Pharmaceuticals and Medical Devices Safety Information

No. 308 December 2013

Table of Contents

1. Review of Driving Precautions in Package Inserts of Ethical Drugs 5

2. Important Safety Information 8

(1) Bosentan Hydrate 8

3. Revision of Precautions (No. 252) 10

Donepezil Hydrochloride (and 5 others) 10

4. List of Products Subject to Early Post-marketing Phase Vigilance 13

(Reference) Handling of Fire during Long-term Oxygen Therapy 16

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

Published by
Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

Translated by
Pharmaceuticals and Medical Devices Agency

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

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

Pharmaceuticals and Medical Devices Safety Information
No. 308 December 2013

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Review of Driving Precautions in Package Inserts of Ethical Drugs**		The MHLW and PMDA are reviewing information described in package inserts of drugs for which disturbed consciousness and relevant adverse reactions are reported, focusing on alerts about potentially hazardous activities including driving. This section provides a background of the review and a summary of the Precautions revisions required for the marketing authorization holders of the drugs on November 26, 2013.	5
2	**Important Safety Information**	*P* *C*	**Bosentan Hydrate:** Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated November 26, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.	8
3	**Revision of Precautions (No. 252)**		Donepezil Hydrochloride (and 5 others)	10
4	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of December 1, 2013.	13
Reference	**Handling of Fire during Long-term Oxygen Therapy**		Fatal fire accidents believed to be caused by smoking, etc., have occurred repeatedly in patients using Long-term Oxygen Therapy (LTOT). Healthcare professionals, patients, and their families are advised again not to smoke during LTOT and to keep the oxygen concentrator away from sources of fire, such as a heater.	16

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
JIMGA	Japan Industrial and Medical Gases Association
LTOT	Long-term oxygen therapy
MAH	Marketing authorization holder
TEN	Toxic epidermal necrolysis
WHO	World Health Organization

1

Review of Driving Precautions in Package Inserts of Ethical Drugs

1. Introduction

Special precautions need to be exercised when taking drugs with known adverse reactions such as decreased level of consciousness, loss of consciousness, altered state of consciousness, syncope, and sudden onset of sleep before engaging in potentially hazardous activities such as driving, machine operations, and working at heights (hereinafter collectively called driving, etc.) since it may pose a hazard to others.

Precautions against driving, etc. are included in the package inserts of drugs with known psychoneurotic adverse reactions such as decreased level of consciousness, loss of consciousness, altered state of consciousness, syncope, and sudden onset of sleep that resulted in traffic accidents or drugs that cannot be ruled out from contributing to traffic accidents because of similar drugs for which precautions have already been recommended to prevent possible accidents.

However, package inserts of some drugs lack such precautions because no accident has been reported or no causal relationship has been identified between drug use and reported accidents.

In the Recommendation for Distribution and Safety of Pharmaceutical Products Based on Administrative Evaluation and Inspection[1], the Ministry of Internal Affairs and Communications advised the MHLW on March 22, 2013 to consider including a precaution against driving, etc. in the Precaution section in the package inserts of drugs with known adverse reactions such as disturbed consciousness and promptly instruct the marketing authorization holders (MAHs) to revise the package inserts of their products if such a precaution is necessary. In accordance with the Recommendation, the MHLW and PMDA are currently discussing whether package insert revision will be necessary for drugs with known or reported adverse reactions such as disturbed consciousness.

・1 (The title of the recommendation is provisionally translated.)
Ministry of Internal Affairs and Communications "Recommendation for Distribution and Safety of Pharmaceutical Products Based on Administrative Evaluation and Inspection"
http://www.soumu.go.jp/main_content/000213386.pdf (only available in Japanese language)

2. Discussion about precautions against driving, etc.

Based on the Recommendation of the Ministry of Internal Affairs and Communications, PMDA selected ethical drugs that included known adverse reactions such as disturbed consciousness (decreased level of consciousness, loss of consciousness, altered state of consciousness, syncope, and sudden onset of sleep) in their package inserts and included no precaution against driving, etc. to discuss the necessity for such a precaution.

Specifically, the following discussions were held for drugs with reported adverse reactions such as disturbed consciousness but no precaution against driving, etc. is included in their package inserts.

1) No precaution is necessary for drugs whose users are not expected to drive, such as drugs exclusively taken by children, inpatients or patients with serious disorders.
2) Except for the drugs described in 1), driving, etc. should be prohibited after taking drugs with multiple reports of serious accidents possibly associated with their use or of which use may result in serious accidents based on the past adverse reaction reports on the drugs and/or accidents

reported with similar drugs even if no serious accident has been reported.

3) Regarding drugs that are considered unlikely to contribute to serious incidents, a precaution should be provided against driving, etc. after taking drugs with a number of reports on adverse reactions such as disturbed consciousness and those for which precautions need to be exercised when driving, etc. after taking based on the package inserts of similar drugs, overseas package inserts, and the pharmacological actions.

Based on the discussions, a new precaution was determined necessary for the following drugs. The MHLW instructed the MAHs to revise the Precautions on November 26.

Drug name	Additional precaution against driving, etc.
・ Donepezil hydrochloride	Ability to operate machinery such as driving may decrease in patients with Alzheimer's type dementia. Disturbed consciousness, dizziness, and sleepiness, etc. may occur in association with this drug. Patients should be thoroughly instructed to refrain from engaging in potentially hazardous machine operations such as driving.
・ Levofloxacin hydrate (oral and injectable dosage form) ・ Beraprost sodium ・ Azithromycin hydrate (tablets for adults, dry syrup for adults, injectable dosage form) ・ Ofloxacin (oral dosage form) ・ Garenoxacin mesilate hydrate ・ Telaprevir ・ Famciclovir	Disturbed consciousness, etc. may occur. Patients should be thoroughly instructed to pay attention when engaging in potentially hazardous machine operations such as driving.
・ Pilsicainide hydrochloride hydrate (oral dosage form) ・ Propafenone hydrochloride ・ Bepridil hydrochloride hydrate	Dizziness, etc. may occur. Patients should be thoroughly instructed to pay attention when engaging in potentially hazardous machine operations such as driving.
・ Aciclovir (oral and injectable dosage form) ・ Valaciclovir hydrochloride	Disturbed consciousness, etc. may occur. Patients should be thoroughly instructed to pay attention when engaging in potentially hazardous machine operations such as driving. Disturbed consciousness more readily occurs especially in patients with renal impairment. Patients should be advised to refrain from engaging in potentially hazardous machine operations depending on patient's condition.

Note: See "3 Revision of Precautions" for the brand names.

3. Future plans

PMDA is currently reviewing the package inserts of antidiabetics to see if any precautions against driving, etc., are included. Package insert revisions will be instructed if additional precautions are considered necessary.

Package inserts of drugs that already prohibit or advise against driving will be reviewed and revised as necessary if any new information that may help ensure safe drug use is obtained.

4. Conclusion

The Recommendation of the Ministry of Internal Affairs and Communications advises the MHLW to review the package inserts of drugs prohibiting driving and to thoroughly ensure physicians and pharmacists provide patients with precautions against driving, etc. when prescribing or dispensing such drugs.

In line with the Recommendation, the MHLW issued Advising Patients Not to Operate Machinery including Driving During Treatment with Some Pharmaceutical Products (PFSB/GAD Notification 0529-2 and PFSB/SD Notification 0529-2 dated May 29, 2013, by the Director of General Affairs Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau)[2] to the prefectural governments to ensure that appropriate information is provided by physicians and pharmacists to patients.

Healthcare professionals are encouraged to provide necessary information to patients to ensure proper drug use.

• 2 (The title of the notification is provisionally translated.)
Ministry of Health, Labour and Welfare Laws and Regulations Database Service
PFSB/GAD Notification 0529-2 and PFSB/SD Notification 0529-2 dated May 29, 2013, by the Director of General Affairs Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau
(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 November 26, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Bosentan Hydrate

Brand Name (name of company)	Tracleer Tablet 62.5 mg (Actelion Pharmaceuticals Japan Ltd.)
Therapeutic Category	Cardiovascular agents-Miscellaneous
Indications	Pulmonary arterial hypertension (WHO Functional Classes II, III, and IV)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Cardiac failure, congestive cardiac failure: Cardiac failure may be aggravated. Patients should be carefully monitored during administration of this drug and if fluid retention, rapid increased weight, and symptoms/signs of cardiac failure (shortness of breath, palpitations, increased cardiothoracic ratio, pleural effusion, etc.) are aggravated or occur, appropriate measures such as discontinuation of administration should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 5 months (April 2010 to September 2013)

- Cardiac failure/congestive cardiac failure-associated cases: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 6,100 (April 2012 to March 2013)
Launched in Japan: June 2005

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Pulmonary hypertension (right ventricular failure, hepatic congestion, anaemia, hyperlipidaemia)	62.5 mg for 14 days ↓ 125 mg for 71 days ↓ 62.5 mg Continued	**Right ventricular failure** 19 months before administration: The patient started receiving sildenafil citrate at 20 mg × 3 times/day. At the start of administration: The patient was in World Health Organization (WHO) Functional Class III (before administration). Day 1 of administration: Administration of bosentan hydrate was started at 31.25 mg × twice/day. Day 15 of administration: The dose of bosentan hydrate was increased to 62.5 mg × twice/day.

				Day 58 of administration (day of onset): Aggravation of right heart failure occurred. The dose of spironolactone was increased by one tablet to treat the heart failure. Day 29 of onset: The dose of bosentan hydrate was decreased to 31.25 mg × twice/day. Day 57 of onset: Aggravation of right heart failure improved.
	Concomitant medications: warfarin potassium, sildenafil citrate, spironolactone, furosemide, sodium ferrous citrate, pravastatin sodium			

3

Revision of Precautions (No. 252)

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 November 26, 2013 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1

Central nervous system agents-Miscellaneous

Donepezil Hydrochloride

Brand Name	Aricept Tablets 3 mg, 5 mg, 10 mg, Aricept Fine Granules 0.5%, Aricept D Tablets 3 mg, 5 mg, 10 mg, Aricept Oral Jelly 3 mg, 5 mg, 10 mg, Aricept Dry Syrup 1% (Eisai Co., Ltd.) and the others
Important Precautions	Prolonged QT, ventricular tachycardia (including torsades de pointes), ventricular fibrillation, sick sinus syndrome, sinus arrest, severe bradycardia, heart block (sinoatrial block, atrioventricular block), etc. may occur in association with administration of this drug. Particularly patients with a heart disease (myocardial infarction, valve disease, cardiomyopathy, etc.) or an electrolyte abnormality (hypokalaemia, etc.) should be carefully monitored. Ability to operate machinery such as driving may decrease in patients with Alzheimer's type dementia. Disturbed consciousness, dizziness, and sleepiness, etc. may occur in association with this drug. Patients should be thoroughly instructed to refrain from engaging in potentially hazardous machine operations such as driving.
Adverse Reactions (clinically significant adverse reactions)	**Prolonged QT, ventricular tachycardia (including torsades de pointes), ventricular fibrillation, sick sinus syndrome, sinus arrest, severe bradycardia, heart block, syncope**: Prolonged QT, ventricular tachycardia (including torsades de pointes), ventricular fibrillation, sick sinus syndrome, sinus arrest, severe bradycardia, heart block (sinoatrial block, atrioventricular block), and syncope may occur, resulting in cardiac arrest. If these symptoms are observed, appropriate measures such as discontinuation of administration should be taken. **Myocardial infarction, cardiac failure**: Myocardial infarction and cardiac failure may occur. If these symptoms are observed, appropriate measures such as discontinuation of administration should be taken. **Decreased platelets**: **Decreased platelets** may occur. Patients should be carefully monitored through blood tests, etc. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

2

Antiarrhythmic agents

(1) Pilsicainide Hydrochloride Hydrate (oral dosage form)
(2) Propafenone Hydrochloride
(3) Bepridil Hydrochloride Hydrate

Brand Name

(1) SUNRYTHM CAPSULES 25 mg, 50 mg (Daiichi-Sankyo Company, Limited) and the others
(2) Pronon Tablets 100 mg, 150 mg (Toa Eiyo Ltd.) and the others
(3) Bepricor Tablets 50 mg, 100 mg (MSD K.K.)

Important Precautions

Dizziness, etc. may occur. Patients should be thoroughly instructed to pay attention when engaging in potentially hazardous machine operations such as driving.

3

Diuretics

Furosemide

Brand Name

Lasix 10 mg Tab., 20 mg Tab., 40 mg Tab., Lasix 4% Fine Granule, Lasix 20 mg Injection, 100 mg Injection, Eutensin Capsule 40 mg (Sanofi K.K.) and the others

Adverse Reactions (clinically significant adverse reactions)

Aplastic anaemia, pancytopenia, agranulocytosis, decreased platelets, pure red cell aplasia: Aplastic anaemia, pancytopenia, agranulocytosis, decreased platelets, and pure red cell aplasia may occur. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

4

Cardiovascular agents-Miscellaneous
Blood and body fluid agents-Miscellaneous
Acting mainly on gram-positive bacteria and mycoplasma
Synthetic antibacterials
Antivirals

(1) Beraprost Sodium
(2) Azithromycin Hydrate (tablets for adults, dry syrup for adults, injectable dosage form)
(3) Ofloxacin (oral dosage form)
(4) Garenoxacin Mesilate Hydrate
(5) Levofloxacin Hydrate (injectable and oral dosage form)
(6) Telaprevir
(7) Famciclovir

Brand Name

(1) DORNER Tablets 20 μg (Toray Industries, Inc.), PROCYLIN Tablets 20 (Kaken Pharmaceutical Co., Ltd.), Careload LA Tablets 60 μg (Toray Industries, Inc.), BERASUS LA Tablets 60 μg (Kaken Pharmaceutical Co., Ltd.) and the others
(2) ZITHROMAC SR Dry Syrup for Adults 2 g, ZITHROMAC Tablets 250 mg, 600 mg, ZITHROMAC Intravenous use 500 mg (Pfizer Japan Inc.)
(3) TARIVID TABLETS 100 mg (Daiichi Sankyo Company, Limited) and the others
(4) Geninax Tablets 200 mg (Toyama Chemical Co., Ltd.)
(5) CRAVIT INTRAVENOUS DRIP INFUSION BAG 500 mg/100 mL, CRAVIT

INTRAVENOUS DRIP INFUSION 500 mg/20 mL, CRAVIT TABLETS 250 mg, 500 mg, CRAVIT FINE GRANULES 10% (Daiichi Sankyo Company, Limited) and the others
(6) TELAVIC Tablets 250 mg (Mitsubishi Tanabe Pharma Corporation)
(7) Famvir Tab. 250 mg (Asahi Kasei Pharma Corporation)

Important Precautions

Disturbed consciousness, etc. may occur. Patients should be thoroughly instructed to pay attention when engaging in potentially hazardous machine operations such as driving.

5

Acting mainly on gram-positive bacteria

Clindamycin Hydrochloride
Clindamycin Phosphate (injectable dosage form)

Brand Name

Dalacin Capsules 75 mg, 150 mg (Pfizer Japan Inc.)
Dalacin S Injection 300 mg, 600 mg (Pfizer Japan Inc.) and the others

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, exfoliative dermatitis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, acute generalised exanthematous pustulosis, and exfoliative dermatitis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Drug-induced hypersensitivity syndrome: Rash and pyrexia may occur as the initial symptoms followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, swollen lymph nodes, increased white blood cell, eosinophilia, and atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised.

<Reference Information> Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

---

6

Antivirals

(1) Aciclovir (oral and injectable dosage form)
(2) Valaciclovir Hydrochloride

Brand Name

(1) Zovirax Tablets 200, 400, Zovirax Granules 40%, Zovirax for I.V. infusion 250 (GlaxoSmithKline K.K.) and the others
(2) VALTREX Tablets 500, VALTREX Granules 50% (GlaxoSmithKline K.K.) and the others

Important Precautions

Disturbed consciousness, etc. may occur. Patients should be thoroughly instructed to pay attention when engaging in potentially hazardous machine operations such as driving. Disturbed consciousness, etc. more readily occur especially in patients with renal impairment. Patients should be advised to refrain from engaging in potentially hazardous machine operations depending on the patient's condition.

4

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of December 1, 2013)

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

	Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
◎	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*1	Ono Pharmaceutical Co., Ltd.	November 22, 2013
◎	Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL*2, EYLEA solution for IVT inj. Kit 40 mg/mL*2	Bayer Yakuhin, Ltd.	November 22, 2013
◎	Topiramate TOPINA Tablets 25 mg, 50 mg, 100 mg*3	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
◎	Paliperidone Palmitate XEPLION Aqueous Suspension for IM Injection Syringe 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	Janssen Pharmaceutical K.K.	November 19, 2013
	Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) Prevenar13 Suspension Liquid for Injection	Pfizer Japan Inc.	October 28, 2013
	Hydroxyethylated Starch 130000 VOLUVEN 6% solution for infusion	Fresenius Kabi Japan K.K.	October 25, 2013
	Fentanyl Citrate E-fen buccal tablet 50 μg, 100 μg, 200 μg, 400 μg, 600 μg, 800 μg	Teikoku Seiyaku Co., Ltd.	September 26, 2013
	Norethisterone/Ethinylestradiol	Nobelpharma Co., Ltd.	September 26,

	LUNABELL tablets ULD		2013
	Aminolevulinic Acid Hydrochloride ALAGLIO Oral 1.5 g	SBI Pharmaceuticals Co., Ltd.	September 26, 2013
	Aminolevulinic Acid Hydrochloride Alabel Oral 1.5 g	Nobelpharma Co., Ltd.	September 18, 2013
	Lixisenatide Lyxumia Subcutaneous Injection 300 μg	Sanofi K.K.	September 17, 2013
	Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 10 μg PLASTIC SYRING, 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*[4]	Kyowa Hakko Kirin Co., Ltd.	September 13, 2013
	Tolvaptan Samsca tablets 7.5 mg*[5]	Otsuka Pharmaceutical Co., Ltd.	September 13, 2013
	Eculizumab (Genetical Recombination) Soliris Drip Infusion 300 mg*[6]	Alexion Pharma G.K.	September 13, 2013
	Pertuzumab (Genetical Recombination) PERJETA Intravenous Infusion 420 mg/14 mL	Chugai Pharmaceutical Co., Ltd.	September 12, 2013
	Bisoprolol Bisono tape 4 mg, 8 mg	Toa Eiyo Ltd.	September 10, 2013
	Irbesartan/Trichlormethiazide Irtra Combination Tablets LD, HD	Shionogi & Co., Ltd.	September 4, 2013
	Topiroxostat (1) TOPILORIC Tablets 20 mg, 40 mg, 60 mg (2) URIADEC Tab. 20 mg, 40 mg, 60 mg	(1) Fujiyakuhin Co., Ltd. (2) Sanwa Kagaku Kenkyusho CO., LTD.	September 4, 2013
	Ibandronate Sodium Hydrate Bonviva IV Injection 1 mg Syringe	Chugai Pharmaceutical Co., Ltd.	August 29, 2013
	Abatacept (Genetical Recombination) ORENCIA SYRINGE FOR S.C. INJECTION 125 mg/1 mL	Bristol-Myers K.K.	August 27, 2013
	Hemin Normosang Infusion 250 mg	Orphan Pacific, Inc.	August 23, 2013
	Palivizumab (Genetical Recombination) Synagis for Intramuscular Injection 50 mg, 100 mg*[7] Synagis Intramuscular Solution 50 mg, 100 mg*[7]	AbbVie G.K.	August 20, 2013
	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*[8]	Novartis Pharma K.K.	August 20, 2013
	Omalizumab (Genetical Recombination) Xolair for s.c. injection 150 mg, 75 mg*[9]	Novartis Pharma K.K.	August 20, 2013
	Tofacitinib Citrate XELJANZ Tablets 5 mg	Pfizer Japan Inc.	July 30, 2013
	Metreleptin (Genetical Recombination) Metreleptin for Subcutaneous Injection 11.25 mg "SHIONOGI"	Shionogi & Co., Ltd.	July 25, 2013
	Saxagliptin Hydrate ONGLYZA Tablets 2.5 mg, 5 mg	Kyowa Hakko Kirin Co., Ltd.	July 9, 2013

	Oxybutynin Hydrochloride NEOXY TAPE 73.5 mg	Hisamitsu Pharmaceutical Co., Inc.	June 27, 2013
	Clofarabine Evoltra 20 mg I.V. Infusion	Sanofi K.K.	June 21, 2013
	Lidocaine Penles Tape 18 mg*10	Nitto Denko Corporation	June 14, 2013
	Tacrolimus Hydrate Prograf Capsules 0.5 mg, 1 mg*11	Astellas Pharma Inc.	June 14, 2013
	Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*12	Chugai Pharmaceutical Co., Ltd.	June 14, 2013
	Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg*13	Nippon Shinyaku Co., Ltd.	June 14, 2013
	Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%*14	Otsuka Pharmaceutical Co., Ltd.	June 14, 2013
	Dexmedetomidine Hydrochloride (1) Precedex Intravenous Solution 200 μg "Hospira"*15 (2) PRECEDEX Intravenous Solution 200 μg "Maruishi"*15	(1) Hospira Japan Co., Ltd. (2) Maruishi Pharmaceutical Co., Ltd.	June 14, 2013
	Denosumab (Genetical Recombination) PRALIA SUBCUTANEOUS INJECTION 60 mg SYRINGE	Daiichi Sankyo Company, Limited	June 11, 2013
	Acotiamide Hydrochloride Hydrate Acofide Tablets 100 mg	Zeria Pharmaceutical Co., Ltd.	June 6, 2013

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

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

*3 An additional administration for “pediatrics”

*4 An additional administration for “pediatrics”

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

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

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

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

*9 An additional administration for “pediatrics”

*10 An additional indication for “the relief of pain in laser irradiation treatment of the skin”

*11 An additional indication for “the treatment of patients with interstitial pneumonia associated with polymyositis/ dermatomyositis”

*12 An additional indication for “the treatment of patients with malignant glioma”

*13 An additional indication for “the treatment of chronic pain cannot be managed by treatments with non-opioid analgesics”

*14 An additional indication for “the treatment of patients with depression/depressive state (to be used only when the patient does not sufficiently respond to conventional therapy)”

*15 An additional indication for “sedation in surgery or treatment without intubation under local anesthesia”

Handling of Fire during 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 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 Japan Industrial and Medical Gases Association (JIMGA) have prepared and distributed leaflets and videos 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.

Table 1 shows Cases of serious health damage due to fire in the houses of patients using LTOT for which information was updated as of the end of November 2013 by the JIMGA.

2. 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. Ministry of Health, Labour and Welfare: Handling of Fire during Long-term Oxygen Therapy
   http://www.mhlw.go.jp/stf/houdou/2r98520000003m15_1.html (only available in Japanese language)
2. Cases of serious health damage due to fire in the houses of patients using LTOT (Japan Industrial and Medical Gases Association)
   http://www2.jimga.or.jp/dl/iryo/mem/hot/hot_jiko.pdf (only available in Japanese language)
3. "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 (only available in Japanese language)

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 [as of the end of November 2013])

No	Date 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 altar
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?)
38	June 2012	Okayama	80s (M)	Death	Smoking
39	November 2012	Kyoto	70s (F)	Death (by fire)	(unknown: space heater?)
40	November 2012	Osaka	60s (M)	Death (by fire)	(unknown; smoking?)
41	March 2013	Fukuoka	80s (M)	Death (by fire)	(unknown)
42	August 2013	Okinawa	70s (M)	Severe (burn injury in airway)	(unknown)
43	November 2013	Niigata	80s (F)	Death (by fire)	(unknown: space heater?)
44	November 2013	Yamagata	70s (M)	Death (by fire)	(unknown)