# Pharmaceuticals and Medical Devices Safety Information

**No. 323 May 2015**

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

Available information is listed here

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**Published by**
**Ministry of Health, Labour and Welfare**

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# Pharmaceuticals and Medical Devices Safety Information

**No. 323 May 2015**

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


## [ Outline of Information ]



*E*: Distribution of Dear Healthcare Professional Letters of Emergency Communications *R*: Distribution of Dear Healthcare Professional Letters of Rapid Communications *P*: Revision of Precautions *C*: Case Reports

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

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

## Abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| Al-P | Alkaline Phosphatase |
| ALT (GPT) | Alanine aminotransferase (Glutamate pyruvate transaminase) |
| AST (GOT) | Aspartate aminotransferase (Glutamate oxaloacetate transaminase) |
| CK (CPK) | Creatine kinase (Creatine phosphokinase) |
| CRP | C-reactive protein |
| EAD | Economic Affairs Division |
| EPPV | Early Post-marketing Phase Vigilance |
| γ-GTP | Gamma-glutamyl transpeptidase |
| GS 1 | Global Standard One |
| HPB | Health Policy Bureau |
| IgE | Immunoglobulin E |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| ITF | Interleaved Two of Five |
| JAN | Japanese Accepted Names for Pharmaceuticals |
| JIS | Japanese Industrial Standards |
| MAH | Marketing authorization holder |
| MHLW | Ministry of Health, Labour and Welfare |
| PFSB | Pharmaceutical and Food Safety Bureau |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PTP | Press through package |
| SD | Safety Division |
| T-Bil | Total bilirubin |
| TEN | Toxic epidermal necrolysis |
| WBC | White blood cell |

# 1

# Utilization of New Bar Code Labeling and Termination of JAN/ITF Code Labeling on Prescription Drugs

## 1. Introduction

Regarding the bar code labeling on prescription drugs, the Japanese Accepted Names for Pharmaceuticals (JAN) code and Interleaved Two of Five (ITF) code will not be labeled on prescription drugs that are released by manufacturers on and after July 2015 (July 2016 for products with special reasons). Only the new bar code will be labeled thereafter.

Note that JAN/ITF code labeling will be terminated. The outline of related guidance is presented again to utilize the new bar code labeling.

## 2. Utilization of new bar code labeling

In current "Procedures for Bar Code Labeling on Prescription Drugs" ("Partial Amendment of the 'Procedures for Bar Code Labeling on Prescription Drugs'" (Joint Notification of Health Policy Bureau (HPB)/Economic Affairs Division (EAD) No. 0629-2 and Pharmaceutical and Food Safety Bureau (PFSB)/Safety Division (SD) Notification No. 0629-2, by the Director of the EAD, HPB and by the Director of the SD, PFSB, Ministry of Health, Labour and Welfare (MHLW), dated June 29, 2012), products subject to labeling are prescription drugs ([1] specified biological products, [2] biological products, [3] injections, [4] oral agents, and [5] topical agents). Packaging form units are classified into the following 3 types: I) dispensing packaging unit, II) distribution packaging unit, and III) supply packaging unit[*1]. According to the type of prescription drugs and packaging form units, new bar code[*2] labeling of commodity code, expiration date, quantity, and lot number or code are essentially required ("a") or optionally required ("b") as described in the following Table 1.

(*1) Packaging units: There are 3-stage packaging units as follows:
- Dispensing packaging unit: This is the minimum packaging unit in which marketing authorization holders (MAHs) pack drugs for marketing. Press through package (PTP) sheet, vial, etc. fall under this category.
- Distribution packaging unit: This is generally the minimum packaging unit in which distributors such as wholesalers sell products to purchasers such as medical institutions and pharmacies. A box containing 100 PTP sheets, etc. fall under this category.
- Supply packaging unit: This is generally a packaging unit comprising multiple distribution packaging units packed by MAHs. A carton containing 10 distribution packaging units of boxes, etc. fall under this category.

(*2) New bar code: Global Standard One (GS 1) data bar specified by the Japanese Industrial Standards (JIS) X 0509
or Code 128 specified by the JIS X 0504

Table 1 Prescription drugs subject to bar code labeling

| Types of prescription drug | I) Dispensing packaging unit | | | II) Distribution packaging unit | | | III) Supply packaging unit | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comm-odity code | Expiration date | Lot number or code | Comm-odity code | Expiration date | Lot number or code | Comm-odity code | Expiration date | Quantity | Lot number or code |
| (1) Specified biological products | a | a | a | a | a | a | a | a | a | a |
| (2) Biological products | a | b | b | a | a | a | a | a | a | a |
| (3) Injections | a | b | b | a | b | b | b | b | b | b |
| (4) Oral agents | a* | b | b | a | b | b | b | b | b | b |
| (5)Topical agents | a* | b | b | a | b | b | b | b | b | b |

Note 1:"a" shows that it is essentially required to label (required labeling), and "b" shows that it is not necessarily required to label (optional labeling).

Note 2:Regarding items with a mark "*", the bar code labeling is essentially required on products released by MAHs after July 2015 (July 2016 for products with special reasons such as those manufactured only once a year).

Items of distribution packaging units and supply packaging units in which optional labeling is required (expiration date, quantity, and lot number or code; commodity code is also included for supply packaging units.) is to be sequentially labeled from MAHs that can perform bar code labeling. Bar code labeling is required from the viewpoint of the optimization of distribution. However, the safety and relief of patients are expected to be more secure by the advancing of bar code labeling by pharmaceutical companies and taking measures to ensure exact and appropriate traceability such as conducting lot management with utilizing this labeling by medical institutions, pharmacies, and drug wholesalers.

From the perspective of preventing medical accidents due to the mix-up of prescription drugs and ensuring the traceability, healthcare professionals are requested to collaborate on the utilization of the new bar codes.

## 3. Termination of JAN/ITF code labeling on prescription drugs

As mentioned at the beginning of this section, the termination of JAN/ITF code[*3] labeling is approaching. Medical institutions and other healthcare professionals utilizing these codes for their businesses are requested to take necessary measures to prevent troubles in their businesses.

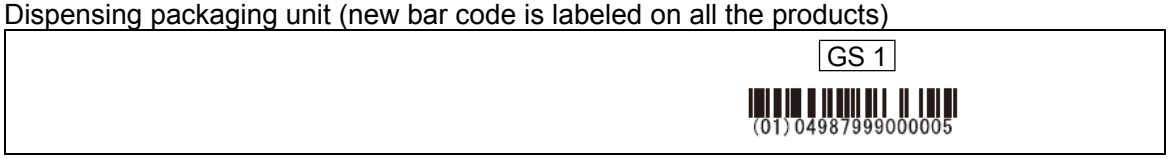
(*3) JAN Code: Bar code specified by the JIS X 0507
ITF Code: Bar code specified by the JIS X 0502

[Reference 1] URL of related notifications, etc.

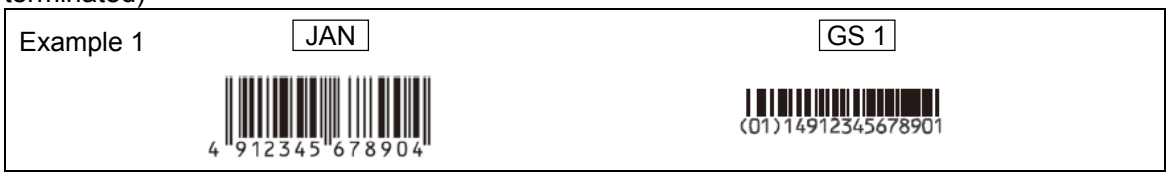
- Partial Amendment of the "Procedure for Bar Code Labeling on Prescription Drugs"
  (Joint Notification of HPB/EAD No. 0629-2 and PFSB/SD Notification No. 0629-2, by the Director of the EAD, HPB and by the Director of the SD, PFSB, MHLW, dated June 29, 2012) (only available in Japanese language) http://www.pmda.go.jp/files/000144647.pdf
- Questions and Answers (Q&A) on the Partial Amendment of the "Procedure for Bar Code Labeling on Prescription Drugs"
  (Administrative notice from the SD, PFSB, MHLW, dated June 29, 2012) (only available in Japanese language) http://www.pmda.go.jp/files/000145941.pdf
- Pharmaceuticals and Medical Devices Safety Information No. 298
  http://www.pmda.go.jp/files/000153205.pdf
- "Partial Amendment of the 'Procedure for Bar Code Labeling on Prescription Drugs' for the Prevention of Medical Accidents"
  http://www1.mhlw.go.jp/kinkyu/iyaku_j/iyaku_j/anzenseijyouhou/298-1.pdf

[Reference 2] Examples of bar code labeling

1. Dispensing packaging unit (new bar code is labeled on all the products)




2. Distribution packaging unit (left, JAN code; right, new bar code; JAN code labeling will be terminated)





Note: “GS 1” in the above figures means GS 1 data bar.
The labeling sample shown in the upper figure is GS 1 data bar limited and that shown in lower figure is GS 1 data bar limited composite symbol with Composite Component A.

3. Supply packaging unit (left, ITF code; right, new bar code; ITF code labeling will be terminated)


Note: “GS 1-128” in the above figure means Code 128.

# 2
# Important Safety Information

Regarding the revision of the Precautions section of the package inserts of drugs in accordance with the Notification dated April 23, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are presented in this section.

## 1 Asunaprevir and Daclatasvir Hydrochloride

| | |
|---|---|
| **Brand name (name of company)** | Asunaprevir: Sunvepra Capsules 100 mg (Bristol-Myers K.K.)<br>Daclatasvir Hydrochloride: Daklinza Tablets 60 mg (Bristol-Myers K.K.) |
| **Therapeutic category** | Antivirals |
| **Indications** | Improvement of viraemia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C |

### PRECAUTIONS (underlined parts are revised)

**Adverse reactions (clinically significant adverse reactions)**

Erythema multiforme: Erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

**Reference information**

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 7 months (from initial marketing to March 2015)
Case of adverse events suggestive of erythema multiforme: 6 cases* (no fatal case)
*Case of events for which a causality to the combination therapy with daclatasvir hydrochloride and asunaprevir could not be ruled out.
The number of patients using these drugs estimated by MAH: 20 000 (from initial marketing to February 2015)
Launched in Japan: September 2014

### Case summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 70s | Chronic hepatitis C (hypertension, osteoporosis, depression, and hypercholesterolaemia) | Daklinza Tablets 60 mg and Sunvepra Capsules 200 mg for 14 days | **Erythema multiforme**<br>The patient had a history of prior treatment with peginterferon alfa-2b (genetical recombination) plus ribavirin.<br>The patient had a medical history of drug eruption (antibiotic).<br>Approximately 19 years before administration:<br>chronic hepatitis C was diagnosed.<br>Day 1 of administration:<br>The combination therapy with Daklinza Tablets 60 mg once daily and Sunvepra Capsules 100 mg twice daily was started.<br>Day 12 of administration:<br>Pyrexia of 39°C developed.<br>Day 14 of administration:<br>The patient visited the outpatient department because of subsequent, continuous slight fever. Mild jaundice was observed. |

| | | | | |
|---|---|---|---|---|
| | | | | Day 15 of administration (day of discontinuation):<br>Urticarial erythema was observed over the whole body in the morning, and the patient revisited the outpatient department. She particularly complained of myalgia in the upper arm. Creatine phosphokinase (CPK) level was 767 IU/L. She was diagnosed with erythema multiforme exudativum on the body trunk and limbs.<br>The administration of Daklinza Tablets and Sunvepra Capsules were discontinued.<br>Intravenous drip infusion of hydrocortisone sodium succinate 200 mg and physiological saline 100 mL were administered, and injection of glycyrrhizin/glycine/cysteine injection 60 mL/day was administered. The same treatments were performed on 1 and 3 days after discontinuation.<br>The administration of fexofenadine hydrochloride tablets 60 mg/day was started.<br>1 day after discontinuation:<br>Oral administration of prednisolone 30 mg/day was started.<br>3 days after discontinuation:<br>The patient recovered from pyrexia.<br>4 days after discontinuation:<br>The administration of fexofenadine hydrochloride tablets 60 mg/day was terminated.<br>6 days after discontinuation:<br>The dose of prednisolone was reduced to 20 mg/day.<br>14 days after discontinuation:<br>The patient recovered from erythema multiforme exudativum, jaundice, myalgia, and increased CPK.<br>18 days after discontinuation:<br>The dose of prednisolone was reduced to 10 mg/day.<br>28 days after discontinuation:<br>The dose of prednisolone was reduced to 5 mg/day. |
| | Concomitant medications: candesartan cilexetil, alfacalcidol, and taurine | | | |

**Laboratory examination**

| | Day 1 of administration | Day 14 of administration | Day 15 of administration (day of discontinuation) | 14 days after discontinuation |
|---|---|---|---|---|
| WBC (/mm$^3$) | 3 700 | 7 100 | 10 400 | 8 700 |
| Lymphocytes (%) | - | - | 10 | 15 |
| Neutrophils (%) | - | - | 84 | 80 |
| CRP (mg/dL) | - | - | 4.53 | ≤ 0.05 |
| AST (IU/L) | 75 | 26 | 40 | 19 |
| ALT (IU/L) | 56 | 20 | 30 | 16 |
| Al-P (IU/L) | 265 | - | 201 | 346 |
| γ-GTP (IU/L) | 20 | 29 | 50 | 30 |
| T-Bil (mg/dL) | 1.2 | 2.9 | 3.6 | 0.9 |
| Blood creatinine (mg/dL) | 0.48 | 0.59 | 1.16 | 0.54 |
| CK (IU/L) | - | - | 767 | 35 |
| IgE (mg/dL) | - | 35 | - | - |
| IgM (mg/dL) | - | 57 | - | - |
| IgG (mg/dL) | - | 1 365 | - | - |

## Case summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Female 50s | Chronic hepatitis C (hypothyroidism) | Daklinza Tablets 60 mg and Sunvepra Capsules 200 mg for 38 days | **Erythema multiforme**<br>The patient had a history of a prior treatment with interferon alfa-2b (genetical recombination) plus ribavirin and peginterferon alfa-2b (genetical recombination) plus ribavirin.<br>Day 1 of administration:<br>The combination therapy with Daklinza Tablets 60 mg once daily and Sunvepra Capsules 100 mg twice daily was started.<br>Day 37 of administration:<br>Skin eruption developed.<br>Day 39 of administration (day of discontinuation):<br>Skin eruption gradually aggravated. The patient visited to the emergency outpatient department. Erythema multiforme exudativum was diagnosed and she was admitted to the hospital.<br>According to a dermatologist's findings, no abnormality was found in palpebral conjunctiva, bulbar conjunctiva, or oral mucosa.<br>Macular erythema multiforme exudativum was observed on the face and the upper body.<br>The administration of Daklinza Tablets and Sunvepra Capsules was discontinued.<br>Steroid pulse therapy was started (until 2 days after discontinuation of medication).<br>3 days after discontinuation:<br>Oral administration of prednisolone 40 mg was started.<br>8 days after discontinuation:<br>Erythema multiforme exudativum was improved. |
| | Concomitant medications: ursodeoxycholic acid, ascorbic acid/calcium pantothenate, and levothyroxine sodium hydrate | | | |

## Laboratory examination

| | Day 39 of administration (day of discontinuation) |
|---|---|
| WBC (/mm$^3$) | 5 600 |
| Lymphocytes (%) | 24.0 |
| Eosinophil (%) | 0.5 |
| Neutrophils (%) | 70.9 |
| CRP (mg/dL) | 0.03 |
| AST (IU/L) | 35 |
| ALT (IU/L) | 24 |
| γ-GTP (IU/L) | 45 |
| T-Bil (mg/dL) | 1.3 |
| Blood creatinine (mg/dL) | 0.63 |

# 3

# Revision of Precautions (No. 265)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated April 23, 2015.

## 1

**Psychotropics**

### Duloxetine Hydrochloride

| | |
|---|---|
| **Brand name** | Cymbalta Capsules 20 mg and 30 mg (Shionogi & Co., Ltd) |
| **Adverse reactions (clinically significant adverse reactions)** | Neuroleptic malignant syndrome: Neuroleptic malignant syndrome may occur. If any abnormalities such as fever, akinetic mutism, strong muscle rigidity, swallowing difficult, tachycardia, blood pressure fluctuation, diaphoresis, increased white blood cell (WBC) count, increased serum creatine kinase (creatine phosphokinase) (CK [CPK]), etc. are observed, administration of this drug should be discontinued. Then whole-body control such as body cooling and rehydration should be conducted, and appropriate measures should be taken. In addition, decreased kidney function with myoglobinuria may lead to acute renal failure, and caution should therefore be exercised. |

## 2

**Antihypertensives**

### Azilsartan

| | |
|---|---|
| **Brand name** | Azilva Tablets 10 mg, 20 mg, and 40 mg (Takeda Pharmaceutical Co., Ltd) |
| **Adverse reactions (clinically significant adverse reactions)** | Hepatic function disorder: Hepatic function disorder associated with elevated aspartate aminotransferase (AST or glutamate oxaloacetate transaminase [GOT]), alanine aminotransferase (ALT or glutamate pyruvate transaminase [GPT]), and gamma-glutamyl transpeptidase (γ-GTP) levels may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted. |

## 3

**Blood and body fluid agents-Miscellaneous**

### Clopidogrel Sulfate

| | |
|---|---|
| **Brand name** | Plavix Tablets 25 mg, 75 mg, and the others (Sanofi K.K., and the others) |
| **Adverse reactions (clinically significant adverse reactions)** | Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme exudativum, and acute generalised exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme exudativum, and/or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted. |

4 **Blood and body fluid agents-Miscellaneous**

## Clopidogrel Sulfate/Aspirin

| | |
|---|---|
| **Brand name** | Complavin Combination Tablets (Sanofi K.K.) |
| **Adverse reactions (clinically significant adverse reactions)** | Toxic epidermal necrolysis (TEN, oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme exudativum, acute generalised exanthematous pustulosis, and exfoliative dermatitis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme exudativum, acute generalised exanthematous pustulosis, and/or exfoliative dermatitis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted. |

5 **Acting mainly on gram-positive and gram-negative bacteria**

## Cefotaxime Sodium

| | |
|---|---|
| **Brand name** | Claforan Injections 0.5 g and 1 g (Sanofi K.K.), Cefotax Injections 0.5 g and 1 g (Nichi-iko Sanofi K.K.) |
| **Adverse reactions (clinically significant adverse reactions)** | Toxic epidermal necrolysis (TEN, oculomucocutaneous syndrome (Stevens-Johnson syndrome), and acute generalised exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, and/or acute generalised exanthematous pustulosis may occur. If these symptoms are observed, administration of this drug should be discontinued and appropriate measures should be adopted. |

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

(As of April 30, 2015)
◎: Products for which EPPV was initiated after April 1, 2015

| | Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | elosulfase alfa (genetical recombination)<br>Vimizim Intravenous Infusions 5 mg | BioMarin Pharmaceutical Japan Inc. | April 23, 2015 |
| ◎ | N/A<br>Allergen Extract Mites Subcutaneous Injections for Treatment “Torii” 10,000 JAU/mL, 100 000 JAU/mL | Torii Pharmaceutical Co., Ltd. | April 21, 2015 |
| ◎ | nitisinone<br>Orfadin Capsules 2 mg, 5 mg, 10 mg | Astellas Pharma Inc. | April 14, 2015 |
| ◎ | dolutegravir sodium/lamivudine/abacavir sulfate<br>Triumeq Combination Tablets | ViiV Healthcare K.K. | April 10, 2015 |
| ◎ | benzoyl peroxide<br>Bepio Gel 2.5% | Maruho Co., Ltd. | April 1, 2015 |
| | efraloctocog alfa (genetical recombination)<br>Eloctate Intravenous 250, 500, 750, 1000, 1500, 2000, 3000 | Biogen Idec Japan Ltd. | March 9, 2015 |
| | secukinumab (genetical recombination)<br>Cosentyx for S.C. Injection 150 mg Syringe, Cosentyx for S.C. Injection 150 mg | Novartis Pharma K.K. | February 27, 2015 |
| | vonoprazan fumarate<br>Takecab Tablets 10 mg, 20 mg | Takeda Pharmaceutical Company Limited | February 26, 2015 |
| | vemurafenib<br>Zelboraf Tablets 240 mg | Chugai Pharmaceutical Co., Ltd. | February 26, 2015 |
| | rabeprazole sodium<br>Pariet Tablets 5 mg, 10 mg*1 | Eisai Co., Ltd. | February 26, 2015 |
| | empagliflozin<br>Jardiance Tablets 10 mg, 25 mg | Nippon Boehringer Ingelheim Co., Ltd. | February 24, 2015 |
| | streptozocin<br>Zanosar IV Infusion 1 g | Nobelpharma Co., Ltd. | February 23, 2015 |
| | fexofenadine hydrochloride<br>Allegra 5% Dry Syrup | Sanofi K.K. | January 19, 2015 |

| Nonproprietary name<br>Brand name on | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| alemtuzumab (genetical recombination)<br>MabCampath 30 mg I.V. Infusion | Sanofi K.K. | January 15, 2015 |
| sirolimus<br>Rapalimus Tablets 1 mg | Nobelpharma Co., Ltd. | December 22, 2014 |
| caspofungin acetate<br>Cancidas for Intravenous Drip Infusion 50 mg, 70 mg*2 | MSD K.K. | December 18, 2014 |
| darbepoetin alfa (genetical recombination)<br>Nesp Injection 5 μg Plastic Syringe, 10 μg Plastic Syringe, 15 μg Plastic Syringe, 20 μg Plastic Syringe, 30 μg Plastic Syringe, 40 μg Plastic Syringe, 60 μg Plastic Syringe, 120 μg Plastic Syringe, 180 μg Plastic Syringe*3 | Kyowa Hakko Kirin Co., Ltd. | December 18, 2014 |
| midazolam<br>Midafresa Injection 0.1% | Alfresa Pharma Corporation | December 17, 2014 |
| rilpivirine hydrochloride/tenofovir disoproxil fumarate/emtricitabine<br>Complera Combination Tablets | Janssen Pharmaceutical K.K. | December 12, 2014 |
| bosutinib hydrate<br>Bosulif Tablets 100 mg | Pfizer Japan Inc. | December 5, 2014 |
| progesterone<br>Lutinus Vaginal Tablets 100 mg | Ferring Pharmaceuticals Co., Ltd. | December 5, 2014 |
| ripasudil hydrochloride hydrate<br>Glanatec Ophthalmic Solution 0.4% | Kowa Company, Ltd. | December 2, 2014 |
| anhydrous caffeine<br>Respia Injection or oral solution 60 mg | Nobelpharma Co., Ltd. | December 1, 2014 |
| pegfilgrastim (genetical recombination)<br>G-lasta Subcutaneous Injection 3.6 mg | Kyowa Hakko Kirin Co., Ltd. | November 28, 2014 |
| suvorexant<br>Belsomra Tablets 15 mg, 20 mg | MSD K.K. | November 26, 2014 |
| vaniprevir<br>Vanihep Capsules 150 mg | MSD K.K. | November 25, 2014 |
| anagrelide hydrochloride hydrate<br>Agrylin Capsules 0.5 mg | Shire Japan KK | November 25, 2014 |
| tiotropium bromide hydrate<br>Spiriva 2.5 μg Respimat 60 puffs*4 | Nippon Boehringer Ingelheim Co., Ltd. | November 18, 2014 |
| aflibercept (genetical recombination)<br>Eylea Solution Intravitreal Injections 40 mg/mL, Eylea Solution Intravitreal Injections Kit 40 mg/mL*5 | Bayer Yakuhin, Ltd. | November 18, 2014 |
| Freeze-dried activated human blood coagulation factor VII concentrate containing factor X<br>Byclot for Intravenous Injection | The Chemo-Sero-Therapeutic Research Institute | November 11, 2014 |
| edoxaban tosilate hydrate<br>Lixiana Tablets 15 mg, 30 mg, 60 mg*6 | Daiichi Sankyo Company, Limited | September 26, 2014 |

*1 An additional indication for “the treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low doses of aspirin”
*2 An additional administration for “pediatrics”
*3 An additional indication for “the treatment of patients with anaemia associated with myelodysplastic syndrome”
*4 An additional indication for “the remission of various symptoms associated with airway obstructive disorder in

patients with the following diseases: bronchial asthma (to be used only in patients with severe and persistent disease)"

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

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