Erythema multiforme major
EPPV	Early Post-marketing Phase Vigilance
JIMGA	Japan Industrial and Medical Gases Association
LTOT	Long-term oxygen therapy
MAH	Marketing authorization holder
VPA	Sodium valproate

1

Lamotrigine-induced Severe Drug Eruption and Compliance with Dosage and Administration

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Lamotrigine	Lamictal Tablets 2 mg For Children, Lamictal Tablets 5 mg For Children, Lamictal Tablets 25 mg, 100 mg (GlaxoSmithKline K.K.)
Therapeutic Category	Antiepileptics, psychotropics	
Indications	Concomitant therapy with antiepileptics for the following types of seizure in epileptic patients who do not sufficiently respond to other antiepileptics Partial seizure (including secondary generalized seizure), tonic-clonic seizure, and generalized seizure associated with Lennox-Gastaut syndrome Suppression of recurrent/relapsed mood episodes in patients with bipolar disorder	

1. Introduction

Lamotrigine was approved as a treatment for epilepsy in October 2008, and the additional indication for “suppression of recurrent/relapsed mood episodes in patients with bipolar disorder” was approved in July 2011. According to the MAH, an estimated cumulative 92,000 patients (approximately 62,000 patients with epilepsy and approximately 30,000 patients with bipolar disorder) have used lamotrigine since the initial marketing in December 2008 until October 2011.

The “WARNINGS,” “Important Precautions,” and “Clinically Significant Adverse Reactions” sections of the lamotrigine package insert include alerts against serious skin disorders such as oculomucocutaneous syndrome and toxic epidermal necrolysis since its initial marketing.

Since a high incidence of skin disorders has been reported in cases where lamotrigine is administered at a dose exceeding the authorized dosage, the “Precautions of Dosage and Administration” section also alerts healthcare professionals to carefully select concomitant drugs and comply with the "Dosage and Administration." However, many cases of serious skin disorders involving noncompliance with the "Dosage and Administration" have been still reported.

Accordingly, MHLW required MAHs to issue further alerts. PMDA has been also providing information to healthcare professionals for proper use of lamotrigine. Details are described below.

2. Dosage and administration of lamotrigine and occurrence of skin disorders

Skin disorders associated with lamotrigine reported in epileptic patients receiving lamotrigine/sodium valproate (VPA) in the Japanese clinical trials are shown in Table 1. The incidence of skin disorders was 10.4% (18/173) in patients receiving dose exceeding the authorized dose of lamotrigine and 2.9% (3/102) in those receiving the authorized dose. This suggests the use of a dose exceeding authorized dose of lamotrigine is one of the risk factors for increased occurrence of skin disorders. Therefore, compliance with the approved "Dosage and Administration" is important.

Table 1 Occurence of skin disorders reported in Japanese clinical trials
(See the lower table for the specific doses)

	Dose exceeding the authorized dose (concomitant with VPA)	Authorized dose (concomitant with VPA)
Number of cases of skin disorders[Note 1]	Serious 5 Non-serious 10 Unknown 3	Serious 1 Non-serious 2
Incidence of skin disorders (number of cases/number of cases analyzed)	10.4% (18/173)	2.9% (3/102)

Note 1: All reported cases of rash, including enanthema

Lamotrigine doses in the clinical trials (concomitant with VPA)

	Dose exceeding the authorized dose (concomitant with VPA)	Authorized dose (concomitant with VPA)
In children	0.2 mg/kg/day (Week 1-2) 0.5 mg/kg/day (Week 3-4) ≥1 mg/kg/day (Week 5-8) ≤ 5 mg/kg/day or ≤ 3 mg/kg/day (Week 9-12)	0.15 mg/kg/day (Week 1-2) 0.3 mg/kg/day (Week 3-4) Gradually increased by ≤ 0.3 mg/kg/day every 1 or 2 weeks (Week 5 or later) 1-3 mg/kg/day (up to 200 mg) (maintenance dose)
	Concomitant use of VPA and drug(s) that induces glucuronidation of lamotrigine 0.5 mg/kg/day (Week 1-2) 1 mg/kg/day (Week 3-4) ≥2 mg/kg/day (Week 5-8) ≤ 5 mg/kg/day (Week 9-12)	0.15 mg/kg/day (Week 1-2) 0.3 mg/kg/day (Week 3-4) Gradually increased by ≤ 0.3 mg/kg/day every 1 or 2 weeks (Week 5 or later) 1-5 mg/kg/day (up to 200 mg) (maintenance dose)
In adults	<Trial 1> Initial dose was 50 mg/day; the dose was increased every 2 weeks (weekly increase was permitted in inpatients) up to maintenance dose (maximum daily dose; 200 mg/day). The treatment was continued at the maintenance dose for 8 weeks. <Trial 2> Initial dose was 25 mg/day; the dose was adjusted up to 150 mg/day. <Trial 3> (i) Concomitant use of VPA and at least one drug that induces glucuronidation Initial dose was 25 mg/day; the dose was increased every 4 weeks (the initial dose was changed at Week 2). The treatment was continued at the maintenance dose for 8 weeks. (maximum daily dose) (ii) Concomitant use of VPA only Initial dose was 25 mg on alternate days; the dose was increased every 4 weeks (the initial dose was changed at Week 2). The treatment was continued at the maintenance dose for 8 weeks (maximum daily dose).	12.5 mg/day (25 mg on alternate-days administration) (Week 1-2) 25 mg/day (Week 3-4) Gradually increased by 25-50 mg every 1 or 2 weeks (Week 5 or later) 100-200 mg/day (maintenance dose)

3. Case summaries

Cases of oculomucocutaneous syndrome that developed after administration of lamotrigine are presented below.

Case 1

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
Female 30s	Epilepsy (none)	25 mg (alternate-day) for 14 days ↓ 25 mg for 7 days ↓ 50 mg for 16 days	**Stevens-Johnson syndrome** Day 1 of administration: The patient started receiving lamotrigine. Day 36 of administration: Generalised pruritus and hot feeling developed. Day 37 of administration (day of discontinuation): Administration of lamotrigine was discontinued. 1 day after discontinuation: The patient visited the dermatology department at the same hospital. The patient was admitted to the hospital for suspected drug eruption. After admission, steroid pulse therapy (drip infusion of methylprednisolone 500 mg/day) was performed. 3 days after discontinuation: Steroid pulse therapy (drip infusion) was completed. Infusion was switched to oral administration (prednisolone 60 mg/day). Convulsive seizure occurred. 4 days after discontinuation: Oral administration of zonisamide and gabapentin was started. Steroid pulse therapy was performed again. 16 days after discontinuation: Drug eruption gradually remitted and the patient was discharged from the hospital. 21 days after discontinuation: The patient started outpatient treatment. <Dermatological findings> Specific symptom: erythema multiforme Mucosal findings - Site: lips; Detail of symptom: fissures at corners of the mouth. Ratio of lesion to body surface area: approximately 90% Skin biopsy: erythema multiforme <Diagnosis> Erythema multiforme (EM) major Dermatologist's comment: It may be attributed to concomitant use of lamotrigine and valproic acid. Pyrexia of 37.3°C Drug lymphocyte stimulation test (DLST): positive
Concomitant medications (suspected drug): sodium valproate			

Case 2

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
Female 20s	Bipolar II disorder (none)	12.5 mg (alternate-day) for 9 days ↓ 25 mg for unknown duration	**Stevens-Johnson syndrome** Day 1 of administration: The patient started receiving lamotrigine for bipolar II disorder (12.5 mg/day). Day 10 of administration: The dose of lamotrigine was increased to 25 mg/day. Day 16 of administration: The patient started to have red eyes. Day 17 of administration: The lips became swollen and numb. The patient visited an emergency hospital. Ophthalmic medication and antibiotic were prescribed for suspected bacterial infection. Day 18 of administration: Symptoms generally worsened. The eye symptoms improved slightly, probably because of response to the ophthalmic solution. Day 20 of administration: The patient visited Hospital A (general medicine). Bacterial infection was suspected. Day 21 of administration: After visiting Hospital B (internal medicine), the patient visited the internal medicine department at Hospital C. After that, the patient visited the dermatology department at Hospital C. The patient was found to have Stevens-Johnson syndrome, and she was admitted to the hospital. Numbness developed in the tips of her hands. After admission, steroid therapy was started. Day 36 of administration: Stevens-Johnson syndrome remitted. The patient was discharged from Hospital C. <Mucosal findings> Eye, eyelid lesions: hyperaemia, eye discharge Lip, oral lesions: erosion, scab Vulval lesion: unknown Diagnosis: Stevens-Johnson syndrome Treatment: intravenous drip infusion and oral administration of steroids History of drug allergy: none Recent development of infection: none Concomitant medications: anticonvulsant Pyrexia: unknown According to the patient, pyrexia occurred (+) before Day 21 of administration, but her temperature was continuously in the normal range after admission on Day 21 of administration. Ratio of skin lesion to overall body surface area: approximately 10% Skin biopsy: A chest skin biopsy showed only mild lymphocytic infiltration around blood vessels in the superficial dermis. DLST: negative
Concomitant medications (suspected drugs): sodium valproate, lithium carbonate, milnacipran hydrochloride, fluvoxamine maleate, flunitrazepam			

4. Safety measures

Some of the reported cases involved patients who did not seek treatment immediately despite their awareness of the initial symptoms of serious skin disorders after administration of lamotrigine. Others involved patients for whom treatment was delayed due to lack of appropriate diagnosis.

Based on the review of reported cases, the following information has been newly provided.

1. Thoroughly comply with "Dosage and Administration"
   - ✓ The maximum daily dose should not be exceeded.
   - ✓ Dose increase should not be attempted earlier than the specified timing.
   - ✓ When using lamotrigine with VPA, the treatment should be given every other day rather than everyday for the first 2 weeks. (in adults only)
2. Ensure patients are given medication instructions about possible serious skin disorders:
   - ✓ Adverse reactions such as serious skin disorders may occur.
   - ✓ The patient should see his/her doctor immediately if he/she has any initial symptoms of a serious skin disorder.
   - ✓ The dosage and administration should be adhered to.

<Initial symptoms>

Ocular hyperaemia	Pharynx pain	Sore lips/ oral sore
Pyrexia (≥ 38°C)	General malaise	Rash

5. Provision of information and future actions

MHLW required MAHs to provide healthcare professionals with information on possible adverse reactions to lamotrigine. The MAH has been directly providing written alerts to healthcare professionals since December 2011. The same alerts have been also provided in “Information for Proper Use of Drug from the MAH” on the PMDA website, along with presentations of materials for promotion of proper drug use.

The PMDA has been requiring healthcare professionals to ensure compliance with the dosage and administration of lamotrigine and patient instructions in “PMDA Alert for Proper Use of Drug” on its website. Healthcare professionals are encouraged to advise patients and their families to see their doctor immediately when any initial symptoms of a serious skin disorder appears during the treatment with lamotrigine and to confirm their understanding of the advice.

See the PMDA website for details.

http://www.info.pmda.go.jp/iyaku_info/oshirase_index.html

Table 2 Approved "Dosage and Administration" of lamotrigine

Concomitant use of antiepileptics in epileptic patients (adult)

	Concomitant use of VPA	No concomitant use of VPA	
		(1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 1)]	(2) Concomitant use of other antiepileptic(s)[Note 2)]
Week1-2	12.5 mg/day (25 mg on alternate-days administration)	50 mg/day (once daily)	Same as the doses for the concomitant use of VPA
Week 3-4	25 mg/day (once daily)	100 mg/day (twice daily in divided doses)	
Week 5 or later	Gradually increased by 25-50 mg every 1 or 2 weeks	Gradually increased by ≤ 100 mg every 1 or 2 weeks	
Maintenance dose	100-200mg/day (twice daily in divided doses)	200-400mg/day (twice daily in divided doses)	

Concomitant use of antiepileptics in epileptic patients (children)

	Concomitant use of VPA		No concomitant use of VPA	
	Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 1)]	No concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 1)]	(1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 1)]	(2) Concomitant use of other antiepileptic(s) Note 2)
Week1-2	0.15 mg/kg/day (once daily)		0.6 mg/kg/day (twice daily in divided doses)	Same as the doses for the concomitant use of VPA
Week 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 every 1 or 2 weeks		Gradually increased by ≤ 1.2 mg/kg every 1 or 2 weeks	
Maintenance dose	1-5mg/kg/day (up to 200 mg) (twice daily in divided doses)	1-3mg/kg/day (up to 200 mg) (twice daily in divided doses)	5-15 mg/kg/day (up to 400 mg) (twice daily in divided doses)	

For suppression of recurrent/relapsed mood episode in patients with bipolar disorder (adult)

	Lamotrigine alone	Concomitant use of VPA	No concomitant use of VPA[Note 3)]	
			(1) Concomitant use of drug(s) that induces glucuronidation of lamotrigine[Note 1)]	(2) Concomitant use of other drug(s) Note 4)
Week1-2	25 mg/day (once daily)	12.5 mg/day (25 mg on alternate-days administration)	50 mg/day (once daily)	Same as the doses for lamotrigine alone
Week 3-4	50 mg/day (once daily or twice daily in divided doses)	25 mg/day (once daily)	100 mg/day (twice daily in divided doses)	
Week 5	100 mg/day (once daily or twice daily in divided doses)	50 mg/day (once daily or twice daily in divided doses)	200 mg/day (twice daily in divided doses)	
Week 6 or later	200 mg/day (up to 400 mg/day) (once daily or twice daily in divided doses) (dose increase by ≤ 100 mg at an interval of 1 week or longer)	100 mg/day (up to 200 mg/day) (once daily or twice daily in divided doses) (dose increase by ≤ 50 mg 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 up to 100 mg at an interval of 1 week or longer)	

Note 1) Drugs that induces glucuronidation of lamotrigine, including phenytoin, carbamazepine, phenobarbital, and priomidone
Note 2) Drugs that do not/may not affect the glucuronidation of lamotrigine, including zonisamide, gabapentine, and topiramate
Note 3) Patients receiving drug(s) that may not affect the glucuronidation of lamotrigine should follow the dosage and administration of lamotrigine used concomitantly with VPA .
Note 4) Drugs that do not affect the glucuronidation of lamotrigine, including lithium and olanzapine

2

Fatal Fire Accidents Involving Patients during Use of Long-term Oxygen Therapy

1. Introduction

Long-term oxygen therapy (LTOT) is an at-home treatment for chronic respiratory failure patients to inhale highly-concentrated oxygen by using an oxygen concentrator, liquid oxygen units, and oxygen cylinders (hereinafter referred to as an "oxygen concentrator"). The Japan Industrial and Medical Gases Association (JIMGA) estimates LTOT was used in approximately 155,000 patients in Japan in FY2009.

The oxygen concentrator can be used safely when properly used in accordance with the instructions in the package insert and the user's manual. Since oxygen is a combustion-enhancing gas, however, sources of fire should be handled with the utmost care. The package insert and the user's manual contain precautions not to put any sources of fire close to the oxygen concentrator. Moreover, the MHLW and the JIMGA have prepared and distributed leaflets and DVDs for handling of fire during LTOT to alert patients and their families.

However, fatal fire accidents believed to be caused by smoking, etc. have still occurred repeatedly in patients using LTOT. Accordingly, healthcare professionals, patients, and their families are advised again to take thorough precautions.

2. Fatal accidents

Cases of fatal accidents involving the use of an oxygen concentrator reported since 2003 are shown in Table 1. In 2011, 5 fatal fire accidents were reported.

3. Request for taking thorough safety measures

As the MHLW and the JIMGA have issued an alert against fire accidents, patients using LTOT and their families need to take the following precautions against handling of fire when using the oxygen concentrator. Healthcare professionals are advised again to thoroughly alert patients and their families.

1) Sources of fire including smoking near an oxygen concentrator while using LTOT, may cause items such as cannulas and clothing to ignite, resulting in severe burn injuries or house fires.
2) Any sources of fire should not be put within 2 meters of an oxygen concentrator. Smoking is strictly prohibited especially while using LTOT.
3) Oxygen will not cause items such as cannulas and clothing to ignite or cause home fires when properly used in accordance with the user's manual and appropriate precautions against fire. You are advised to use oxygen therapy in accordance with the instructions given by the doctor without being unduly afraid.

<References>

1) Joint HPB/GAD Notification No. 0115-1, HPB/GMSD Notification No. 0115-1, and PFSB/SD Notification No. 0115-1, by the Directors of General Affairs Division and Guidance of Medical Service

Division, Health Policy Bureau, and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated January 15, 2010, "Handling of Fire during Long-term Oxygen Therapy (Request for alert and provision of information to users)"
http://www.mhlw.go.jp/stf/houdou/2r98520000003m15-img/2r98520000003m9w.pdf

2) Medical Safety Information No. 4 of the Pharmaceuticals and Medical Devices Agency "Precautions against Smoking and Use of Fire in Long-term Oxygen Therapy (LTOT)" (Pharmaceuticals and Medical Devices Agency)
http://www.info.pmda.go.jp/anzen_pmda/file/iryo_anzen04.pdf

3) DVD "Precautions against Handling of Fire during Long-term Oxygen Therapy" (Japan Industrial and Medical Gases Association)
http://www.jimga.or.jp/front/bin/ptlist.phtml?Category=7041

4) "Risk of Fire during Long-term Oxygen Therapy: Cigarette Fire Spread by Oxygen!!" (Kobe City Fire Bureau)
http://www.city.kobe.lg.jp/safety/fire/information/zaitakusanso.html

Table 1 Cases of serious health damage due to fire in the houses of patients using LTOT (Prepared by Japan Industrial and Medical Gases Association)

No	Time of occurrence	Location (Prefecture)	Age (sex)	Health damage	Cause (including suspected cause)
1	December 2003	Shizuoka	70s (M)	Death (by fire)	Smoking
2	May 2004	Tokyo	80s (F)	Death	(unknown; fire origin, kitchen)
3	February 2005	Tochigi	70s (M)	Death	Smoking
4	March 2005	Hiroshima	60s (M)	Death (by fire)	Smoking (in bed)
5	March 2005	Fukushima	80s (M)	Death (by fire)	Current leakage (electric blanket)
6	July 2005	Hyogo	60s (M)	Death (by fire)	Smoking
7	November 2005	Hiroshima	70s (M)	Death (by fire)	(unknown; smoking in bed)
8	March 2006	Okayama	80s (M)	Death (by fire)	(unknown)
9	May 2006	Tokyo	80s (M)	Death (burn injury)	Cigarette not put out properly
10	August 2006	Kyoto	80s (F)	Death (CO intoxication)	Smoking (in bed)
11	August 2006	Hyogo	60s (F)	Serious injury (burn injury) → Death	Smoking
12	October 2006	Kyoto	70s (M)	Death (by fire)	Smoking
13	December 2006	Kyoto	10s (F)	Death	Space heater
14	March 2007	Nagano	50s (M)	Death (by fire)	Smoking
15	March 2007	Aichi	40s (M)	Death (by fire)	(unknown)
16	April 2007	Chiba	60s (M)	Death (by fire)	(unknown)
17	May 2007	Hyogo	80s (F)	Serious injury (burn injury of the face)	Smoking
18	November 2007	Fukushima	80s (M)	Death	Smoking
19	December 2007	Tokyo	80s (F)	Death	(unknown; fire origin, kitchen)
20	March 2008	Yamaguchi	70s (F)	Death	Smoking

21	November 2008	Tokyo	70s (M)	Death	Ignition of incense with a lighter
22	January 2009	Nara	≥ 90 (M)	Death (by fire)	Space heater
23	February 2009	Kagoshima	50s (M)	Death (by fire)	Smoking
24	March 2009	Chiba	80s (M)	Death (by fire)	Space heater or family alter
25	May 2009	Saitama	70s (F)	Death (by fire)	(unknown; fire origin, near the power source)
26	October 2009	Kyoto	80s (M)	Death (by fire)	Smoking
27	November 2009	Hyogo	60s (F)	Death (by fire)	(unknown)
28	December 2009	Tokyo	70s (M)	Serious injury (burn injury) → Death	(unknown)
29	January 2010	Osaka	80s (M)	Serious injury (burn injury) → Death	Smoking
30	September 2010	Kanagawa	60s (M)	Death (by fire)	(unknown; cigarette not put out properly?)
31	September 2010	Tokyo	70s (M)	Death (by fire)	(unknown; non-smoker)
32	November 2010	Tokushima	80s (M)	Death (by fire)	(unknown)
33	January 2011	Osaka	40s (F)	Death	(unknown; smoking?)
34	January 2011	Hyogo	80s (M)	Death (by fire)	(unknown)
35	April 2011	Nagano	70s (F)	Death (by fire)	Cigarette not put out properly
36	April 2011	Okayama	60s (M)	Death (by fire)	Cigarette not put out properly
37	September 2011	Wakayama	70s (M)	Death (by fire)	(unknown; lighted candle?)

3

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 Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of the drug in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of January 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Edoxaban Tosilate Hydrate LIXIANA TABLETS 15 mg, 30 mg	Daiichi Sankyo Company, Limited	July 19, 2011
Eribulin Mesilate Halaven injection 1 mg	Eisai Co., Ltd.	July 19, 2011
Tramadol Hydrochloride/Acetaminophen TRAMCET Combination Tablets	Janssen Pharmaceutical K.K.	July 19, 2011
Rivastigmine EXELON PATCH 4.5 mg, 9 mg, 13.5 mg, 18 mg	Novartis Pharma K.K.	July 19, 2011
Rivastigmine RIVASTACH Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Ono Pharmaceutical Co., Ltd.	July 19, 2011
Epoetin Beta Pegol (Genetical Recombination) MIRCERA Injection Syringe 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg	Chugai Pharmaceutical Co., Ltd.	July 20, 2011
Pramipexole Hydrochloride Hydrate Mirapex-LA Tablets 0.375 mg, 1.5 mg	Nippon Boehringer Ingelheim Co., Ltd.	July 20, 2011
Mitiglinide Calcium Hydrate/Voglibose GLUBES Combination Tab.	Kissei Pharmaceutical Co., Ltd.	July 22, 2011
Desflurane Suprane Inhalational Anesthetic Solution	Baxter Limited	July 29, 2011
Buprenorphine NORSPAN TAPE 5 mg, 10 mg, 20 mg	Mundipharma K.K.	August 4, 2011
Escitalopram Oxalate LEXAPRO Tab. 10mg	Mochida Pharmaceutical Co., Ltd.	August 22, 2011
Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (Yeast Origin) GARDASIL Aqueous Suspension for Intramuscular Injection, GARDASIL Aqueous Suspension for Intramuscular Injection Syringe	MSD K.K.	August 26, 2011
Pancrelipase LipaCreon Granules 300 mg Sachet, LipaCreon Capsules 150 mg	Abbott Japan Co., Ltd.	August 30, 2011

Levobupivacaine Hydrochloride POPSCAINE 0.5% inj. 50 mg/10 mL, POPSCAINE 0.5% inj. syringe 50 mg/10 mL	Maruishi Pharmaceutical Co., Ltd.	September 7, 2011
Vorinostat ZOLINZA Capsules 100 mg	MSD K.K.	September 14, 2011
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg	AstraZeneca K.K.	September 15, 2011
Landiolol Hydrochloride COREBETA for Intravenous 12.5 mg	Ono Pharmaceutical Co., Ltd.	September 15, 2011
Linagliptin Trazenta Tablets 5 mg	Nippon Boehringer Ingelheim Co., Ltd.	September 15, 2011
Golimumab (Genetical Recombination) Simponi Subcutaneous Injection Syringe 50 mg	Janssen Pharmaceutical K.K.	September 16, 2011
Minodronic Acid Hydrate Bonoteo Tablets 50 mg	Astellas Pharma Inc.	September 16, 2011
Minodronic Acid Hydrate RECALBON Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	September 16, 2011
Mirabegron Betanis Tablets 25 mg, 50 mg	Astellas Pharma Inc.	September 16, 2011
Alogliptin Benzoate/Pioglitazone Hydrochloride LIOVEL Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	September 20, 2011
Indacaterol Maleate onbrez inhalation capsules 150 μg	Novartis Pharma K.K.	September 20, 2011
Daptomycin CUBICIN IV 350 mg	MSD K.K.	September 22, 2011
Itraconazole ITRIZOLE Oral Solution 1%*[1]	Janssen Pharmaceutical K.K.	September 26, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 μg, 180 μg*[2]	Chugai Pharmaceutical Co., Ltd.	September 26, 2011
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*[3]	Chugai Pharmaceutical Co., Ltd.	September 26, 2011
Olopatadine Hydrochloride ALLELOCK Granules 0.5%*[4]	Kyowa Hakko Kirin Co., Ltd.	November 15, 2011
Live Attenuated Human Rotavirus Vaccine, Oral Rotarix Oral Solution	GlaxoSmithKline K.K.	November 21, 2011
Imiquimod BESELNA CREAM 5%*[5]	Mochida Pharmaceutical Co., Ltd.	November 25, 2011
Teriparatide Acetate Teribone Inj. 56.5 μg	Asahi Kasei Pharma Corporation	November 25, 2011
Fulvestrant FASLODEX intramuscular injection 250 mg	AstraZeneca K.K.	November 25, 2011
Modafinil MODIODAL Tablets 100 mg*[6]	Alfresa Pharma Corporation	November 25, 2011
Telaprevir TELAVIC Tablets 250 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride IMUSERA Capsules 0.5 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011

Fingolimod Hydrochloride GILENYA Capsules 0.5 mg	Novartis Pharma K.K.	November 28, 2011
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg	Pfizer Japan Inc.	December 7, 2011
Canakinumab (Genetical Recombination) ILARIS for s.c. injection 150 mg	Novartis Pharma K.K.	December 7, 2011
Fosaprepitant Meglumine PROEMEND for Intravenous Infusion 150 mg	Ono Pharmaceutical Co., Ltd.	December 9, 2011
Everolimus AFINITOR tablets 5 mg*[7]	Novartis Pharma K.K.	December 22, 2011
Everolimus Certican Tablets 0.25 mg, 0.5 mg, 0.75 mg*[8]	Novartis Pharma K.K.	December 22, 2011
Pranlukast Hydrate ONON drysyrup 10%*[9]	Ono Pharmaceutical Co., Ltd.	December 22, 2011
Peginterferon Alfa-2b (Genetical Recombination) PEGINTRON Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL*[10]	MSD K.K.	December 22, 2011
Ribavirin REBETOL Capsules 200 mg*[11]	MSD K.K.	December 22, 2011

*1 Additional indications for "treatment of patients with fungal infection caused by *Aspergillus*, *Cryptococcus*, *Blastomyces*, or *Histoplasma* (fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, blastomycosis, histoplasmosis)", "treatment of patients with febrile neutropenia of suspected fungal infection", and "prophylaxis of deep mycosis in patients with haematological malignancy possibly associated with neutropenia or patients who underwent hematopoietic stem cell transplantation"

*2 An additional indication for "improvement of viraemia in chronic active hepatitis B

*3 An additional indication for "treatment of patients with inoperable or recurrent breast cancer"

*4 An additional administration for "pediatrics (aged 2 to under age of 7)"

*5 An additional indication for "treatment of patients with actinic keratosis (limited to face or baldness)"

*6 An additional indication for "treatment of excessive daytime sleepiness in patients with obstructive sleep apnoea syndrome who receive treatment for airway obstruction with continuous positive airway pressure (CPAP) therapy, etc."

*7 An additional indication for "treatment of patients with pancreatic neuroendocrine tumour"

*8 An additional indication for "prophylaxis rejection in renal transplantation"

*9 An additional indication for "treatment of patients with allergic rhinitis"

*10 An additional indication for "improvement of viraemia in compensated cirrhosis C in combination therapy with ribavirin"

*11 An additional indication for "improvement of viraemia in compensated cirrhosis C in combination therapy with peginterferon alfa-2b (genetical recombination)"