Pharmaceuticals and Medical Devices Safety Information

No. 300 March 2013

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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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Pharmaceuticals and Medical Devices Safety Information
No. 300 March 2013

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

[Outline of Information]

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
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
ALP	Alkaline phosphatase
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
EPPV	Early Post-marketing Phase Vigilance
GPSP	Good Post-marketing Study Practice
GVP	Good Vigilance Practice
MAH	Marketing authorization holder
RMP	Risk Management Plan
γ-GTP	gamma-glutamyl transpeptidase

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Implementation of the "Risk Management Plan"

1. Introduction

The "Risk Management Plan" (RMP) describes a set of pharmacovigilance activities designed to minimize the risks of drugs based on the identified safety issues of individual drugs. The activities include investigations and information collection through use-results surveys and Early Post-marketing Phase Vigilance, etc., as well as additional information provision to healthcare professionals.

The RMP is required for new drugs and biosimilars/follow-on biologics for which approval applications are submitted on or after April 1, 2013.

This section introduces the outline of the system and future actions, etc. and encourages healthcare professionals to utilize the Risk Management Plan that is to be published on the PMDA website (http://www.pmda.go.jp/) (only available in Japanese language).

2. Outline of the "Risk Management Plan"

All drugs have some risks (adverse drug reactions) along with their efficacy. Although it is impossible to completely eliminate the risks, it is important to take measures to minimize them as long as possible and manage them appropriately. So far, necessary safety measures have been taken in accordance with the Pharmaceutical Affairs Law. Necessary precautions are included in the "Precautions" of package inserts to reduce the risks through approval review process, and adverse drug reaction reporting system, Early Post-marketing Phase Vigilance system, Periodic Safety Update Reports system, and re-examination/re-evaluation system are implemented. In addition, “Pharmacovigilance Planning”[1)], which is internationally-harmonized guideline, was issued and has been used as a reference for developing a plan for post-marketing surveys/studies.

In order to ensure the safety of drugs, it is important to determine measures for appropriate management of the risks of drugs at any time from the development phase to the regulatory review and the post-marketing phase. The introduction of the RMP aims to document such current actions for each drug to share the information among the stakeholders for the purpose of ensuring further enhancements of post-marketing safety measures. The "Risk Management Planning Guidance"[2)] and "Preparation of the Risk Management Plan"[3)] were issued in April, 2012 to specify guidance for the preparation of RMP, RMP formats and handling of submission, etc., and to require preparation of RMP for new drugs and biosimilars/follow on biologics for which approval applications are submitted on or after April 1, 2013.

The RMP basically consists of three elements, namely "Safety Specifications," the "Pharmacovigilance Plan," and the "Risk Minimization Plan." The "Safety Specifications" should be identified based on obtained findings. Based on each identified “Safety Specification”, the "Pharmacovigilance Plan" and the "Risk Minimization Plan" should be prepared. In addition, a plan for surveys/studies on efficacy should also be prepared as necessary. The RMP is documentation that summarizes all these plans.

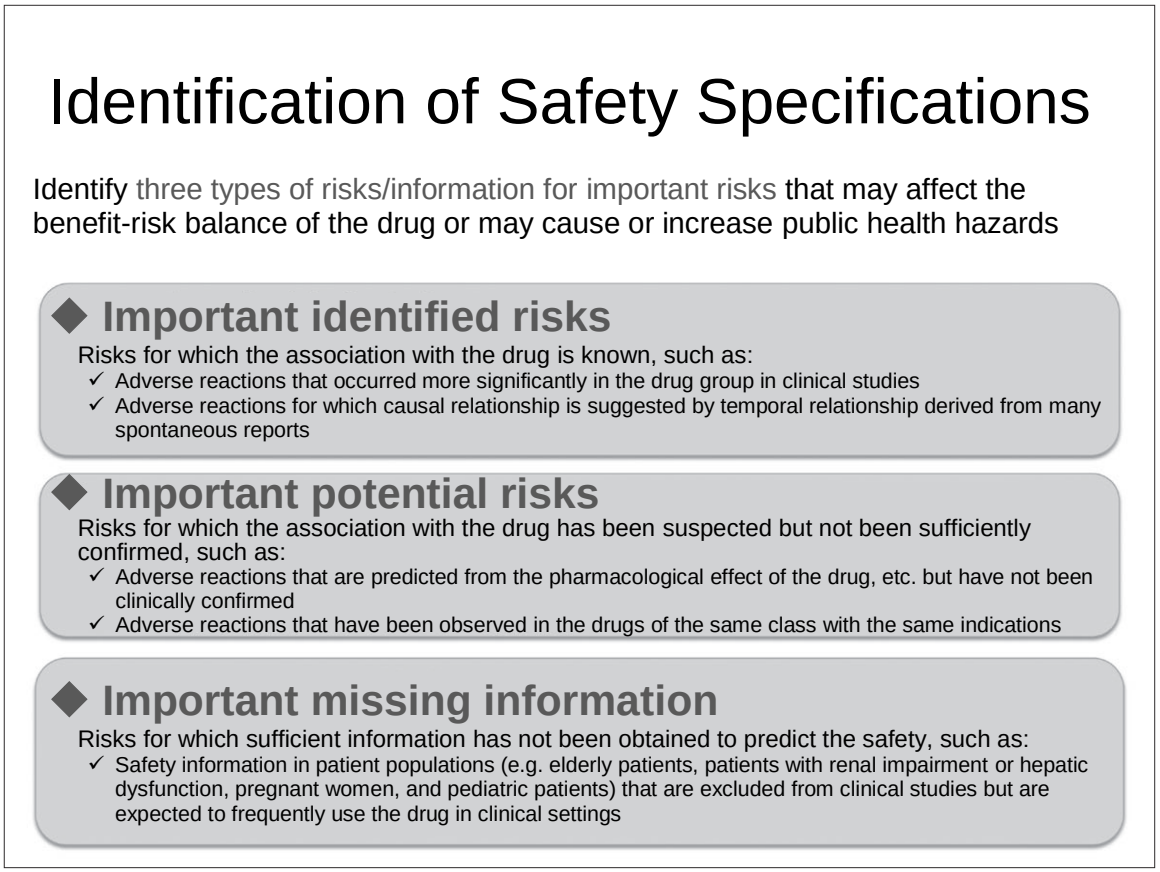
(1) Safety Specifications

In "Safety Specifications," marketing authorization holders (MAHs) identify three types of risks/information, namely "important identified risks," "important potential risks," and "important

missing information," for risks identified based on information obtained in the development phase and/or post-marketing adverse reaction reports that are critical. Important risks mean risks that may affect the benefit-risk balance of the drug or may cause or increase public health hazards. (**Figure 1**)

For example, the adverse reactions with sufficient evidence of a causal relationship with the drug, such as reactions for which the association with the drug has been confirmed by clinical data or reactions for which causal relationship is suggested by temporal relationship derived from many spontaneous reports in the post-marketing phase, are regarded as "important identified risks." The adverse reactions that did have not been observed in clinical studies of the drug but are predicted from non-clinical data or are observed in drugs of the same class with the same indications are regarded as "important potential risks." Moreover, for example, in case the drug is expected to be frequently used in clinical settings in elderly patients, patients with renal impairment/hepatic dysfunction or any other patient populations that were excluded from clinical studies of the drug, missing information for predicting the safety of the drug is regarded as "important missing information."

Figure 1



(2) Pharmacovigilance Plan

A "Pharmacovigilance Plan" is a plan for post-marketing surveys/studies that are conducted to collect information based on the identified "Safety Specifications." This consists of "routine pharmacovigilance activities" and "additional pharmacovigilance activities."

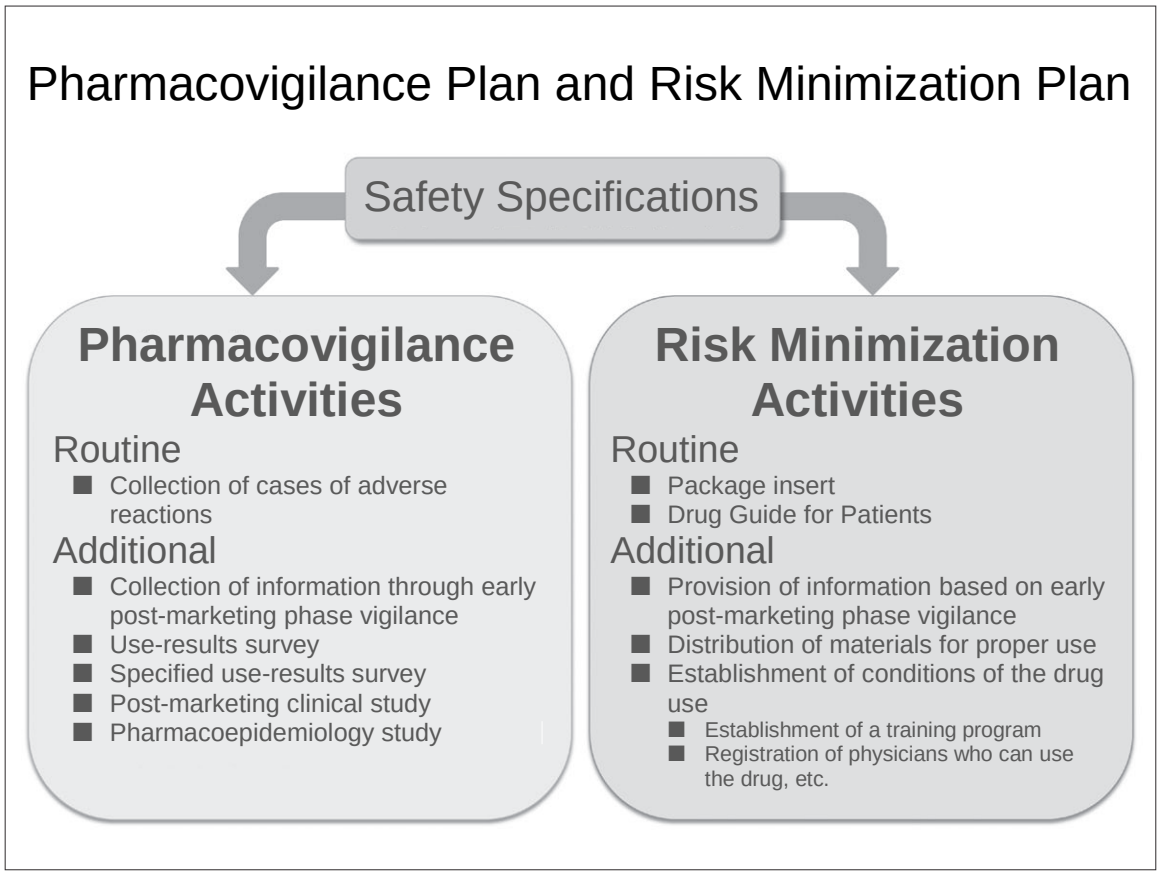
In general, cases of adverse reactions and literature information, etc. are collected for all drugs after marketing, and this is regarded as "routine pharmacovigilance activities." Additional activities, such as "Early Post-marketing Phase Vigilance" of new drugs or "use-results surveys" and "post-marketing clinical studies" that are conducted for re-examination/re-evaluation application, are regarded as "additional pharmacovigilance activities." (**Figure 2**)

(3) Risk Minimization Plan

A "Risk Minimization Plan" is a plan for safety measures taken to minimize the risks that are identified based on information obtained in the development phase and post-marketing adverse reaction reports.

The information about adverse reactions and the precautions in specific populations are described in the "Precautions" of package inserts. This information provision is a basic safety measure commonly taken for all drugs and is regarded as a "routine risk minimization activities." For further reduction of significant risks, some drugs may require frequent alerting to healthcare professionals through Early Post-marketing Phase Vigilance, distributing of materials to ensure the proper use of drugs that require caution, or establishing conditions such as prescribing of the drug only by registered physicians and administering the drug only after obtaining the patients' informed consent. These activities are conducted in addition to regular information provision through package inserts and are regarded as "additional risk minimization activities". (**Figure 2**)

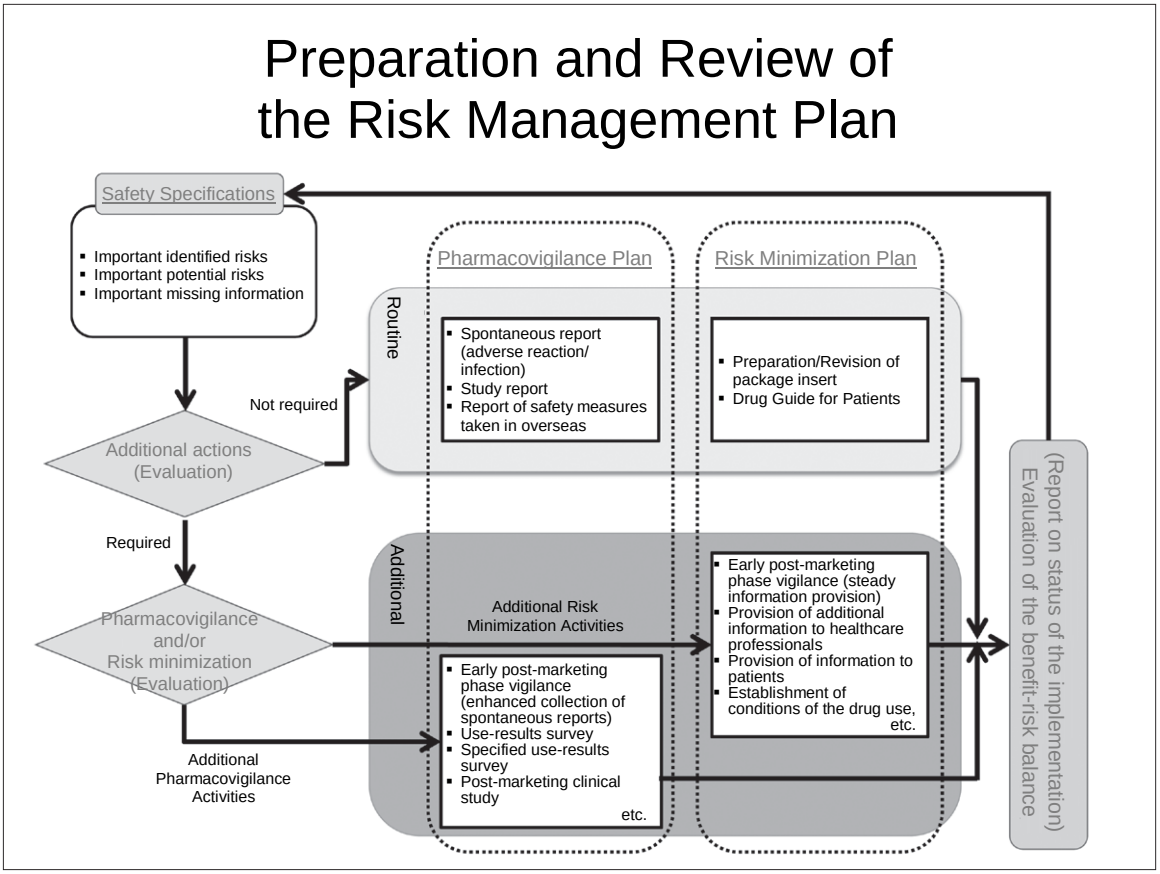
Figure 2



(4) Review of the Risk Management Plan

Even after the RMP has been prepared, it should be reviewed based on new safety/efficacy information obtained after marketing of the drug. Review is required when, for example, the content of the Safety Specifications need to be changed due to identification of new adverse reactions and new findings are obtained after the completion of a survey or study conducted based on the plan. In this way, the RMP will be continuously prepared, implemented, evaluated, and reviewed throughout the life cycle of the drug. (**Figure 3**) The results of the review will be reported to PMDA to confirm its appropriateness.

Figure 3



3. Future actions

In order to ensure preparation and implementation of the RMP, the RMP is to be mandatory for marketing approval, and its preparation and implementation are to be included in the post-marketing safety management regulations that the MAHs should comply with. Therefore, relevant ministerial ordinances ("Ministerial Ordinance on Good Vigilance Practice for drugs, quasi-drugs, cosmetics, and medical devices" [GVP Ordinance] and Ministerial Ordinance on Good Post-marketing Study Practice for drugs [GPSP Ordinance]) were revised on March 11, 2013, and the revised ministerial ordinances will be enforced on October 1, 2014 after the transition period. Accordingly, drugs that will be approved on or after this day require preparation and implementation of a Risk Management Plan as an approval condition.

For generic drugs, several pilot programs to prepare the RMPs are ongoing in companies that are interested in participating in the program. The RMP for generic drugs will be implemented after discussion about the method of operation based on pilot programs results.

4. Requests to healthcare professionals

For new drugs and biosimilars/follow-on biologics for which approval applications are submitted on or after April 1, 2013, a draft RMP must be submitted at the time of submission of approval application and a finalized RMP must be submitted after approval through discussion during application review. In addition, submission of an RMP will be required for approved products for which new safety concerns are identified on or after April 1, 2013. Risk Management Plans submitted in this way will be posted on the PMDA website for publication.

Healthcare professionals are encouraged to know the contents of the RMP and use it for proper use of drugs by understanding what types of risks are known for individual drugs at present and what

safety measures has been being taken to minimize such risks. Also, healthcare professionals are requested to understand what kind of surveys/studies are being conducted according to the types of risks and cooperate actively with such surveys/studies because understanding and cooperation of healthcare professionals is necessary for smooth implementation of post-marketing surveys/studies.

<References> (including provisionally translated titles)

1) Pharmacovigilance Planning (Joint PFSB/ELD Notification No. 0916001 and PFSB/SD Notification No. 0916001 dated September 16, 2005, by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
(International Conference on Harmonisation (ICH) website)
http://www.pmda.go.jp/ich/e/e2e_05_9_16e.pdf

2) Risk Management Plan Guidance (Joint PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012, by the Director of SD and the Director of ELD PFSB, MHLW)
(PMDA website)
http://www.pmda.go.jp/english/service/pdf/mhlw/PFSB-SD_Notification120411-1.pdf

3) Preparation of the Risk Management Plan (Joint PFSB/ELD Notification No. 0426-2 and PFSB/SD Notification No. 0426-1 dated April 26, 2012, by the Director of ELD and the Director of SD, PFSB, MHLW)
(PMDA website) (only available in Japanese language)
http://www.info.pmda.go.jp/iyaku/file/h240426-001.pdf

2

Revision of Precautions (No. 244)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated February 19, 2013.

1

Estrogen and progesterone preparations
Mixed hormone preparations

Estradiol (ESTRANA, Julina, DIVIGEL, FEMIEST)
Estradiol Benzoate
Estradiol Valerate
Estradiol Dipropionate
Estriol (oral dosage form)
Estriol Tripropionate
Conjugated Estrogen
Estradiol/Norethisterone Acetate
Estradiol/Levonorgestrel
Testosterone/Estradiol
Testosterone Enanthate/Estradiol Valerate
Testosterone Enanthate/Testosterone Propionate/ Estradiol Valerate

Brand Name

ESTRANA TAPE 0.72 mg (Hisamitsu Pharmaceutical Co., Inc.), and the others
OVAHORMON AQUEOUS SUSPENSION 0.2, 1 (Aska Pharmaceutical Co., Ltd.)
PELANIN DEPOT 5 mg for Intramuscular Inj., 10 mg for Intramuscular Inj. (Mochida Pharmaceutical Co., Ltd.), and the others
OVAHORMON DEPOT INTRAMUSCULAR INJECTION 5 mg (Aska Pharmaceutical. Co., Ltd.)
ESTRIEL Tablets 100γ, 0.5 mg, 1 mg (Mochida Pharmaceutical Co., Ltd.), and the others
ESTRIEL DEPOT 10 mg for Inj. (Mochida Pharmaceutical Co., Ltd.)
PREMARIN TABLETS 0.625 mg (Pfizer Japan Inc.)
MENOAID COMBIPATCH (Aska Pharmaceutical. Co., Ltd.)
Wellnara Combination Tablet (Bayer Yakuhin, Ltd.)
BOTHERMON AQUEOUS SUSPENSION (Aska Pharmaceutical. Co., Ltd.)
Primodian-Depot intramuscular injection (Fuji Pharma Co., Ltd.) and the others
BOTHERMON DEPOT INTRAMUSCULAR INJECTION (Aska Pharmaceutical. Co., Ltd.)

Contraindications

Patients with untreated endometrial hyperplasia

2 **Estrogen and progesterone preparations**

Ethinylestradiol

Brand Name	PROSEXOL TABLETS 0.5 mg (Aska Pharmaceutical. Co., Ltd.)
Contraindications	Patients with untreated endometrial hyperplasia
Important Precautions	When this drug is administered to women, interview including histories of diseases and genetic predisposition should be taken, and breast examination and gynecological examination (including cytology of the endometrium and endometrial thickness measurement by ultrasonography for women with intact uterus) should be performed before initiating therapy with this drug. After starting administration of this drug, periodic breast examinations and gynecological examinations should be performed.

3 **Mixed hormone preparations**

Norethisterone/Mestranol
(preparations with the indication for climacteric disturbance)

Brand Name	SOPHIA-A TABLETS (Aska Pharmaceutical Co., Ltd.), and the others
Contraindications	Patients with untreated endometrial hyperplasia
Important Precautions	Interview including histories of diseases and genetic predisposition should be taken, and breast examination and gynecological examination (including cytology of the endometrium and endometrial thickness measurement by ultrasonography for women with intact uterus) should be performed before initiating therapy with this drug. After starting administration of this drug, periodic breast examinations and gynecological examinations should be performed.

4 **Antiarrhythmic agents**

Propafenone Hydrochloride

Brand Name	Pronon Tablets 100 mg, 150 mg (Toa Eiyo Ltd..), and the others
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfuncti or jaundice on with elevations of AST (GOT), ALT (GPT), Al-P, bilirubin, γ-GTP, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

5 **Pituitary hormone preparations**
Estrogen and progesterone preparations
Hormones-Miscellaneous
Genital organ agents

Purified Human Menopausal Gonadotrophin
Human Menopausal Gonadotrophin
Human Chorionic Gonadotrophin
Follitropin Beta (Genetical Recombination)
Follitropin Alfa (Genetical Recombination)
Estriol (injectable dosage form, preparations for vaginal application)
Clomifene Citrate
Gonadorelin Acetate (1.2 mg, 2.4 mg)

Cyclofenil

Brand Name	GONAPURE INJECTION 75, 150 (Aska Pharmaceutical. Co., Ltd.), and the others HMG for Intramuscular Injection 75 Unit "F", 150 Unit "F" (Fuji Pharma Co., Ltd.), and the others HCG Mochida 3,000 units for Intramuscular Inj., HCG Mochida 5,000 units for Intramuscular Inj., HCG Mochida 10,000 units for Intramuscular Inj. (Mochida Pharmaceutical Co., Ltd.), and the others FOLLISTIM Injection 50, 75, 150, FOLLISTIM Injection 300 IU Cartridge, 600 IU Cartridge, 900 IU Cartridge (MSD K.K.) Gonalef for Subcutaneous Injection 75, 150, Gonalef for Subcutaneous Injection Pen 300, 450, 900 (Merck Serono Co., Ltd.) HOLIN FOR INTRAMUSCULAR INJECTION 10 mg, HOLIN-V VAGINAL TABLETS 1 mg (Aska Pharmaceutical Co., Ltd.), and the others SPACROMIN Tablets 50 mg (Pola Pharma Inc.), and the others HYPOCRINE Injection 1.2, 2.4 (Mitsubishi Tanabe Pharma Corporation) SEXOVID TABLETS 100 mg (Aska Pharmaceutical Co., Ltd)
Careful Administration	Patients with untreated endometrial hyperplasia

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 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 March 1, 2013)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Fexofenadine Hydrochloride/Pseudoephedrine Hydrochloride dellegra Combination Tablets	Sanofi K.K.	February 28, 2013
Sodium Risedronate Hydrate Actonel Tab. 75 mg	Ajinomoto Pharmaceuticals Co., Ltd.	February 28, 2013
Sodium Risedronate Hydrate BENET Tablets 75 mg.	Takeda Pharmaceutical Company Limited	February 28, 2013
Apixaban Eliquis tablets 2.5 mg, 5 mg	Bristol-Myers K.K.	February 26, 2013
Levocarnitine L-Cartin FF oral solution 10%, L-Cartin FF injection 1000 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013
Rotigotine Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013
Atovaquone/Proguanil Hydrochloride Malarone Combination Tablets	GlaxoSmithKline K.K.	February 22, 2013
Tetrabenazine CHOREAZINE Tablets 12.5 mg	Alfresa Pharma Corporation	February 22, 2013
Famciclovir Famvir Tab. 250 mg*[1]	Asahi Kasei Pharma Corporation	February 21, 2013
Sodium Phenylbutyrate Buphenyl Tablets 500 mg, Buphenyl Granules 94%	Orphan Pacific, Inc.	January 17, 2013
Lanreotide Acetate Somatuline 60 mg for s.c. Injection, Somatuline 90 mg for s.c. Injection, Somatuline 120 mg for s.c. Injection	Teijin Pharma Limited.	January 17, 2013
Omega-3-acid ethyl esters LOTRIGA Granular Capsule 2 g	Takeda Pharmaceutical Company Limited	January 10, 2013
Carmustine Gliadel 7.7 mg Implant	Nobelpharma Co., Ltd.	January 9, 2013
Tobramycin TOBI Inhalation solution 300 mg	Novartis Pharma K.K.	January 9, 2013

Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg*2	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012
Irbesartan/Amlodipine Besilate AIMIX Combination Tablet LD, HD	Dainippon Sumitomo Pharma Co., Ltd.	December 19, 2012
Olanzapine Zyprexa Rapid Acting Intra-Muscular Injection 10 mg	Eli Lilly Japan K.K.	December 3, 2012
Anagliptin SUINY Tab. 100 mg	Sanwa Kagaku Kenkyusho Co., Ltd.	November 30, 2012
Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL	Bayer Yakuhin, Ltd.	November 27, 2012
Stiripentol DIACOMIT DRYSYRUP 250 mg, 500 mg, DIACOMIT CAPSULES 250 mg	Meiji Seika Pharma Co., Ltd	November 27, 2012
Glycopyrronium Bromide seebri inhalation capsules 50 μg	Novartis Pharma K.K.	November 22, 2012
Tigecycline Tygacil Injection 50 mg	Pfizer Japan Inc.	November 22, 2012
Lubiprostone Amitiza Capsules 24 μg	Sucampo Pharma Ltd.	November 22, 2012
Botulinum Toxin Type A BOTOX for injection 50 Unit, 100Unit*3	GlaxoSmithKline K.K.	November 21, 2012
Everolimus AFINITOR tablets 5 mg, 2.5 mg*4, AFINITOR dispersible tablets 2 mg, 3 mg*5	Novartis Pharma K.K.	November 21, 2012
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg*6	Wakamoto Co., Ltd.	November 21, 2012
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine TETRABIK Subcutaneous Injection Syringe	The Research Foundation for Microbial Diseases of Osaka University	October 31, 2012
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine Quattrovac Subcutaneous Injection Syringe	The Chemo-Sero-Therapeutic Research Institute	October 31, 2012
Degarelix Acetate Gonax 80 mg for Subcutaneous Injection, Gonax 120 mg for Subcutaneous Injection	Astellas Pharma. Inc.	October 23, 2012
Clopidogrel Sulfate PLAVIX 25 mg Tablets, 75 mg Tablets*7	Sanofi K.K.	September 28, 2012
Tazobactam Sodium/Piperacillin Sodium ZOSYN for Intravenous Injection 2.25, 4.5*8	Taiho Pharmaceutical Co., Ltd.	September 28, 2012
Pazopanib Hydrochloride Votrient Tablets 200 mg	GlaxoSmithKline K.K.	September 28, 2012
Iguratimod KOLBET Tablets 25 mg	Toyama Chemical Co., Ltd.	September 12, 2012
Iguratimod Careram Tablets 25 mg	Eisai Co., Ltd.	September 12, 2012
Teneligliptin Hydrobromide Hydrate TENELIA Tablets 20 mg	Mitsubishi Tanabe Pharma Corporation	September 10, 2012
Formoterol Fumarate Hydrate Oxis 9 μg Turbuhaler 28 doses, 60 doses*9	AstraZeneca K.K.	September 3, 2012

*1 An additional indication for “treatment of patients with herpes simplex”

*2 An additional indication for “treatment of patients with central diabetes insipidus”

*3 An additional indication for “treatment of patients with severe primary axillary hyperhidrosis”

*4 An additional indication for “treatment of patients with renal angiomyolipoma associated with tuberous sclerosis, subependymal giant cell astrocytoma associated with tuberous sclerosis”

*5 An additional indication for “treatment of patients with subependymal giant cell astrocytoma associated with tuberous sclerosis”

*6 An additional indication for “treatment of patients with diabetic macular oedema”

*7 An additional indication for “prevention of thrombus and embolus formation in patients with peripheral arterial disease”

*8 An additional indication for “treatment of patients with peritonitis, intra-abdominal abscess, cholecystitis, or cholangitis”

*9 An additional indication for “remission of various symptoms associated with airway obstructive disorder in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)”