Pharmaceuticals and Medical Devices Safety Information

No. 312 April 2014 rev.1*

Table of Contents

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

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

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. 312 April 2014

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Use of Topical Ketoprofen during Pregnancy**	*C* *P*	Cases of foetal ductus arteriosus systole have been reported in Japan after maternal use of the topical non-steroidal anti-inflammatory drug ketoprofen during the third trimester. A case of oligohydramnios also has been reported in Japan after maternal use of ketoprofen tapes during the second trimester. On March 25, 2014, the MHLW/PMDA required marketing authorization holders to revise the Precautions section in package inserts. Details are presented in this section.	4
2	**Important Safety Information**	*C* *P*	**Ketoprofen (tapes) (and 2 others):** Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated March 25, 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.	9
3	**Revision of Precautions (No. 255)**		Ketoprofen (injectable dosage form, suppository) (and 7 others)	18
4	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of April 1, 2014.	21

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

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

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

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

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

Abbreviations

ADRs	Adverse drug reactions
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
DBP	Diastolic blood pressure
DIHS	Drug-induced hypersensitivity syndrome
EPPV	Early Post-marketing Phase Vigilance
FDP	Fibrin/fibrinogen degradation product
FLAIR	Fluid-attenuated inversion recovery
HHV-6	Human herpesvirus 6
IgG	Immunoglobulin G
IU	International unit
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
PLT	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PRES	Posterior reversible encephalopathy syndrome
PT	Prothrombin Time
RBC	Red blood cell count
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
T-Bil	Total bilirubin
TC	Paclitaxel and carboplatin
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Use of Topical Ketoprofen during Pregnancy

Active ingredient	Ketoprofen (For topical use)
Brand Name (name of company)	(1) MOHRUS TAPE 20 mg, MOHRUS TAPE L 40 mg (Hisamitsu Pharmaceutical Co., Inc.) (2) EPATEC GEL 3%, EPATEC LOTION 3%, EPATEC CREAM 3% (Zeria Pharmaceutical Co., Ltd.), SECTOR GEL 3%, SECTOR LOTION 3%, SECTOR CREAM 3% (Hisamitsu Pharmaceutical Co., Inc.) MILTAX PAP 30mg (Nipro Patch Co., Ltd.) MOHRUS PAP 30 mg, 60 mg (Hisamitsu Pharmaceutical Co., Inc.) and the others
Therapeutic Category	Analgesics, antipruritics, astringents, anti-inflammatory agents
Indications	(1) 1. Relief of pain and inflammation associated with the following disorders and symptoms: Lumbago (myofascial lower back pain, spinal osteoarthritis, discopathy, lumbar vertebrae sprain), osteoarthritis, scapulohumeral periarthritis, tendinitis/tendovaginitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow), myalgia, post-traumatic swelling and pain 2. Relief of local joint pain in rheumatoid arthritis (2) Relief of pain and inflammation associated with the following disorders and symptoms Osteoarthritis, scapulohumeral periarthritis, tendinitis/tendovaginitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow), myalgia, post-traumatic swelling and pain

1. Introduction

Topical ketoprofen, a non-steroidal anti-inflammatory drug, was approved as an ethical drug in the dosage forms of gel, poultice, lotion, cream, and tape to be used for topical pain relief and anti-inflammation in July 1986, March 1988, September 1988, March 1989, and August 1995, respectively.

While the use of ketoprofen suppository and injection during the third trimester of pregnancy has been contraindicated, dermatologic ketoprofen was not.

Cases of foetal ductus arteriosus systole and other symptoms in pregnant women have been reported after use of ketoprofen tapes, MHLW required marketing authorization holders (MAHs) to revise the Precautions section in package inserts of topical ketoprofen products, including the tape formula, to include a contraindication in the third trimester and other associated information. Details are provided in the following section.

2. Background

Cases of foetal ductus arteriosus systole in women who continuously used multiple sheets of ketoprofen tape during the third trimester were reported in Japan. In December 2008, the MAHs revised the Precautions to advise women in the third trimester to use the ketoprofen tapes carefully. After

receiving another report on a similar case, the MAHs distributed information materials to healthcare professionals to raise caution against continuous use of multiple sheets of ketoprofen tape in the third trimester in November 2011.

After that, similar cases were further reported. PMDA discussed the necessity of further alerting pregnant women.

Based on a reported case in which foetal ductus arteriosus systole occurred in a woman who used a sheet of ketoprofen tape a day for 1 week during the third trimester, the number of reported cases and the contraindication of ketoprofen suppository and injection in the third trimester, PMDA decided that an alert for the use of ketoprofen tape was also needed in the same way as ketoprofen suppository and injection. Since ketoprofen for topicalal use other than the tape form may also cause the same adverse reaction, MHLW instructed all the relevant MAHs to revise the Precautions section to include a contraindication against the use in the third trimester on March 25, 2014.

Oligohydramnios was also reported in a woman who used ketoprofen tape in the second trimester of pregnancy. PMDA decided that an alert against the use of ketoprofen-containing products in the second trimester was necessary, and MHLW instructed the MAHs to include an advice for careful use such as use at the lowest effective dose for the shortest necessary duration in the Use in Pregnant, Parturient and Nursing Women section.

3. Incidence of foetal ductus arteriosus systole and oligohydramnios associated with ketoprofen tape

Four cases of foetal ductus arteriosus systole in the third trimester and one case of oligohydramnios in the second trimester were reported between the initial marketing of ketoprofen tape in December 1995 and January 10, 2014. (Table 1)

Table 1 Adverse events with Ketoprofen tapes

Case	Year of reporting	Gestational stage	Dose	Duration of use	Adverse reaction (Preferred term)	Outcome
1	2005	In the end stage of pregnancy	80 mg/day	Approximately 10 days	Foetal ductus arteriosus stenosis	Recovered
2	2008	Pre-pregnancy to 35 weeks	140 to 240 mg/day	≥35 weeks	Ductus arteriosus premature closure	Improved
3	2011	After 36 weeks	5 to 6 sheets/day (dose unknown)	Approximately 5 weeks	Ductus arteriosus premature closure	Improved
4	2011	34 to 35 weeks	20 mg/day	1 week	Foetal ductus arteriosus stenosis	Recovered
5	2013	Until 23 weeks	120 mg/day	≥23 days	Oligohydramnios	Recovered

Two cases of adverse reactions reported after the distribution of information material to alert healthcare professionals in November 2011 are shown below.

<Case 4> Ketoprofen (tape)

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
Female 30s	Unknown (unknown)	20 mg/ 7 days	**Foetal ductus arteriosus systole** Day 1 of administration: The patient received ketoprofen tapes that were prescribed for another person and started using one sheet of them per day, at the end of gestation week 34. Drugs other than the topical ketoprofen product were not used. Day 7 of administration (day of completion): The patient used the ketoprofen tapes for 1 week and stopped using this drug at the end of gestation week 35. Day of delivery: The patient was transported by ambulance at 36 weeks and 1 day of gestation. The examination showed pulmonary hypertension and enlargement of the right ventricle in the fetus, and caesarian section was performed. The infant's body weight was 3 421 g and Apgar score was 8/10. Foetal ductus arteriosus systole was suspected. Date unknown: The infant recovered without sequela by 5 months.
Concomitant medications: none			

<Case 5> Ketoprofen (tape)

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
Female 20s	Juvenile rheumatoid arthritis, exacerbated pain (none)	Dose unknown ↓ 120 mg Unknown	**Oligohydramnios** The patient had been treated with methotrexate, etanercept, and prednisolone for juvenile rheumatoid arthritis. Administration of these drugs was discontinued immediately after the pregnancy was confirmed. After that, joint symptoms were aggravated, administration of prednisolone was only resumed. Oral acetaminophen was used for relief of pain. Day 1 of administration: The patient started using ketoprofen tapes without consulting her healthcare professionals for aggravated joint pain associated with juvenile rheumatoid arthritis. Date unknown: At around gestation week 20, the patient started using a total of 6 sheets of ketoprofen tape per day for aggravated pain in the inner elbows, inner wrists and knees. Date unknown: At 20 weeks and 3 days of gestation, the periodic prenatal checkup showed no abnormality. Day of onset: The patient visited the obstetric clinic for a periodic prenatal checkup at 23 weeks and 3 days of gestation. Amniotic fluid was almost absent. Amniotic fluid index was immeasurable. The maximum depth was barely 2 cm. Foetal growth was normal. Presence of stomach bubble, kidneys, and

			bladder was noted. No organic abnormality was found in the kidneys and urinary tract of the foetus. Pelvic examination showed no rupture of the membrane. The patient was diagnosed with unexplained oligohydramnios. The patient was admitted to the hospital for close monitoring. Day 2 of onset (day of discontinuation): Use of ketoprofen tape was discontinued. Oral administration of prednisolone and acetaminophen was continued. Day 3 of onset (1 day after discontinuation): Amniotic fluid gradually increased. Day 9 of onset (7 days after discontinuation): The patient was discharged from the hospital after sufficient recovery of amniotic fluid. Good fetal growth was confirmed. The patient was to be followed up on an outpatient basis. Day 15 of onset (13 days after discontinuation): At 25 weeks and 3 days of gestation, the amniotic fluid volume turned normal. Oligohydramnios was resolved. Day 104 of onset (102 days after discontinuation): No fetal abnormalities were noted and the patient's gestation period was 38 weeks. Day of delivery: At gestation week 39, the patient and the fetus were both healthy. The patient had a natural birth. The patient was discharged from the hospital after a good postpartum course. 1 month after delivery: At 1-month checkup, the mother and the infant had no health issues. 6 months after delivery: At 6-month checkup, no abnormality was noted.
Concomitant medications: prednisolone, acetaminophen			

4. Precautions concerning use during pregnancy

As shown in **Table 2**, precautions against the use during pregnancy were added in the section of Contraindications and Use in Pregnant, Parturient and Nursing Women as a result of the revision of the package insert in March 2014. Healthcare professionals are encouraged to be aware of the following precautions and to take appropriate measures.

(1) Foetal ductus arteriosus systole may occur in pregnant women during the third trimester. Topical ketoprofen should not be administered.

(2) When a ketoprofen product is administered to pregnant women during the second trimester, this drug should be used at the lowest effective dose for the shortest necessary duration, taking into account that oligohydramnios have been reported after maternal use of ketoprofen tapes during the second trimester.

Although no foetal ductus arteriosus systole has been reported in association with other topical non-steroidal anti-inflammatory drugs, it may occur when these drugs are used in pregnant women during the third trimester of pregnancy considering the mechanism of action. Therefore, they should be administered only if potential benefits outweigh risks.

For details of revisions, please see "2. Important Safety Information" on page 9 of this document.

Table 2 Precautions section in package inserts of topical ketoprofen products (as of April 2014)

Contraindications	Pregnant women in the third trimester
Use in Pregnant, Parturient And Nursing Women	1. Foetal ductus arteriosus systole may occur when topical ketoprofen is used in pregnant women during the third trimester. This drug should not be administered in the third trimester of pregnancy. 2. Safety of topical ketoprofen is not established in pregnant (excluding the third trimester), parturient and nursing women. This drug should be administered only if potential benefits outweigh the risks. 3. A case of oligohydramnios has been reported after maternal use of topical ketoprofen during the second trimester. This drug should be used at the lowest effective dose for the shortest necessary duration.

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated March 25, 2014, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Ketoprofen (tape)

Brand Name (name of company)	MOHRUS TAPE 20 mg, MOHRUS TAPE L 40 mg (Hisamitsu Pharmaceutical Co., Inc.) and the others
Therapeutic Category	Analgesics, antipruritics, astringents, anti-inflammatory agents
Indications	1. Relief of pain and inflammation associated with the following disorders and symptoms Lumbago (myofascial lower back pain, spinal osteoarthritis, discopathy, lumbar sprain), osteoarthritis, scapulohumeral periarthritis, tendinitis/ tendovaginitis, peritendinitis, humeral epicondylitis (e.g. tennis elbow), myalgia, post-traumatic swelling and pain 2. Relief of local joint pain in rheumatoid arthritis

PRECAUTIONS (underlined parts are revised)

Contraindications

Pregnant women in the third trimester (See "Use in Pregnant, Parturient And Nursing Women")

Use in Pregnant, Parturient And Nursing Women

Foetal ductus arteriosus systole may occur when topical ketoprofen is used in pregnant women during the third trimester. This drug should not be administered in the third trimester of pregnancy.

Safety of topical ketoprofen is not established in pregnant (excluding the third trimester), parturient and nursing women. This drug should be administered only if potential benefits outweigh the risks.

A case of oligohydramnios has been reported after maternal use of topical ketoprofen during the second trimester. This drug should be used at the lowest effective dose for the shortest necessary duration.

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 10 months (April 2010 to January 2014)

- Cases associated with foetal ductus arteriosus systole: 2 cases (no fatal cases)
- Oligohydramnios: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 9.17 million (October 2012 to September 2013)
Launched in Japan: December 1995

2 Paclitaxel (excluding paclitaxel protein-bound particles for injectable suspension)

Brand Name (name of company)	TAXOL INJECTION 30 mg, 100 mg (Bristol-Myers K.K.) and the others
Therapeutic Category	Antineoplastics-Plant extract preparations
Indications	Ovarian cancer, non-small cell lung cancer, breast cancer, gastric cancer, endometrial cancer, relapsed or metastatic head and neck cancer, relapsed or metastatic oesophageal cancer, angiosarcoma, advanced or relapsed cervix carcinoma, relapsed or refractory germ cell tumor (testicular tumor, ovarian tumor, extragonadal tumor)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Tumour lysis syndrome: Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels and performing a renal function test, etc. If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g. administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

Leukoencephalopathy (including posterior reversible encephalopathy syndrome [PRES]): Leukoencephalopathy (including PRES) may occur. If symptoms including staggering gait, convulsion, headache, visual disturbance, hypertension, or disturbed consciousness 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 11 months (April 2010 to February 2014)

- Tumour lysis syndrome: 0 cases (no fatal cases)
- Leukoencephalopathy-associated cases: 5 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 13 000 (2013)
Launched in Japan: October 1997

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Lung carcinoma cell type unspecified stage III (hypertension/ gastrooesophageal reflux disease)	330 mg/ 3 courses	**PRES** Day 1 of administration: The patient was complicated with interstitial pneumonia, and chemotherapy with carboplatin and paclitaxel was performed for 3 courses. (From the end day of 3 courses) 22 days after administration: Headache dull occurred. 25 days after administration: The patients had pyrexia of 37.7°C and visited hospital. Ptosis of the right corner of the mouth was noted. T2-weighted image and fluid attenuated inversion recovery (FLAIR) image of a brain magnetic resonance imaging (MRI) showed high signal intensity in bilateral frontal

				lobes. The patient was admitted to hospital. Administration of concentrated glycerin/fructose and betamethasone sodium phosphate was started for the treatment of brain oedema, and intravenous injection of nicardipine was started for the treatment of hypertension. 28 days after administration: A brain MRI (gadolinium-contrasted) was performed and showed no metastases to brain. Leukoencephalopathy was suspected. 31 days after administration: Lumbar puncture was performed. The cerebrospinal fluid properties were not markedly changed. 38 days after administration: Ptosis of the right corner of the mouth was alleviated. 39 days after administration: Brain MRI was performed again, and the range of abnormal signals decreased. 44 days after administration: Mild ptosis of the right corner of the mouth remained, but the patient was discharged from hospital. Approximately 6 months after administration: On a brain MRI, abnormal signals almost disappeared. Approximately 14 months after administration: On a brain MRI, abnormal signals almost disappeared. Ptosis of the right corner of the mouth improved.
	The other suspected medications: carboplatin injection Concomitant medications: loxoprofen sodium tablets, acetaminophen tablets			

Laboratory Examination

Laboratory parameter (unit)		Before start of administration	21 days after administration	25 days after administration	30 days after administration	84 days after administration
Body temperature (°C)		—	37.6	—	—	—
Pulse rate (/min)		—	89	—	—	—
SBP (mmHg)		—	150	—	—	—
DBP (mmHg)		—	94	—	—	—
RBC ($\times 10^4$/mm^3)		448	226	236	249	360
Hemoglobin (g/dL)		14.3	7.3	7.3	8.1	12.5
WBC (/mm^3)		9 400	5 000	6 400	7 200	6 100
Differential leukocyte count (%)	Neutrophils	68.8	57.0	75.5	65.0	46.5
	Eosinophils	2.9	0	0.5	0	2.5
	Basophils	0.2	1.0	0	0	0.2
	Monocytes	4.8	10.0	4.4	11.0	6.6
	Lymphocytes	23.3	32.0	19.6	24.0	44.2
PLT ($\times 10^4$/mm^3)		22.9	4.0	9.8	40.7	17.7
AST (GOT) (IU/L)		21	18	18	16	19
ALT (GPT) (IU/L)		22	17	16	17	15
ALP (IU/L)		368	379	370	303	320
γ-GTP (IU/L)		75	50	54	58	44
LDH (IU/L)		236	178	200	184	177
T-Bil (mg/dL)		0.30	0.43	0.53	0.48	0.48
BUN (mg/dL)		15	18	12	20	19
Serum Cr (mg/dL)		0.60	0.88	0.89	0.84	0.78
Blood glucose level (mg/dL)		118	129	148	86	118
K (mEq/L)		5.2	4.4	4.0	9.4	9.5
Na (mEq/L)		139	139	132	135	141
Ca (mEq/L)		10.8	9.1	9.3	9.4	9.5
Albumin (g/dL)		4.2	3.9	—	3.7	4.3

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Uterine cancer, ovarian cancer (none)	270 mg × 1/ 1 course	**PRES** The patient underwent hysterectomy and bilateral adnexectomy. Day 1 of administration: The patient received an initial dose for paclitaxel and carboplatin (TC therapy). 10 days after administration: The patient was discharged from hospital. 12 days after administration: In the afternoon, the patient had convulsion at home, and visited hospital with a family member by ambulance. Vomiting occurred after the visit. Approximately 2 hours later, blood pressure at the visit was 135/70 mmHg. After head computed tomography (CT) was performed, convulsion occurred again. Chloral hydrate rectal suppository (250 mg) was inserted into the rectum, and oxygen was administered. Because of blood pressure 200/100 mmHg, nicardipine hydrochloride 1 mg was intravenously injected, and a head MRI was performed on the same day. A radiologist notified of suspected PRES. For the reduction of blood pressure and prophylaxis for convulsion, or possibility that the condition might shift to subarachnoid haemorrhage (SAH), treatment was provided in consideration of SAH. 13 days after administration: The patient was fully conscious. No vomiting/convulsion occurred. 15 days after administration: Sodium valproate was orally administered. 29 days after administration: Administration of chloral hydrate suppository was discontinued. 46 days after administration: While concomitantly using oral sodium valproate and oral antihypertensive drug, the second course of TC therapy was performed. <Head MRI> 12 days after administration: T2-weighted image and FLAIR image showed high signal intensity in the bilateral areas extending from occipital lobes to parietal lobes, bilateral corona radiata, and posterior region of bilateral centrum semiovale, and then PRES was suspected. 19 days after administration: The high signal intensity on T2-weighted image and FLAIR image, which was pointed out on previous head MRI, substantially decreased (with no inconsistency as the course of PRES). A linear lesion was noted in the left occipital lobe and low signal intensity was identified on the T1-weighted image. Therefore there was a possibility that the disease remained.
	The other suspected medications: carboplatin injection			

Laboratory Examination

Laboratory parameter (unit)		2 days before administration	Before start of administration	5 days after administration	12 days after administration	15 days after administration	17 days after administration
Body temperature (°C)		36.5	—	36.6	38.2	—	—
Pulse rate (/min)		77	—	75	110	—	—
SBP (mmHg)		133	—	145	200	—	—
DBP (mmHg)		77	—	91	110	—	—
RBC ($\times 10^4/mm^3$)		361	—	398	393	333	350
Hemoglobin (g/dL)		11.4	—	12.3	12.2	10.5	10.7
WBC ($/mm^3$)		4 700	—	3 900	4 900	2 000	7 500
Differential leukocyte count (%)	Neutrophils	66.9	—	78.7	80.6	39.1	82.7
	Eosinophils	2.5	—	2.9	0.1	2.5	0.5
	Basophils	0.3	—	0.1	1.7	0.9	0.2
	Monocytes	10.1	—	0.9	9.0	17.4	5.5
	Lymphocytes	20.2	—	17.4	8.6	40.1	11.1
PLT ($\times 10^4/mm^3$)		16.7	—	14.5	9.1	7.3	10.7
PT (%)		—	—	—	96.1	—	—
FDP (μg/mL)		—	—	—	11.4	—	—
D-dimer (ng/mL)		—	—	—	4.3	—	—
AST (GOT) (IU/L)		17	—	51	20	—	—
ALT (GPT) (IU/L)		12	—	34	19	—	—
Blood glucose level (mg/dL)		—	—	—	136	—	—
BUN (mg/dL)		4.5	—	8.5	6.2	—	—
Serum Cr (mg/dL)		0.4	—	0.3	0.3	—	—
K (mEq/L)		4.9	—	3.9	3.8	—	—
Na (mEq/L)		140	—	136	137	—	—
Urine output (mL/24hr)		1 600	—	—	—	3 000	1 650

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 70s	Breast cancer (metastases to bone/metastases to liver)	90mg Once a week (3 times a month) × 23 times	**PRES** Day 1 of administration: The patient started receiving paclitaxel (90 mg/day). 232 days after administration: PRES developed. Administration of paclitaxel was terminated (total dose of 2 070 mg). 237 days after administration: The patient fell in the afternoon when going out. After that, the patient also experienced paralysis in her right upper limb, and then visited this hospital without reservation and was admitted to the hospital. Diffusion-weighted imaging of brain MRI after hospital admission showed high intensity mainly in the white matter of the bilateral occipital lobes and left frontal lobe, and as such the patient was diagnosed with PRES. As an anti-brain oedema agent, 2 vials of edaravone (60 mg/day) were intravenously infused (for 14 days from 237 days after administration). Rehabilitation exercises were performed. Activities of daily living were improved by edaravone and rehabilitation exercises. 257 days after administration:

				The bilateral occipital lobe lesions disappeared. 275 days after administration: Brain MRI showed a finding in a part of the left motor area of the left frontal lobe, but improvement was found.
	Concomitant medications: ranitidine hydrochloride, dexamethasone sodium phosphate, chlorpheniramine maleate			

Laboratory Examination

Laboratory parameter (unit)		Before start of administration	232 days after administration	246 days after administration
RBC	($\times 10^4$/μL)	—	323	327
Hemoglobin	(g/dL)	—	10.6	10.5
Hematocrit	(%)	—	31.7	32.6
MCV	(fL)	—	98.1	99.7
MCH	(pg)	—	32.8	32.1
MCHC	(%)	—	33.4	32.2
WBC	(/μL)	—	6 600	3 400
Segmented cells	(%)	—	67	48
Lymphocytes	(%)	—	28	33
Monocytes	(%)	—	4	15
Eosinophils	(%)	—	—	1
PLT	($\times 10^4$/μL)	—	20.7	19.2
AST (GOT)	(IU/L)	—	57	45
ALT (GPT)	(IU/L)	—	50	28
LDH	(IU/L)	—	309	245
ALP	(IU/L)	—	869	682
γ-GTP	(IU/L)	—	820	582
Cholinesterase	(IU/L)	—	208	176
T-Bil	(mg/dL)	—	0.91	0.93
BUN	(mg/dL)	—	11.2	8.5
Blood Cr	(mg/dL)	—	0.54	0.41
Uric acid	(mg/dL)	—	4.3	—
Total protein	(g/dL)	—	5.4	4.7
Albumin	(g/dL)	—	3.2	2.8
CRP	(mg/dL)	—	1.94	1.76
Blood glucose level	(mg/dL)	—	107	87
Na	(mEq/L)	—	144	146
K	(mEq/L)	—	3.8	3.5
Cl	(mEq/L)	—	107	108
Ca	(mg/dL)	—	9	8.6

3 Levetiracetam

Brand Name (name of company)	E Keppra Tablets 250 mg, 500 mg, E Keppra Dry Syrup 50% (UCB Japan Co. Ltd.)
Therapeutic Category	Antiepileptics
Indications	Concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizure) in patients who fail to show satisfactory response to other antiepileptic drugs

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Drug-induced hypersensitivity syndrome (DIHS): Rash or pyrexia may occur as the initial symptoms and signs followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, lymphadenopathy, increased white blood cells, increased eosinocyte, and atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken. The reactivation of viruses including Human Herpes virus 6 (HHV-6) has been found frequently associated with DIHS. Symptoms such as rash, pyrexia, and/or hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 5 months (from initial marketing to January 2014)

- DIHS-associated cases: 5 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 76 000 (2013)

Launched in Japan: (1) Tablet: September 2010
(2) Dry Syrup: August 2013

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 30s	Epilepsy (none)	250 mg Unknown (for approximately 1 month)	**Erythema exudativum multiforme (severe drug eruption suspected to be DIHS)** Several weeks after the start of administration: The patient experienced erythema on the back. 5 days after the onset of erythema: Pharynx pain, stomatitis, erythema multiforme on the limbs, and diffuse erythema on the abdomen appeared. 12 days after the onset of erythema: Pyrexia in the 38°C level developed. 13 days after the onset of erythema: The blood tests showed an elevation of hepatic enzymes and the patient was admitted to hospital. Acute hepatitis and acute nephritis developed. Findings at admission • Bulbar conjunctiva: No jaundice/hyperaemia and no anaemia • Abdomen: Flat and soft, with impalpable liver/spleen, no tenderness, audible intestinal peristalsis sound, inaudible vascular murmur

				• Diffuse light erythema was found on the chest and back. • Erythema exudativum multiforme was found on the limbs. After admission: Symptomatic therapy with non-steroidal anti-inflammatory drugs did not improve the symptoms and test data. Day 4 of hospitalization (day of discontinuation): DIHS, drug fever, drug eruption, drug-induced liver injury, and drug-induced renal injury were suspected. Oral administration of carbamazepine and levetiracetam was discontinued. Chest/abdominal CT findings showed patterns of bilateral kidney enlargement and perinephritis. Skin biopsy showed inflammatory cell infiltration, mainly of lymphocytes and eosinophils in the epidermis. As treatment for adverse events, the patient received fluid replacement and was kept at rest. Day 15 of hospitalization: The patient was discharged from hospital. Erythema exudativum multiforme, acute hepatitis, acute nephritis resolved.
	Concomitant medications: carbamazepine, phenytoin			

Laboratory Examination

		Day of admission	Day of discontinuation (Day 4 of hospitalization)	22 days after discontinuation
AST	(IU/L)	150	223	21
ALT	(IU/L)	257	430	40
Eosinophils	(/μL)	—	1 125	703
HHV-6 IgG		—	1:40	1:160
BUN	(mg/dL)	8.2	24.7	18.1
Cr	(mg/dL)	0.68	1.4	1.09

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Epilepsy (diabetes mellitus)	1 000 mg for 36 days	**Suspected DIHS** The patient received levetiracetam 1 000 mg/day in addition to carbamazepine 400 mg. Day 33 of administration: The patient experienced drug eruption. Day 36 of administration (day of discontinuation): Skin symptoms and abnormal hepatic function were noted, the condition was diagnosed as drug eruption, and then administration of levetiracetam was discontinued. Prednisolone 15 mg/day (for 6 days) and antihistamine drug were prescribed. 6 days after discontinuation: No improvement of drug eruption was found and dehydration, pyrexia, and renal impairment were observed, the patient was admitted to hospital. After hospital admission, prednisolone 60 mg/day was administered (for 8 days), and a transfusion (1 500 mL) was performed.

				14 days after discontinuation: In addition to drug eruption, the patient had symptoms such as laryngeal pain, bloating, and diarrhoea, but recovered considerably from them after treatment for approximately 1 week. C-reactive protein (CRP) became normal, and renal function also improved. Because erythema remained, intravenous steroid was switched to oral corticosteroid 40 mg instead of discontinuation. After that, the dose of oral steroid was tapered. 26 days after discontinuation: The patient recovered from the symptoms and treatment with corticosteroid was discontinued. 29 days after discontinuation: Due to seizure, phenobarbital 80 mg/day was prescribed. 30 days after discontinuation: Due to skin eruption, administration of phenobarbital was discontinued. 31 days after discontinuation: Carbamazepine 400 mg/day was prescribed. Skin eruption occurred again and administration of carbamazepine was discontinued.
	The other suspected medications: carbamazepine Concomitant medications: nifedipine, olmesartan medoxomil, warfarin potassium, rosuvastatin calcium, esomeprazole magnesium hydrate, alogliptin benzoate			

Laboratory Examination

	Day 1 of administration	Day 36 of administration (day of discontinuation)	6 days after discontinuation (day of admission)	9 days after discontinuation (day 3 of hospitalization)	28 days after discontinuation
AST (IU/L)	29	66	37	50	15
ALT (IU/L)	33	65	43	42	17
LDH (IU/L)	194	371	473	450	279
γGT (IU/L)	—	128	94	—	—
BUN (mg/dL)	—	—	—	18.5	18.7
Cr (mg/dL)	0.93	1.02	2.23	0.90	1.55
CRP	—	—	—	1.06	—
Eosinophils (/μL)	—	—	—	2 835	—

3

Revision of Precautions (No. 255)

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 March 25, 2014 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1

Antipyretics and analgesics, anti-inflammatory agents

Ketoprofen (injection, suppository)

Brand Name	Aneol Suppository 50, 75 (Iwaki Seiyaku Co., Ltd.), EPATEC Supp. 50, 75 (Biomedix. Co., Ltd.) and the others, CAPISTEN IM 50 mg (Kissei Pharmaceutical Co., Ltd.) and the others
Use in Pregnant, Parturient And Nursing Women	Pregnant women (excluding the third trimester) or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks. A case of oligohydramnios has been reported after maternal use of topical ketoprofen during the second trimester. This drug should be used at the lowest effective dose for the shortest necessary duration.

2

Antiparkinsonian agents

Rotigotine

Brand Name	Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg (Otsuka Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction** Hepatic dysfunction with elevations of aspartate aminotransferase (AST or glutamate oxaloacetate transaminase [GOT]), alanine aminotransferase (ALT or glutamate pyruvate transaminase [GPT]), A1-P, γ-GTP, etc., may occur. In such cases, appropriate measures such as dose reduction, temporary or permanent discontinuation of administration should be taken.

3

Psychotropics

Mirtazapine

Brand Name	REMERON Tablets 15 mg (MSD K.K.), REFLEX TABLETS 15 mg (Meiji Seika Pharma Co., Ltd.)
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:** Prolonged QT or ventricular tachycardia 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

Analgesics, anti-itchings, astringents, anti-inflammatory agents

Ibuprofen Piconol

Brand Name	STADERM OINTMENT 5%, STADERM CREAM 5% (Torii Pharmaceutical Co., Ltd.), VESICUM Ointment 5%, VESICUM Cream 5% (Hisamitsu Pharmaceutical Co., Inc.)
Use in Pregnant, Parturient And Nursing Women	Cases of foetal ductus arteriosus systole have been reported after maternal use of the topical non-steroidal anti-inflammatory drug during the third trimester.

5

Analgesics, anti-itchings, astringents, anti-inflammatory agents

(1) Indometacin (topical preparation)
(2) Diclofenac Sodium (topical preparation)
(3) Piroxicam (topical preparation)
(4) Flurbiprofen (topical preparation)
(5) Loxoprofen Sodium Hydrate (topical preparation)

Brand Name	(1) ACONIP PAP 70 mg (Teika Pharmaceutical Co., Ltd.), IDOMETHINE KOWA PAP 70 mg, IDOMETHINE KOWA GEL 1%, IDOMETHINE KOWA SOL 1%, IDOMETHINE KOWA CREAM 1% (Kowa Company. Ltd.), INSIDE PAP 70 mg (Hisamitsu Pharmaceutical Co., Inc.), INTENURSE PAP 70 mg (Toko Pharmaceutical Industrial Co., Ltd.), Inteban Ointment 1%, Inteban Cream 1%, Inteban External Solution 1% (Dainippon Sumitomo Pharma Co., Ltd.), Catlep Tape 35 mg, 70 mg, Catlep Pap 70 mg (Teikoku Seiyaku Co., Ltd.), KORIFUMECIN PAP 70 mg (Towaseiyaku Co., Ltd.), ZEMPACK PAP 70 (Kyukyu Pharmaceutical Co., Ltd.), HAPSTAR-ID 70mg (Oishi Koseido Co., Ltd.), LACTION PAP 70 mg (Teika Pharmaceutical Co., Ltd.) and the others (2) Naboal Tape 15 mg, Naboal Tape L 30 mg, NABOAL PAP 70 mg, 140 mg, NABOAL GEL 1% (Hisamitsu Pharmaceutical Co., Inc.), Voltaren Tape 15 mg, 30 mg, Voltaren Gel 1%, Voltaren Lotion 1% (Dojin Iyaku Kako Co., Ltd.) and the others (3) BAXO Ointment 0.5% (Toyama Chemical Co., Ltd.), Feldene Ointment 0.5% (Pfizer Japan Inc.) (4) ADOFEED PAP 40 mg, 80 mg (Lead Chemical Co., Ltd.), STAYBAN PAP 40 mg (Tokuhon Corporation), ZEPOLAS TAPE 20 mg, 40 mg, ZEPOLAS PAP 40 mg, 80 mg (Mikasa Seiyaku Co., Ltd.), FULRUBAN PAP 40 mg (Taikyo Pharmaceutical Co., Ltd.), YAKUBAN TAPE 20 mg, 40 mg, 60 mg (Tokuhon Corporation) and the others (5) LOXONIN TAPE 50 mg, 100 mg, LOXONIN PAP 100 mg (Lead Chemical Co., Ltd.), LOXONIN GEL 1% (Daiichi Sankyo Company, Limited.) and the others
Use in Pregnant, Parturient And Nursing Women	Cases of foetal ductus arteriosus systole have been reported after maternal use of the topical non-steroidal anti-inflammatory drug during the third trimester.

6 Analgesics, anti-itchings, astringents, anti-inflammatory agents

Ketoprofen (cream, gel, lotion, poultice)

Brand Name	EPATEC GEL 3%, EPATEC LOTION 3%, EPATEC CREAM 3% (Zeria Pharmaceutical Co., Ltd.), SECTOR GEL 3%, SECTOR LOTION 3%, SECTOR CREAM 3% (Hisamitsu Pharmaceutical Co., Inc.), MILTAX PAP 30 mg (Nipro Patch Co., Ltd.), MOHRUS PAP 30 mg, 60 mg (Hisamitsu Pharmaceutical Co., Inc.) and the others
Contraindications	Pregnant women in the third trimester (See "Use in Pregnant, Parturient And Nursing Women")
Use in Pregnant, Parturient And Nursing Women	Foetal ductus arteriosus systole may occur when topical ketoprofen is used in pregnant women during the third trimester. This drug should not be administered in the third trimester of pregnancy. Safety of topical ketoprofen is not established in pregnant (excluding the third trimester), parturient and nursing women. This drug should be administered only if potential benefits outweigh the risks. A case of oligohydramnios has been reported aftermaternal use of topical ketoprofen during the second trimester. This drug should be used at the lowest effective dose for the shortest necessary duration.

7 Gout preparations

Potassium Citrate/Sodium Citrate Hydrate

Brand Name	Uralyt Combination Tablet, Uralyt Combination Powder (Nippon Chemiphar Co., Ltd.) and the others
Careful Administration	Patients with impaired renal function
Important Precautions	Attention should be paid to changes in patient's serum electrolytes during treatment with this drug. In particular, when this drug is administered to patients with renal function impairment or when this drug is administered long-term, blood potassium level, renal function, etc., should be examined periodically. Also, if hyperkalaemia is observed, administration of this drug should be discontinued.
Adverse Reactions (clinically significant adverse reactions)	**Hyperkalaemia:** Hyperkalaemia may occur. Bradycardia, general malaise, feeling of weakness, etc., may occur associated with hyperkalaemia. Patients should be carefully monitored and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

8 Antineoplastics-Miscellaneous

Nilotinib Hydrochloride Hydrate

Brand Name	Tasigna Capsules 150 mg, 200 mg (Novartis Pharma K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Cerebral infarction, transient ischaemic attack:** Cerebral infarction or transient ischaemic attack 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

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 reactions (ADRs) 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 ADRs. EPPV is specified as a condition of approval.

(As of April 1, 2014)

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

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Tolvaptan Samsca tablets 7.5 mg, 15 mg*1	Otsuka Pharmaceutical Co., Ltd.	March 24, 2014
◎	Fluticasone Furoate Allermist 27.5μg 56 metered Nasal Spray*2	GlaxoSmithKline K.K.	March 17, 2014
◎	Pazopanib Hydrochloride Votrient Tablets 200 mg*3	GlaxoSmithKline K.K.	March 17, 2014
◎	Mogamulizumab (Genetical Recombination) POTELIGEO Injection 20 mg*4	Kyowa Hakko Kirin Co., Ltd.	March 17, 2014
	Cinacalcet Hydrochloride REGPARA TABLETS 25 mg, 75 mg*5	Kyowa Hakko Kirin Co., Ltd.	February 21, 2014
	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*6	Novartis Pharma K.K.	February 21, 2014
	pH-4 Treated Acid Normal Human Immunoglobulin (Subcutaneous injection) 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) DaTSCAN Injectable	Nihon Medi-Physics Co., Ltd.	January 27, 2014
	Talaporfin Sodium LASERPHYRIN 100 mg FOR INJECTION*7	Meiji Seika Pharma Co., Ltd.	January 20, 2014
	Meropenem Hydrate (1) Meropen Vial for Intravenous Drip Infusion 0.25 g, 0.5 g (2) Meropen Kit for Intravenous Drip Infusion 0.5 g*8	Dainippon Sumitomo Pharma Co., Ltd.	December 20, 2013
	Methylphenidate Hydrochloride Concerta Tablets 18 mg, 27 mg*9	Janssen Pharmaceutical K.K.	December 20, 2013
	Laninamivir Octanoate Hydrate INAVIR DRY POWDER INHALER 20 mg*10	Daiichi Sankyo Company, Limited	December 20, 2013

	Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg*[11]	Janssen Pharmaceutical K.K.	December 20, 2013
	Fentanyl Citrate Abstral Sublingual Tablets 100 μg, 200 μg, 400 μg	Kyowa Hakko Kirin Co., Ltd.	December 12, 2013
	Vilanterol Trifenatate/Fluticasone Furoate Relvar 100 Ellipta 14 doses, Relvar 200 Ellipta 14 doses	GlaxoSmithKline K.K.	December 9, 2013
	Talc Unitalc Intrapleural 4 g	Nobelpharma Co., Ltd.	December 9, 2013
	Simeprevir Sodium SOVRIAD capsules 100 mg	Janssen Pharmaceutical K.K.	December 6, 2013
	Epinastine Hydrochloride ALESION Ophthalmic Solution 0.05%	Santen Pharmaceutical Co., Ltd.	November 25, 2013
	Acetaminophen acelio Intravenous Injection 1000 mg	Terumo Corporation	November 25, 2013
	Landiolol Hydrochloride ONOACT 50 for Injection*[12]	Ono Pharmaceutical Co., Ltd.	November 22, 2013
	Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL*[13], EYLEA solution for IVT inj. Kit 40 mg/mL*[13]	Bayer Yakuhin, Ltd.	November 22, 2013
	Topiramate TOPINA Tablets 25 mg, 50 mg, 100 mg*[14]	Kyowa Hakko Kirin Co., Ltd.	November 22, 2013
	Indacaterol Maleate/Glycopyrronium Bromide ultibro inhalation capsules	Novartis Pharma K.K.	November 20, 2013
	Tafamidis Meglumine Vyndaqel capsules 20 mg	Pfizer Japan Inc.	November 20, 2013
	Fluticasone Propionate/Formoterol Fumarate Hydrate Flutiform 50 Aerosol 56 puffs, 125 Aerosol 56 puffs	Kyorin Pharmaceutical Co., Ltd.	November 19, 2013
	Brinzolamide/Timolol Maleate AZORGA Combination Ophthalmic Suspension	Alcon Japan Ltd.	November 19, 2013
	Paliperidone Palmitate XEPLION Aqueous Suspension for IM Injection Syringe 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	Janssen Pharmaceutical K.K.	November 19, 2013
	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) Prevenar13 Suspension Liquid for Injection	Pfizer Japan Inc.	October 28, 2013
	Hydroxyethylated Starch 130000 VOLUVEN 6% solution for infusion	Fresenius Kabi Japan K.K.	October 25, 2013
	Darbepoetin Alfa (Genetical Recombination) 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	Kyowa Hakko Kirin Co., Ltd.	September 13, 2013

	SYRINGE*15		

*1 An additional indication for “the control of disease progression in patients with autosomal dominant polycystic kidney who already had increased kidney volume and whose kidney volume was further rapidly increasing”

*2 An additional administration for “pediatrics”

*3 An additional indication for “the treatment of patients with radically unresectable or metastatic renal cell carcinoma”

*4 An additional indication for “the treatment of patients with relapsed or refractory CCR4-positive peripheral T-cell lymphoma and patients with relapsed or refractory CCR4-positive cutaneous T-cell lymphoma”

*5 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”

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

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

*8 An additional administration for “pyogenic meningitis”

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

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

*11 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”

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

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

*14 An additional administration for “pediatrics”

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

List of corrections in the PMDSI No.311

Page	10		
Original	Launched in Japan:	(2)	June 2008
Revised	Launched in Japan:	(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.)