# Pharmaceuticals and Medical Devices Safety Information

**No. 311 March 2014** 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) 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**
**Ministry of Health, Labour and Welfare**

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

*Correction to the list in "4. List of Products Subject to Early Post-marketing Phase Vigilance."

# Pharmaceuticals and Medical Devices Safety Information

**No. 311 March 2014**

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

| | |
|---|---|
| ADAMTS13 | A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 |
| ADRs | Adverse drug reactions |
| Alb | Albumin |
| ALP | Alkaline phosphatase |
| ALT (GPT) | Alanine aminotransferase (Glutamate pyruvate transaminase) |
| AST (GOT) | Aspartate aminotransferase (Glutamate oxaloacetate transaminase) |
| BUN | Blood urea nitrogen |
| CAPD | Continuous ambulatory peritoneal dialysis |
| Cr | Creatinine |
| CRP | C-reactive protein |
| CT | Computed tomography |
| ECOG PS | Eastern Cooperative Oncology Group Performance status |
| EPPV | Early Post-marketing Phase Vigilance |
| FDP | Fibrin/fibrinogen degradation product |
| FIB | Fibrinogen |
| GVP | Good Vigilance Practice |
| Hb | Haemoglobin |
| HUS | Haemolytic uraemic syndrome |
| IgE | Immunoglobulin E |
| IU | International unit |
| JCS | Japan Coma Scale |
| LDH | Lactate dehydrogenase |
| MAH | Marketing authorization holder |
| MHLW | Ministry of Health, Labour and Welfare |
| PLT | Platelet |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PMDSI | Pharmaceuticals and Medical Devices Safety Information |
| PT | Prothrombin Time |
| RBC | Red blood cell count |
| ST | Sulfamethoxazole/Trimethoprim |
| T-Bil | Total bilirubin |
| TTP | Thrombotic thrombocytopenic purpura |
| VW | von Willebrand |
| WBC | White blood cell count |
| γ-GTP | gamma-glutamyl transpeptidase |

# 1

# Revised Adverse Reaction Reporting System for Quasi-drugs and Cosmetics

## 1. Introduction

Recently, cases of adverse reactions caused by medicinal cosmetics (quasi-drugs), that were not expected before marketing, such as skin disorders (leukoderma), have reported, and therefore it is necessary to enhance the post-marketing safety measures for quasi-drugs and cosmetics (hereinafter referred to as "cosmetics, etc.") to identify adverse health effects early and take measures.

As one such measure, the adverse reaction reporting system for cosmetics, etc., from marketing authorization holders (MAHs) to the regulatory authorities is enhanced to receive individual case safety reports as well as research reports that have been required to be reported. The revised system has been enforced on April 1, 2014 and a summary of the revised system is presented.

## 2. Revised adverse reaction reporting system for quasi-drugs and cosmetics

When MAHs of drugs, quasi-drugs, cosmetics, and medical devices become aware of any occurrence of adverse reactions/malfunctions caused by their products or research reports, it is mandatory for such MAHs to report them to the MHLW in accordance with the Pharmaceutical Affairs Law Article 77-4-2, Paragraph 1. The scope of reportable information is defined in the Enforcement Ordinance of Pharmaceutical Affairs Law. As shown in **Table 1**, reportable information for cosmetics, etc., was limited to research reports compared to that for drugs and medical devices.

Meanwhile, given the fact that cases of significant adverse reactions caused by medicinal cosmetics, etc., have been reported in recent years, it was determined to revise the Enforcement Ordinance of Pharmaceutical Affairs Law to require reporting of individual cases for any serious adverse reactions caused by cosmetics, etc., as with drugs, in order to identify any similar cases early and immediately take necessary measures if such cases occur in the future (shaded parts in **Table 1**).

**Table 1. Description of safety information that MAHs should report (time frame for reporting is shown in brackets)**

| | Serious adverse reaction reports | | Unknown/ non-serious reports | Report of safety measures taken in overseas | Research reports |
|---|---|---|---|---|---|
| | Death or unknown | Known | | | |
| Drugs, medical devices | Yes (Within 15 days) | Yes (Within 30 days) | Yes (Annual periodic report) | Yes (Within 15 days) | Yes (Within 30 days) |
| Quasi-drugs, cosmetics | Changed from no to yes* (within 15 days) | Changed from no to yes* (within 30 days) | No | No | Yes (Within 30 days) |

*Including cases that require at least 30 days for treatment as well as serious adverse reactions

As with drugs, for cosmetics, etc., whether or not individual cases are reportable are determined by the seriousness criteria of the cases based on International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. Cases that meet

seriousness criteria 1 to 7 in **Table 2** are defined as reportable adverse reactions.

In addition, because cosmetics, etc., have mild effects and are usually used in healthy individuals, it is necessary to collect a wider range of adverse reactions than those for drugs from the viewpoint of risk-benefit balance. Therefore, it was determined only for cosmetics, etc., to include "Cases that require at least 30 days for treatment" (seriousness criteria 8 in **Table 2**), as well as serious adverse reactions, in the scope of individual case reporting.

### Table 2 Adverse reactions caused by quasi-drugs and cosmetics that require individual reporting

| |
|---|
| 1. Death |
| 2. Disability |
| 3. Events that may result in death |
| 4. Events that may result in disability |
| 5. Requiring hospital admission or prolonged hospitalization for treatment |
| 6. severe events corresponding to those shown above |
| 7. Congenital disease or anomaly in next generations |
| 8. Cases that require at least 30 days for treatment |

Article 7 of the Ministerial Ordinance on Good Vigilance Practice (GVP) for drugs, quasi-drugs, cosmetics, and medical devices (GVP Ordinance) stipulates the obligation of MAHs to collect safety management information and its scope. In connection with the enhancement of adverse reaction reporting system, the scope of information that MAHs of cosmetics, etc., are required to collect was also revised to include information from healthcare professionals and government agencies, as with MAHs of drugs, ,as shown in **Table 3.** The GVP Ordinance has been enforced on April 1, 2014.

### Table 3 Scope of safety management information that MAHs of cosmetics, etc., are required to collect

| Before revision | After revision |
|---|---|
| | I Information from healthcare professionals |
| I Information related to academic society reports, literature reports, and other research reports | II Information related to academic society reports, literature reports, and other research reports |
| | III Information from the MHLW and other government agencies, prefectural and city governments, and PMDA |
| | IV Information from governments and corporations of other countries |
| | V Information from other MAHs |
| II Other safety management information | VI Other safety management information |

*The underlined items are the safety management information that has been added.

## 3. Closing comments

The new adverse reaction reporting system for cosmetics, etc., was enforced on April 1, 2014. When any serious adverse reactions by quasi-drugs or cosmetics are suspected and any patients requiring a long-term treatment are noticed, healthcare professionals are encouraged to contact the applicable MAHs and cooperate with investigations to be conducted by the MAHs.

In addition, in the Drugs and Medical Devices Safety Information Reporting System, healthcare professionals have been encouraged to directly report to the MHLW adverse reactions caused by cosmetics, etc., as well as adverse reactions caused by drugs.

### <References>


1) "Adverse Reaction Reporting System for Quasi-drugs and Cosmetics (draft)," materials distributed at the second meeting of 2013 Committee on Drug Safety, November 27, 2013
http://www.mhlw.go.jp/stf/shingi/0000030756.html (only available in Japanese language)

2) "Notification on Enforcement of the Ministerial Ordinance on Partial amendment of Pharmaceutical Affairs Law Enforcement Regulations and Good Vigilance Practice for drugs, quasi-drugs, cosmetics, and medical devices (reporting of adverse reactions etc. to quasi-drugs and cosmetics)," Pharmaceutical and Food Safety Bureau Notification dated February 27, 2014
http://www.info.pmda.go.jp/iyaku/file/h260227-001.pdf (only available in Japanese language)

3) For a detailed description of the Drugs and Medical Devices Safety Information Reporting System and to receive a Drug Safety Information Report Form, please refer to the Pharmaceuticals and Medical Devices Agency (PMDA) website shown below.
Dear healthcare professionals (request for adverse reaction/infection/malfunction reporting)
http://www.info.pmda.go.jp/info/houkoku.html (only available in Japanese language)

# 2

# Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated February 18, 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

## 1 Salazosulfapyridine

| | |
|---|---|
| **Brand Name (name of company)** | (1) Salazopyrin Tablets 500 mg (Pfizer Japan Inc.) and the others<br>(2) Salazopyrin Suppositories 500 mg (Pfizer Japan Inc.)<br>(3) Azulfidine EN tablets 250 mg, 500 mg (Pfizer Inc.), and the others |
| **Therapeutic Category** | Sulfonamides |
| **Indications** | (1) Ulcerative colitis, regional enteritis, nonspecific colitis<br>(2) Ulcerative colitis<br>(3) Rheumatoid arthritis |

### PRECAUTIONS (underlined parts are revised)

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

**Shock, anaphylaxis**: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if any abnormalities such as rash, decreased blood pressure, and/or dyspnoea are observed, administration of this drug should be discontinued and appropriate measures 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 9 months (April 2010 to December 2013)

- Shock, anaphylaxis-associated cases: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 215,000 (June 2012 to May 2013)

Launched in Japan:

(1) January 2009 (The product with an old brand name for this drug was launched in September 1969.)

(2) January 2009 (The product with an old brand name for this drug was launched in June 1982.)

(3) Azulfidine EN tablets 250 mg: August 2002
Azulfidine EN tablets 500 mg: June 2007 (The product with an old brand name for this drug was launched in December 1995.)

## Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 40s | Adult onset Still's disease (None) | 500 mg for 13 days<br>↓<br>Discontinued<br>↓<br>250 mg for 1 day | **Anaphylactic shock**<br>Day 1 of administration:<br>The patient started receiving salazosulfapyridine 500 mg/day, celecoxib, teprenone, and famotidine.<br>Day 13 of administration (day of discontinuation):<br>Due to pyrexia and skin eruption, administration of salazosulfapyridine, celecoxib, teprenone, and famotidine was discontinued.<br>Patch test; Positive for celecoxib, negative for salazosulfapyridine.<br>Drug-induced lymphocyte stimulation test; Positive for celecoxib, negative for salazosulfapyridine.<br>13 days after discontinuation:<br>Pyrexia and skin eruption disappeared. Administration of sodium rabeprazole and diclofenac sodium was started.<br>Day 1 of readministration<br>(day of onset/day of discontinuation of readministration):<br>Several hours after taking salazosulfapyridine 250 mg in the morning, face oedema (particularly lips), pyrexia (38.3°C), erythema (limbs, trunk), and dyspnoea were noted and anaphylactic shock occurred. Systolic blood pressure was 70 mmHg level and oxygen saturation was 88% (room air). Administration of salazosulfapyridine and sodium rabeprazole was discontinued. The patient was admitted to hospital, and received subcutaneous injection of adrenaline 0.3 mg, drip infusion of physiological saline with the clamp wide open, drip infusion of methylprednisolone 500 mg, continuous intravenous infusion of noradrenaline, and oxygen. Blood pressure and other symptoms became stable.<br>5 days after discontinuation of readministration:<br>As oedema, erythema, and pyrexia also disappeared, the patient was discharged from hospital. The patient recovered. |
| | Concomitant medications: sodium rabeprazole, celecoxib, teprenone, famotidine, diclofenac sodium | | | |

## Laboratory Examination

| | Before start of administration | Day 13 of administration | Day 1 of readministration | 1 day after discontinuation of readministration | 3 days after discontinuation of readministration |
|---|---|---|---|---|---|
| WBC (/mm$^3$) | 4,300 | 3,700 | 5,500 | 17,500 | 6,900 |
| Neutrophils (%) | 59.0 | 72.3 | 92.7 | 85.0 | 66.0 |
| Eosinophils (%) | 1.0 | 0.3 | 0.2 | 0 | 1 |
| IgE (IU/mL) | — | 122 | — | 85.5 | — |
| CRP (mg/dL) | 1.00 | 1.32 | 1.86 | 5.82 | 1.73 |

## 2 Sulfamethoxazole/Trimethoprim

| | |
|---|---|
| **Brand Name (name of company)** | (1) Baktar Combination Tablets, Baktar Combination Granules (Shionogi & Co., Ltd.), BACTRAMIN Combination Tablet, BACTRAMIN Combination Granule (Chugai Pharmaceutical Co., Ltd.), and the others<br>(2) BACTRAMIN Injection (Chugai Pharmaceutical Co., Ltd.) |
| **Therapeutic Category** | (1) Chemotherapeutics-Miscellaneous<br>(2) Antiprotozoans |
| **Indications** | (1) 1. General infection(s)<br><Applicable microorganisms> Sulfamethoxazole/trimethoprim (ST)-sensitive strains of Enterococcus, Escherichia coli, Shigella, Salmonella typhi, Salmonella paratyphi, Citrobacter, Klebsiella, Enterobacter, Proteus Morganella morganii, Providencia rettgeri, Haemophilus influenzae<br><Applicable conditions> Pneumonia, secondary infection of chronic respiratory lesions, complicated cystitis, pyelonephritis, infectious enteritis, typhoid, paratyphoid<br>2. Treatment and prophylaxis of pneumocystis pneumonia<br><Applicable microorganisms> Pneumocystis jirovecii<br><Applicable conditions> Pneumocystis pneumonia, prophylaxis of Pneumocystis pneumonia<br>(2) <Applicable microorganisms> Pneumocystis carinii<br><Applicable conditions> Carinii pneumonia |

### PRECAUTIONS (underlined parts are revised)

| | |
|---|---|
| **Adverse Reactions (clinically significant adverse reactions)** | **Thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS)**: TTP (major signs and symptoms; decreased platelets (PLTs), haemolytic anaemia with schizocytes, psychoneurotic symptoms, pyrexia, renal impairment) or HUS (major signs and symptoms; decreased PLTs, haemolytic anaemia with schizocyte, acute renal failure) may occur. Patients should be carefully monitored through blood tests (PLTs, red blood cells, etc.), renal function tests, etc., and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures such as plasma exchange 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 8 months (April 2010 to December 2013)<br>• TTP, HUS-associated cases: 2 cases (no fatal cases)<br>The number of patients using this drug per year estimated by MAHs: Approximately 240,000 (2013)<br>Launched in Japan: Tablet: June 1976<br>Granules: September 1981<br>Injectable dosage form: December 1993 |

## Case Summary

ST combination drugs that were administered to the patient were Baktar Combination Tablets and BACTRAMIN Injection.

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Male 30s | Pneumocystis jirovecii pneumonia (juvenile idiopathic arthritis, chronic renal failure) | Combination tablets<br>2 tablets for 4 days<br>↓<br>Injectable dosage form<br>2 ampoules for 7 days<br>↓<br>Combination tablets<br>2 tablets for 8 days | **TTP**<br>Body height, approximately 120 cm; body weight, approximately 30 kg<br>154 days before administration<br>The patient started receiving peritoneal dialysis (continuous ambulatory peritoneal dialysis [CAPD]) for treatment of chronic renal failure.<br>Day 1 of administration of combination tablets:<br>The patient was admitted to hospital due to pneumonia. Based on computed tomography (CT), Pneumocystis jirovecii pneumonia was suspected, and administration of 2 tablets/day of ST combination tablets was started.<br>Day 2 of administration:<br>Intravenous infusion of prednisolone sodium succinate 80 mg/day was started.<br>Day 4 of administration:<br>Restlessness and irritability occurred. Because it was difficult to give oral medication, ST combination tablets was switched to ST injectable dosage form.<br>Day 5 of administration<br>(Day 1 of administration of injectable dosage form):<br>For treatment of Pneumocystis jirovecii pneumonia, intravenous drip infusion of 2 ampoules/day of ST injectable dosage form was started. CAPD was ongoing.<br>Day 7 of administration:<br>The dose of prednisolone sodium succinate was reduced from 80 mg/day to 40 mg/day.<br>Day 11 of administration:<br>Administration of ST injectable dosage form was discontinued; Because oral administration became possible, the injectable dosage form was switched to the combination tablets on the next day.<br>Day 12 of administration<br>(day of readministration of combination tablets)<br>(day of onset):<br>For Pneumocystis jirovecii pneumonia, administration of 2 tablets/day of ST combination tablets was resumed. Administration was started with dose reduction from intravenous infusion of prednisolone sodium succinate 40 mg/day to oral administration of prednisolone 20 mg/day.<br>Pyrexia in the 37°C level developed.<br>TTP occurred.<br>Day 13 of administration:<br>White blood cell count (WBC) was elevated to the 15000/$mm^3$ level.<br>Day 19 of administration (day of discontinuation):<br>Pyrexia of 39°C occurred. PLT count decreased to 5.3 × $10^4$/$mm^3$. Administration of ST combination tablets was discontinued.<br>1 day after discontinuation:<br>WBC was 38310/$mm^3$ and haemoglobin (Hb) was 7.5 g/dL. |

| | | | | |
|---|---|---|---|---|
| | | | | ST combination tablets was switched to pentamidine isetionate.<br>3 days after discontinuation:<br>Plasma exchange (first session) was started. Subsequently, the second session was performed 4 days after discontinuation, the third session 6 days after, the fourth session 8 days after, and the fifth session 10 days after. Each session was performed with 30 units of fresh frozen plasma preparation.<br>27 days after discontinuation:<br>After that, PLT count and red blood cell increased gradually. The patient recovered from TTP. |
| | Concomitant medications: azithromycin hydrate, ceftriaxone sodium hydrate, prednisolone sodium succinate, prednisolone, olanzapine, lansoprazole | | | |

## Laboratory Examination

| | 5 days before administration | Day 1 of administration | Day 4 of administration | Day 5 of administration | Day 11 of administration | Day 13 of administration | Day of discontinuation | 1 day after discontinuation | 2 days after discontinuation | 3 days after discontinuation | 4 days after discontinuation | 8 days after discontinuation | 22 days after discontinuation | 27 days after discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WBC (/mm$^3$) | 4,380 | 6,230 | 4,090 | 2,610 | 9,340 | 15,450 | 13,240 | 38,310 | 25,290 | 21,030 | 12,920 | 9,710 | 5,860 | 8,950 |
| RBC (× 10$^4$/mm$^3$) | 248 | 237 | 271 | 283 | 297 | 291 | 302 | 262 | 267 | 230 | 270 | 259 | 297 | 309 |
| Hb (g/dL) | 7.2 | 6.7 | 7.9 | 8.1 | 8.5 | 8.2 | 8.6 | 7.5 | 7.5 | 6.5 | 7.8 | 7.8 | 8.6 | 9.1 |
| Plt (× 10$^4$/mm$^3$) | 17.7 | 14.5 | 18.0 | 19.6 | 15.9 | 18.0 | 5.3 | 5.8 | 4.5 | 3.1 | 2.9 | 5.7 | 9.1 | 16.9 |
| Fragmented cells | (+) | (+) | (+) | (+) | (±) | (±) | — | (±) | (+) | (+) | (±) | — | (±) | — |
| Total Bil (mg/dL) | 0.6 | 0.4 | 0.2 | 0.2 | 0.3 | 0.3 | 0.4 | 0.4 | 0.3 | 0.3 | 0.3 | 0.6 | — | — |
| LDH (IU) | 353 | 548 | 383 | 373 | 418 | 433 | 1,019 | 1,359 | 1,365 | 1,119 | 459 | 284 | 426 | 620 |
| BUN (mg/dL) | 79.4 | 83.8 | 87.5 | 87.0 | 38.7 | 48.0 | 72.4 | 71.1 | 80.4 | 72.0 | 67.5 | 73.1 | 59.8 | 75.0 |
| Serum Cr (mg/dL) | 5.37 | 5.96 | 5.83 | 6.07 | 4.44 | 4.44 | 4.45 | 4.59 | 5.01 | 4.77 | 4.14 | 4.36 | 4.46 | 3.77 |
| CRP (mg/dL) | 6.61 | 5.21 | 2.24 | 1.41 | 0.69 | 0.74 | 4.67 | 22.28 | 20.44 | 15.88 | 2.43 | 0.37 | 2.25 | 1.67 |
| FIB (mg/dL) | — | — | 337 | — | — | — | 360 | 333 | 265 | 262 | — | 230 | — | 242 |
| FDP (μg/mL) | — | — | 4.1 | — | — | — | 61.9 | 88.3 | 42.5 | 32.2 | — | 16.8 | 42.6 | 13.1 |
| D-dimer (μg/mL) | — | — | 1.63 | — | — | — | 34.50 | 55.67 | 23.50 | 20.99 | — | 11.69 | 23.83 | 9.50 |
| VW factor activity (%) | — | — | — | — | — | — | — | — | — | 418 | 177 | — | 301 | — |
| ADAMTS13 activity (%) | — | — | — | — | — | — | — | — | — | 33 | — | — | — | — |

## 3 Felbinac (for ethical use)

| | |
|---|---|
| **Brand Name (name of company)** | (1) SELTOUCH Pap 70, 140, SELTOUCH Tape 70 (Teikoku Seiyaku Co., Ltd.), and the others<br>(2) NAPAGELN OINTMENT 3%, NAPAGELN CREAM 3%, NAPAGELN LOTION 3% (Pfizer Japan Inc.), and the others |
| **Therapeutic Category** | Analgesics, antipruritic, astringents, anti-inflammatory agents |
| **Indications** | (1) Relief of pain and inflammation associated with the following disorders and symptoms:<br>Osteoarthritis, periarthritis scapulohumeralis, tendonitis, and tenosynovitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow), myalgia, post-traumatic swelling, and pain<br>(2) Relief of pain and inflammation associated with the following disorders and symptoms:<br>Osteoarthritis, myofascial low back pain, periarthritis scapulohumeralis, tendonitis and tenosynovitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow), myalgia, post-traumatic swelling, and pain |

### PRECAUTIONS (underlined parts are revised)

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

**Shock, anaphylaxis**: Shock or anaphylaxis (urticaria, angioedema, dyspnoea, etc.) 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.

**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 8 months (April 2010 to November 2013)

- Shock, anaphylaxis-associated cases: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 6.46 million (2013)
Launched in Japan:

(1) SELTOUCH Pap 70: June 2008 (The product with an old brand name for this drug was launched in September 1993.)
SELTOUCH Pap 140: October 2007
SELTOUCH Tape 70: February 2011

(2) NAPAGELN OINTMENT 3%: June 2008 (The product with old brand name for this drug was launched in November 1986.)
NAPAGELN CREAM 3%: June 2008 (The product with old brand name for this drug was launched in September 1999.)
NAPAGELN LOTION 3%: June 2008 (The product with old brand name for this drug was launched in June 1990.)

### < Case Summary >

Felbinac (tape)

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 30s | Intervertebral disc herniation （none） | 70 mg for 4 days | **Distressed feeling of chest (anaphylactoid reaction)**<br>Before administration:<br>Symptoms of schizophrenia remitted.<br>Symptoms of cervical disc herniation improved but numbness of the left hand remained.<br>Day 1 of administration:<br>Felbinac was used for the neck (for approximately 12 hours). |

| | | | | |
|---|---|---|---|---|
| | | | | After the start, a tingling sensation occurred, but it disappeared after approximately 20 minutes.<br>Day 2 of administration:<br>The same symptom as above occurred. Felbinac was used for approximately 12 hours similarly.<br>Day 3 of administration (day of onset):<br>After several minutes of use, difficulty in breathing occurred, but the patient thought it was just her imagination and used felbinac for approximately 12 hours.<br>Difficulty in breathing persisted.<br>Day 4 of administration (Day 2 of onset) (day of discontinuation):<br>After several minutes of use, difficulty in breathing occurred more severely than the preceding day.<br>Anaphylactoid symptom was suspected, discontinuation of felbinac was instructed.<br>The symptom promptly disappeared after discontinuation.<br><br>After that, felbinac was not used and the same symptom did not occur. |
| | Concomitant medications: aripiprazole, risperidone, afloqualone, loxoprofen sodium hydrate, mecobalamin, rebamipide, alprazolam, bromazepam | | | |

# 4 Regorafenib Hydrate

| | |
|---|---|
| **Brand Name (name of company)** | Stivarga tablets 40 mg (Bayer Yakuhin, Ltd.) |
| **Therapeutic Category** | Antineoplastics-Miscellaneous |
| **Indications** | Incurable, unresectable, advanced/recurrent colorectal cancer<br>Gastrointestinal stromal tumor that has progressed after chemotherapy |

## PRECAUTIONS (underlined parts are revised)

**Warnings**

Serious hepatic dysfunction may occur and some cases of fulminant hepatitis or hepatic failure leading to fatal outcome have been reported. Patients should be carefully monitored through periodic liver function tests before and during administration of this drug.

**Important Precautions**

Hepatic dysfunction or jaundice with marked elevations of aspartate aminotransferase (AST or glutamate oxaloacetate transaminase [GOT]) or alanine aminotransferase (ALT or glutamate pyruvate transaminase [GPT]) may occur and some cases of fulminant hepatitis or hepatic failure leading to fatal outcome have been reported. Patients should be carefully monitored through periodic liver function tests, etc., before and during administration of this drug. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, or discontinuation of administration should be taken.

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

**Fulminant hepatitis, hepatic failure, hepatic dysfunction, jaundice**: Hepatic dysfunction or jaundice with marked elevations of AST (GOT) or ALT (GPT) may occur and some cases of fulminant hepatitis or hepatic failure leading to fatal outcome have been reported. Patients should be carefully monitored during administration of this drug, and if any abnormalities are observed, the dose of this drug should be reduced or administration of this drug should be suspended or discontinued, and appropriate measures should be taken.

**Interstitial lung disease**: Interstitial lung disease may occur. Patients should be carefully monitored for clinical symptoms such as cough, dyspnoea, and/or pyrexia. If any abnormalities are observed, examinations such as chest X-ray and/or chest CT should be performed. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroid 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 8 months (from initial marketing to January 2014)

- Fulminant hepatitis-associated cases: 2 cases (both are fatal)
- Interstitial lung disease-associated cases: 5 cases (including 2 fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 2,600 (2013)
Launched in Japan: May 2013

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 30s | Colon cancer (metastases to liver, haemorrhagic gastritis, | 160 mg for 21 days (3-week treatment | **Liver disorder**<br>Day 1 of administration:<br>The patient started receiving regorafenib hydrate (160 mg/day). Eastern Cooperative Oncology Group performance status (ECOG-PS) immediately before the |

| | | | | |
|---|---|---|---|---|
| | | smoker, alcohol consumption) | followed by 1-week rest period) | start of administration was 0.<br>Day 8 of administration:<br>Paronychia and anorexia occurred.<br>Day 22 of administration (day of discontinuation) (day of onset):<br>After 3-week administration of regorafenib hydrate, liver disorder and hand and foot syndrome occurred. AST was 169 IU/L and ALT was 131 IU/L. Malaise was not found, and anorexia was mild. Administration of regorafenib hydrate was discontinued.<br>8 days after discontinuation:<br>AST was 2683 IU/L, ALT was 2336 IU/L, and total bilirubin (T-Bil) was 10.2 mg/dL. Anorexia worsened, and malaise, pyrexia, and jaundice occurred. The patient was admitted to hospital. Intravenous infusion of glycyrrhizin/glycine/L-cysteine 60 mL, and oral administration of ursodeoxycholic acid 600 mg and lactulose syrup 65% 60 mL were started (for 8 days). Hand and foot syndrome improved, and paronychia resolved.<br>11 days after discontinuation:<br>The patient complained of sleepiness and malaise. Japan Coma Scale (JCS) was I.<br>12 days after discontinuation:<br>The patient was able to walk, but oral intake decreased.<br>14 days after discontinuation:<br>JCS worsened from II to III. $NH_3$ increased to 178 μg/dL. Amino acid preparation for hepatic failure 500 mL was intravenously infused. The patient was in a state of unrest. Unrest subsided with intravenous infusion of haloperidol 10 mg (24h).<br>15 days after discontinuation:<br>The patient died of liver disorder. |
| | Concomitant medications: none | | | |

## Laboratory Examination

| Parameter | Day 1 of administration | Day 8 of administration | Day 15 of administration | Day 22 of administration; Day of discontinuation; Day of onset | 8 days after discontinuation | 9 days after discontinuation | 10 days after discontinuation | 12 days after discontinuation | 14 days after discontinuation |
|---|---|---|---|---|---|---|---|---|---|
| AST (IU/L) | 21 | 43 | 28 | 169 | 2,683 | 1,929 | 1,608 | 1,106 | 585 |
| ALT (IU/L) | 14 | 46 | 21 | 131 | 2,336 | 1,881 | 1,492 | 988 | 673 |
| LDH (IU/L) | 334 | 477 | 480 | 572 | 1,306 | 671 | 598 | 543 | 608 |
| ALP (IU/L) | 245 | 447 | 410 | 487 | 578 | 512 | 509 | 516 | 556 |
| γ-GTP (IU/L) | 28 | 86 | 56 | 76 | 115 | 92 | 75 | 50 | 38 |
| T-Bil (mg/dL) | 0.5 | 0.9 | 0.7 | 1.2 | 10.2 | 11.5 | 13.1 | 16.2 | 18.9 |
| D-Bil (mg/dL) | — | — | — | — | 7.8 | 9.1 | 10.3 | 12.3 | 12.7 |
| Alb (g/dL) | 3.9 | 3.9 | 4.0 | 3.9 | 3.4 | 3.0 | 2.8 | 2.8 | 3.0 |
| PT (%) | 91 | — | — | — | 44 | — | 38 | — | — |
| $NH_3$ (μg/dL) | — | — | — | — | 41 | — | — | — | 178 |

## Case Summaries

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/ Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Male 60s | Rectal cancer (metastases to lung, brain, and bone) | 160 mg for 6 days (3-week treatment followed by 1-week rest period) | **Interstitial lung disease**<br>Day 1 of administration:<br>The patient started receiving regorafenib hydrate (160 mg/day). ECOG-PS immediately before the start of administration was 2.<br>Day 6 of administration (day of discontinuation) (day of onset):<br>A blood test showed an abnormally high level of C-reactive protein (CRP).<br>X-ray showed no marked change, but the patient was diagnosed with interstitial pneumonia based on CT.<br>The patient had no symptoms. Administration of regorafenib hydrate was discontinued, and steroid pulse therapy was started.<br>Administration of ceftriaxone sodium hydrate (2 g/day) was started.<br>3 days after discontinuation:<br>As the patient had respiratory failure, oxygen inhalation, and administration of prednisolone 50 mg were started.<br>8 days after discontinuation:<br>A plain X-ray showed diffuse ground glass opacities in bilateral lung fields.<br>The antibiotic agent was switched to tazobactam sodium/piperacillin sodium.<br>10 days after discontinuation:<br>The second steroid pulse therapy was started.<br>11 days after discontinuation:<br>CT showed ground glass opacities occupying almost all of the lung fields except the lung metastatic lesions.<br>15 days after discontinuation:<br>The patient died of interstitial pneumonia. |
| | Chest X-ray: (day before administration) Bilateral multiple metastatic lung tumors were noted.<br>(day of onset) There were almost no changes from the state in the preceding session.<br>(8 days after discontinuation) Diffuse ground glass opacities were found in bilateral lung fields.<br>Chest CT: (approximately 2 weeks before administration) Bilateral metastases to lung increased.<br>(day of onset) A random distribution of ground glass opacities appeared bilaterally except the metastases to lung.<br>(11 days after discontinuation) Ground glass opacities occupying almost all of the lung fields except the lung metastatic lesions were noted.<br>β-D glucan: (test date unknown) Negative<br>Candida antigen: (test date unknown) Negative<br>Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6): (day of onset) 824 U/mL | | | |
| | Concomitant medications: none | | | |

## Laboratory Examination

| Parameter | Day before administration | Day 6 of administration; Day of discontinuation; Day of onset | 2 days after discontinuation | 4 days after discontinuation | 8 days after discontinuation | 11 days after discontinuation |
|---|---|---|---|---|---|---|
| WBC (/μL) | 8,160 | 8,400 | 6,560 | 9,690 | 16,010 | 16,560 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Neutrophils (%) | 86.6 | 74.8 | 90.9 | 89.3 | 91.8 | 94.1 |
| Lymphocytes (%) | 5.0 | 7.7 | 4.1 | 3.1 | 1.8 | 2.2 |
| Eosinophils (%) | 2.7 | 6.8 | 0.0 | 0.0 | 0.2 | 0.0 |
| LDH (%) | 964 | 870 | 684 | 1,239 | 857 | 858 |
| CRP (%) | 10.68 | 27.29 | 10.69 | 4.68 | 7.84 | 6.95 |

# 3

# Revision of Precautions (No. 254)

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 18, 2014 (excluding those presented in the preceding section or "2. Important Safety Information" of this Bulletin).

## 1 Psychotropics

## Mianserin Hydrochloride

| | |
|---|---|
| **Brand Name** | Tetramide Tablets 10 mg, 30 mg (MSD K.K.) |
| **Careful Administration** | Patients with or medical history of prolonged QT, patients treated with drugs that are known to cause prolonged QT, patients with marked bradycardia or hypokalaemia, etc. |
| **Adverse Reactions (clinically significant adverse reactions)** | **Prolonged QT, ventricular tachycardia, (including torsades de pointes), ventricular fibrillation**: Prolonged QT, ventricular tachycardia (including torsades de pointes), or ventricular fibrillation 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. |

## 2 Cardiovascular agents-Miscellaneous

## Bixalomer

| | |
|---|---|
| **Brand Name** | Kiklin Capsules 250 mg (Astellas Pharma Inc.) |
| **Adverse Reactions (clinically significant adverse reactions)** | **Intestinal perforation, intestinal obstruction**: Intestinal perforation or intestinal obstruction may occur. Patients should be carefully monitored. If any abnormalities including severe constipation, persistent abdominal pain, and/or vomiting that are suggestive of these disorders are observed, administration of this drug should be discontinued, abdominal examination or imaging tests (plain X-ray, ultrasound, CT, etc.) should be performed, and appropriate measures should be taken. |

## 3 Miscellaneous metabolism agents-Miscellaneous

## Minodronic Acid Hydrate

| | |
|---|---|
| **Brand Name** | Bonoteo Tablets 1 mg, 50 mg (Astellas Pharma Inc.), RECALBON Tablets 1 mg, 50 mg (Ono Pharmaceutical Co., Ltd.) |
| **Adverse Reactions (clinically significant adverse reactions)** | **Hepatic dysfunction, jaundice**: Hepatic dysfunction or jaundice with elevations of AST (GOT), ALT (GPT), etc., 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. |

4 **Kampo product**

## Yokukansan (for ethical use)

**Brand Name**

TSUMURA Yokukansan Extract Granules for Ethical Use (Tsumura & Co.) and the others

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

**Cardiac failure**: Cardiac failure may occur. Patients should be carefully monitored, and if fluid retention, rapidly increased weight, or symptoms/signs of cardiac failure (shortness of breath, increased cardiothoracic ratio, pleural effusion, etc.) are observed, administration of this drug should be discontinued and appropriate measures should be taken.

**Myopathy, rhabdomyolysis**: Myopathy or rhabdomyolysis as a result of hypokalaemia may occur. Patients should be carefully monitored, and if feeling of weakness, muscular weakness, myalgia, convulsion/paralysis of limbs, increased Creatine kinase (Creatine phosphokinase), increased blood myoglobin, or increased urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures such as administration of potassium preparation should be taken.

5 **Over-the-counter drugs**

## Felbinac-containing Products

**Brand Name**

FEITAS SIP, FEITAS SIP HOT, FEITAS 3.5 α, 3.5 αL, 3.5 α HOT, 3.5 αL HOT, FEITAS 5.0 (Hisamitsu Pharmaceutical Co., Inc.), and the others

**Consultation**

The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician, pharmacist, or registered salesperson for a consultation with this package insert.

The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these signs and symptoms.

**Shock (anaphylaxis)**: Immediately after using the product, itchy skin, urticaria, hoarseness, sneezing, itchy throat, difficulty in breathing, palpitations, clouding consciousness, etc., may occur.

6 **Over-the-counter drugs**

## Yokukansan

**Brand Name**

Ohkan (Ohsugi Pharmaceutical Co., Ltd.) and the others

**Consultation**

The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician, pharmacist, or registered salesperson for a consultation with this package insert.

The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these signs and symptoms.

**Cardiac failure**: Respiratory discomfort while moving, getting tired easily, swelling of legs, sudden weight gain

# 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 MAH 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 ADRs. EPPV is specified as a condition of approval.

(As of March 1, 2014)

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

| | Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | Cinacalcet<br>REGPARA TABLETS 25 mg, 75 mg*1 | Kyowa Hakko Kirin Co., Ltd. | February 21, 2014 |
| ◎ | Ranibizumab (Genetical Recombination)<br>LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*2 | Novartis Pharma K.K. | February 21, 2014 |
| | pH-4 Treated Acid Normal Human Immunoglobulin (Subcutaneous injection)<br>Hizentra 20% S.C. Injection 1 g/5 mL, 2 g/10 mL, 4 g/20 mL | CSL Behring K.K. | January 30, 2014 |
| | Ioflupane ($^{123}$I)<br>DaTSCAN Injectable | Nihon Medi-Physics Co., Ltd. | January 27, 2014 |
| | Talaporfin Sodium<br>LASERPHYRIN 100 mg FOR INJECTION*3 | Meiji Seika Pharma Co., Ltd. | January 20, 2014 |
| | Meropenem Hydrate<br>(1) Meropen Vial for Intravenous Drip Infusion 0.25 g, 0.5 g<br>(2) Meropen Kit for Intravenous Drip Infusion 0.5 g*4 | Dainippon Sumitomo Pharma Co., Ltd. | December 20, 2013 |
| | Methylphenidate Hydrochloride<br>Concerta Tablets 18 mg, 27 mg*5 | Janssen Pharmaceutical K.K. | December 20, 2013 |
| | Laninamivir Octanoate Hydrate<br>INAVIR DRY POWDER INHALER 20 mg*6 | Daiichi Sankyo Company, Limited | December 20, 2013 |
| | Fentanyl<br>OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg*7 | Janssen Pharmaceutical K.K. | December 20, 2013 |
| | Fentanyl Citrate<br>Abstral Sublingual Tablets 100 μg, 200 μg, 400 μg | Kyowa Hakko Kirin Co., Ltd. | December 12, 2013 |
| | Vilanterol Trifenatate/Fluticasone Furoate<br>Relvar 100 Ellipta 14 doses, Relvar 200 Ellipta 14 doses | GlaxoSmithKline K.K. | December 9, 2013 |
| | Talc<br>Unitalc Intrapleural 4 g | Nobelpharma Co., Ltd. | December 9, 2013 |

| | | | |
|---|---|---|---|
| | Simeprevir Sodium<br>SOVRIAD capsules 100 mg | Janssen Pharmaceutical K.K. | December 6, 2013 |
| | Epinastine Hydrochloride<br>ALESION Ophthalmic Solution 0.05% | Santen Pharmaceutical Co., Ltd. | November 25, 2013 |
| | Acetaminophen<br>acelio Intravenous Injection 1000 mg | Terumo Corporation | November 25, 2013 |
| | Landiolol Hydrochloride<br>ONOACT 50 for Injection*[8] | Ono Pharmaceutical Co., Ltd. | November 22, 2013 |
| | Aflibercept (Genetical Recombination)<br>EYLEA solution for IVT inj. 40 mg/mL*[9],<br>EYLEA solution for IVT inj. Kit 40 mg/mL*[9] | Bayer Yakuhin, Ltd. | November 22, 2013 |
| | Topiramate<br>TOPINA Tablets 25 mg, 50 mg, 100 mg*[10] | Kyowa Hakko Kirin Co., Ltd. | November 22, 2013 |
| | Indacaterol Maleate/Glycopyrronium Bromide<br>ultibro inhalation capsules | Novartis Pharma K.K. | November 20, 2013 |
| | Tafamidis Meglumine<br>Vyndaqel capsules 20 mg | Pfizer Japan Inc. | November 20, 2013 |
| | Fluticasone Propionate/Formoterol Fumarate Hydrate<br>Flutiform 50 Aerosol 56 puffs, 125 Aerosol 56 puffs | Kyorin Pharmaceutical Co., Ltd. | November 19, 2013 |
| | Brinzolamide/Timolol Maleate<br>AZORGA Combination Ophthalmic Suspension | Alcon Japan Ltd. | November 19, 2013 |
| | Paliperidone Palmitate<br>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 polysaccharide conjugate vaccine (13-valent, adsorbed)<br>Prevenar13 Suspension Liquid for Injection | Pfizer Japan Inc. | October 28, 2013 |
| | Hydroxyethylated Starch 130000<br>VOLUVEN 6% solution for infusion | Fresenius Kabi Japan K.K. | October 25, 2013 |
| | Fentanyl Citrate<br>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<br>LUNABELL tablets ULD | Nobelpharma Co., Ltd. | September 26, 2013 |
| | Aminolevulinic Acid Hydrochloride<br>ALAGLIO Oral 1.5 g | SBI Pharmaceuticals Co., Ltd. | September 26, 2013 |
| | Aminolevulinic Acid Hydrochloride<br>Alabel Oral 1.5 g | Nobelpharma Co., Ltd. | September 18, 2013 |
| | Lixisenatide<br>Lyxumia Subcutaneous Injection 300 μg | Sanofi K.K. | September 17, 2013 |
| | Darbepoetin Alfa (Genetical Recombination)<br>NESP INJECTION 5 μg PLASTIC SYRING, 10 μg PLASTIC SYRING, 15μg PLASTIC SYRINGE, 20 μg PLASTIC SYRINGE, 30 μg PLASTIC SYRINGE, 40 μg PLASTIC SYRINGE, 60 μg PLASTIC SYRINGE, 120 μg PLASTIC SYRINGE, 180 μg PLASTIC SYRINGE*[11] | Kyowa Hakko Kirin Co., Ltd. | September 13, 2013 |
| | Tolvaptan<br>Samsca tablets 7.5 mg*[12] | Otsuka Pharmaceutical Co., Ltd. | September 13, 2013 |

| | | | |
|---|---|---|---|
| | Eculizumab (Genetical Recombination)<br>Soliris Drip Infusion 300 mg*[13] | Alexion Pharma G.K. | September 13, 2013 |
| | Pertuzumab (Genetical Recombination)<br>PERJETA Intravenous Infusion 420 mg/14 mL | Chugai Pharmaceutical Co., Ltd. | September 12, 2013 |
| | Bisoprolol<br>Bisono tape 4 mg, 8 mg | Toa Eiyo Ltd. | September 10, 2013 |
| | Irbesartan/Trichlormethiazide<br>Irtra Combination Tablets LD, HD | Shionogi & Co., Ltd. | September 4, 2013 |
| | Topiroxostat<br>(1) TOPILORIC Tablets 20 mg, 40 mg, 60 mg<br>(2) URIADEC Tab. 20 mg, 40 mg, 60 mg | (1) Fujiyakuhin Co., Ltd.<br>(2) Sanwa Kagaku Kenkyusho CO., LTD. | September 4, 2013 |

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

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

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

*4 An additional administration for “pyogenic meningitis”

*5 An additional administration for “patients aged 18 years or older”

*6 An additional indication for “the prophylaxis of influenza A or B virus infection”

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

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

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

*10 An additional administration for “pediatrics”

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

*12 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”

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