Pharmaceuticals and Medical Devices Safety Information

No. 282 August 2011

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

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No. 282 August 2011

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

Outline of Information

No.	Subject	Measures	Outline of Information	Page
1	**Revision of Contraindications for the Use of Coronary Stent**	*P*	Coronary stent, a medical device percutaneously placed in the coronary artery, improves regional myocardial blood flow by dilating the stenotic artery. Previously, the use of coronary stents has been contraindicated in acute myocardial infarction patients or patients with lesions located in the unprotected left main trunk, etc. However, since these off-label uses are well-recognized in real clinical settings, MHLW conducted a hearing from the Japanese Circulation Society, and PMDA reviewed this matter. Accordingly, the contraindications for coronary stent were revised. The details of the revision and the importance of cooperation between cardiovascular internal physicians and cardiac surgeons when using coronary stents are described in this section.	5
2	**Revision of Contraindications for the Use of Intraocular Lens**	*P*	Intraocular lens (IOL) is a medical device to be inserted in the posterior or anterior chamber of the eye after removing the crystalline lens to improve visual acuity for cataract patients. Previously, the use of IOL has been contraindicated in children or in patients with uncontrolled glaucoma, proliferative diabetic retinopathy, or active uveitis, etc. However, the Japanese Ophthalmological Society and other organizations submitted a petition calling for a review of the contraindications based on the experience and results of IOL use in clinical settings. In view of the above, PMDA conducted a review and the contraindications for IOL were revised. The details are described in this section.	9
3	**Oxaliplatin (and 5 others)**	*P* *C*	This section presents the contents of the revisions and case summaries that served as the basis for these revisions to important adverse reactions included under the Precautions section of package inserts of drugs that have been revised in accordance with the Notification dated July 5, 2011.	13
4	**Pioglitazone Hydrochloride (and 8 others)**		Revision of Precautions (No. XXX)	28
5	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of August 1, 2011.	32

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
AIHA	Autoimmune hemolytic anemia
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AMI	Acute myocardial infarction
APTT	Activated partial thromboplastin time
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BE	Base excess
BMS	Bare metal stent
BUN	Blood urea nitrogen
Ca	Calcium
CABG	Coronary artery bypass grafting
CI	Confidence interval
Cl	Chloride
CRP	C-reactive protein
CT	Computed tomography
DES	Drug-eluting stent
DLST	Drug lymphocyte stimulation test
EACTS	European Association for Cardio-Thoracic Surgery
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
ESC	European Society of Cardiology
FOLFOX6	A regimen consisting of 5-fluorouracil/leucovorin plus oxaliplatin
FY	Fiscal year
HBe	Hepatitis B envelope
HBs	Hepatitis B surface
HCO_3-	Bicarbonate
ICU	Intensive care unit
IOL	Intraocular lens
IU	International unit
JCS	Japan Coma Scale
K	Potassium
LDH	Lactate dehydrogenase
LMT	Left main trunk
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
Na	Sodium
NH_3	Ammonia
P	Phosphorus
PAIgM	Platelet-associated immunoglobulin G
$PaCO_2$	Arterial carbon dioxide partial pressure
PaO_2	Arterial oxygen partial pressure
pH	Hydrogen ion concentration
PLT	Platelet
PS	Performance status
PT	Prothrombin Time
RBC	Red blood cell count
SUS	Steel Use Stainless
US	United States
WBC	White blood cell count
XELOX	A regimen consisting of capecitabine plus oxaliplatin
YAG	Yttrium aluminium garnet
γ-GTP	gamma-glutamyl transpeptidase

1

Revision of Contraindications for the Use of Coronary Stent

1. Introduction

Coronary stent, a medical device percutaneously placed in the coronary artery, improves regional myocardial blood flow by dilating the stenotic artery. The traditional bare metal stent (BMS) and drug-eluting stent (DES), which is a type of stent coated with immunosuppressant, etc to prevent restenosis, are available.

Coronary stents have been contraindicated in patients with acute myocardial infarction (AMI) or with lesions located in the unprotected left main trunk (unprotected LMT).

However, since these off-label uses are well-recognized in real clinical settings, MHLW conducted a hearing from the Japanese Circulation Society, and PMDA reviewed about this matter. Based on the results of the review[1)], following a discussion held on June 22, 2011 at the Subcommittee on Medical Device Safety of Committee on Medical Device Safety (hereinafter referred to as the Subcommittee on Medical Device Safety), the contraindications for coronary stents were revised. The details are described below.

2. Situations regarding coronary stents in Japan and overseas

When the contraindications were first determined, ischemic heart disease patients with coronary stenosis or occlusive lesions were predominantly treated with percutaneous balloon angioplasty. Stent placement in the thrombotic lesion was thought to increase the risk of stent thrombosis. However, with the establishment of antiplatelet therapy using aspirin, etc., coronary stent placement has played a major role in percutaneous coronary intervention.

Through the review of Japanese and overseas clinical studies and the guidelines in the U.S. and Europe, it was found that the use of coronary stents for AMI was effective and safe to a certain extent. Besides, although coronary artery bypass grafting (CABG) was still the first-line treatment for patients with unprotected LMT lesions, it was also found that the outcome of stent placement was comparable to that of CABG in some cases.

3. Results of review and safety measures

In accordance with the review by PMDA, MHLW concluded that there was not enough evidence to support the contraindications for coronary stent use in AMI patients. However, regarding DES, sufficient data for long-term prognosis has not been collected at present compared with BMS, and some cases reported late stent thrombosis which developed more than 1 year after DES placement. Accordingly, DES should be used carefully in AMI patients, and it is appropriate to include this information in the “Warnings” section of package inserts to alert healthcare professionals.

Regarding unprotected LMT lesions, MHLW concluded that the evidence supporting the contraindications in any patients with unprotected LMT lesions was also insufficient. Therefore it is appropriate to add, in the “Warnings” section in the package insert, an alert stating that coronary stents should be used carefully only in patients who are considered to be high risk for CABG based on the patient backgrounds and low risk for coronary stent use based on the anatomical characteristics of the lesion. In addition, it is important to select the optimal treatment for patients after a discussion between cardiovascular internal physicians and cardiac surgeons.

In case coronary stents are used in patients with diabetes mellitus, poor cardiac function, diffuse

lesions, or multivessel disease including proximal left anterior descending lesion, the device should be used appropriately based on cooperation between cardiovascular internal physicians and cardiac surgeons because it has been reported that such patients fail to respond to the stent treatment adequately, compared with CABG.

Based on the review of the Subcommittee on Medical Device Safety, MHLW issued a notification on July 20, 2011 and required the marketing authorization holders (MAHs) of coronary stents to revise the package insert to include the following information presented in pages 6 to 8.

4. Importance of cooperation between cardiovascular internal physicians and cardiac surgeons

This revision of the package insert allows some coronary stents to be used for treatment of patients with AMI and unprotected LMT lesions, who have been traditionally contraindicated without exception. However, when performing a revascularization procedure in a high-risk lesion, it is necessary to conduct a discussion on the indication carefully by a Heart Team consisting of cardiovascular internal physicians, cardiac surgeons and other healthcare professionals based on the patient background and the anatomical characteristics of the lesion. The team-based treatment is also recommended in the Guideline on Myocardial Revascularization in Europe published in September 2010.[2)] Accordingly, in light of the importance of physician-surgeon cooperation, the relevant precautions for indication and treatment were decided to be included in the "Warnings" section in the package insert.

The "Guidelines for Coronary Revascularization (tentative)" is being prepared by the Japanese Circulation Society. After completion and publication of the guidelines, healthcare professionals are encouraged to use the information and ensure patient safety through the proper use of coronary stents.

(1) An example of a drug-eluting stent

Before revision (crossed-out parts to be deleted)	After revision (underlined parts to be added)
[Warnings]	[Warnings]
(N/A)	• In patients with lesions located in the unprotected left main trunk, ostial lesions, or lesions located at a bifurcation, coronary stents should be used, except for emergency, only when cardiovascular internal physicians and cardiac surgeons discuss the indication and consider that the patient is high risk for coronary artery bypass grafting based on the patient background and low risk for coronary stent use based on the anatomical characteristics of the lesion.
(N/A)	• Coronary stents should be used appropriately in patients with diabetes mellitus, poor cardiac function, diffuse lesions, or multivessel disease including proximal left anterior descending lesion, based on cooperation between cardiovascular internal physicians and cardiac surgeons. [It has been reported that patients with these backgrounds or lesions fail to respond to the stent treatment adequately compared with the coronary artery bypass grafting.]

(N/A)	• Coronary stents should be used carefully in patients with acute myocardial infarction (AMI) or in patients whose cardiac enzymes have not declined to the normal level after the development of AMI. [Long-term efficacy and safety of coronary stents in such patients have not been established.]
[Contraindications]	[Contraindications]
Specific patient populations	Specific patient populations
~~• Patients with symptoms of acute myocardial infarction (AMI) or patients whose cardiac enzymes have not declined to the normal level after the development of AMI~~	(deleted)
~~• Patients for whom coronary artery bypass grafting (CABG) is more appropriate~~	(deleted)
~~• Patients with lesions located in the unprotected left main trunk, ostial lesions, or lesions located at a bifurcation~~	(deleted)

(2) An example of a bare metal stent

Before revision (crossed-out parts to be deleted)	After revision (underlined parts to be added)
[Warnings]	[Warnings]
~~○) This device is placed in the blood vessel. The metal contained in this device may elute and induce a metal allergy. In such cases, the effect of the stent may be reduced. Patients should be checked for metal allergies in advance, and indication for stent use should be reconsidered in metal allergy patients.~~	○) (deleted)
(N/A)	• In patients with lesions located in the unprotected left main trunk, ostial lesions, or lesions located at a bifurcation, coronary stents should be used, except for emergency, only when cardiovascular internal physicians and cardiac surgeons discuss the indication and consider that the patient is high risk for use of coronary artery bypass grafting based on the patient background and low risk for coronary stent use based on the anatomical characteristics of the lesion.
(N/A)	• Coronary stents should be used appropriately in patients with diabetes mellitus, poor cardiac function, diffuse lesions, or multivessel disease including proximal left anterior descending lesion, based on cooperation between cardiovascular internal physicians and cardiac surgeons. [It has been reported

	that patients with these backgrounds or lesions fail to respond to the stent treatment adequately compared with coronary artery bypass grafting.]
[Contraindications]	[Contraindications]
• ~~Patients who have experienced a recent (within less than 1 week) acute myocardial infarction~~	• (deleted)
• Patients to whom antiplatelet or anticoagulant therapy is contraindicated	• Same as on the left
• Patients with severe arterial tortuosity or calcification in the lesion or the proximal part that may interfere with adequate predilatation	• Same as on the left
(N/A)	• Patients who have hypersensitivity to the stainless steel SUS (Steel Use Stainless) 316L contained in this stent [Elution of the metal may induce metal allergy.]
[Precautions]	[Precautions]
Precautions (The stent should be used carefully in the following patients.)	Precautions (The stent should be used carefully in the following patients.)
~~(2) The safety and efficacy of the stent has not been established in the following patients.~~	
~~• Patients who have experienced recent acute myocardial infarction~~	• (deleted)
~~• Patients with lesions located in the left main trunk, ostial lesions, or lesions located at a bifurcation~~	• (deleted)
(N/A)	• Patients with acute myocardial infarction (AMI) or patients whose cardiac enzymes have not declined to the normal level after the development of AMI

(3) The following description should be added to the "Important Precautions" of the "Precautions" section in the package insert after establishment of the guidelines for coronary revascularization, which are being prepared by the Japanese Circulation Society.

Refer to the latest information, such as the "Guidelines for Coronary Revascularization (tentative)" of the Japanese Circulation Society when using coronary stents.

<References> (including provisionally translated titles)

1) Documents of the first meeting of the Subcommittee on Medical Device Safety of Committee on Medical Device Safety in 2011 (Revision of "Contraindications" section in the package insert of coronary stent) (only available in Japanese language)
http://www.mhlw.go.jp/stf/shingi/2r9852000001g8ac-att/2r9852000001g8bt.pdf

2) Guidelines on Myocardial Revascularization (European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) 2010)
Text:
http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-revasc-FT.pdf
Appendices:
http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-Appendix-MR.pdf

2

Revision of the Contraindications for the Use of Intraocular Lens

1. Introduction

Intraocular lens (IOL) is a medical device to be implanted in the posterior or anterior chamber of the eye after removing the crystalline lens to improve the visual acuity for cataract patients.

Previously, the use of IOL has been contraindicated in the following patients.

(1) Children
(2) Patients with uncontrolled glaucoma
(3) Patients with proliferative diabetic retinopathy
(4) Patients with active uveitis
(5) Patients with iris neovascularization
(6) Patients with retinal detachment
(7) Patients who had serious adverse events during surgery

However, the Japanese Ophthalmological Society and other organizations submitted to MHLW a petition calling for a review of the contraindications because IOL has been confirmed to be safe and effective in the above patients, with the recent advancement of surgical procedures and devices. Based on the results of the review conducted by PMDA[1)], following discussion held on June 22, 2011 at the Subcommittee on Medical Device Safety, the contraindications for IOL were revised. Details are described below.

2. Situations regarding IOL in Japan and overseas

When the contraindications were first determined, extracapsular cataract extraction (ECCE) was a common method of cataract surgery. In contraindicated patients, there were concerns about postoperative complications and poor prognosis, because ECCE involved a high level of tissue invasion with intraocular manipulation in addition to wide incision. However, according to the review of recent Japanese and overseas literature, it was found that IOL implantation could be conducted much safer and produce improved outcomes in patients who were traditionally contraindicated, with the advancement of surgical devices and lens materials that led to the wide use of phacoemulsification aspiration with a small incision as well as the advancement of procedures and devices for vitreous surgery, establishment of retinal photocoagulation, yttrium aluminium garnet (YAG) laser surgery, and effective antiinflammatory drugs and antibiotics.

3. Results of review and safety measures

By the PMDA's review, it was found that IOL implantation could produce good outcomes in traditionally contraindicated patients who were considered appropriate by ophthalmologists, and it was considered that these contraindications are not supported by enough evidence at present. Accordingly, MHLW concluded that contraindications for the use of IOL in these patients should be removed.

IOL could be beneficial to children under 2 years of age for early prevention of irreversible cataract-related amblyopia caused by impaired development of the optic nerves and visual cortex. However, IOL implantation and manipulation in small eye (lens capsule) can be difficult, and there is a risk that additional surgery may be required due to axial length growth. Therefore, when ophthalmologist appropriately selected the patients, IOL is contraindicated for children under 2 years

of age, and if the use of IOL is considered essential, it should be used carefully.

According to this revision, the following precautions for children should be added to the "Important Precautions" section, etc. in the package insert to alert healthcare professionals.

- IOL implantation should be performed in children under the supervision of ophthalmologists with adequate knowledge and experience of the characteristics of children. Especially, IOL implantation and manipulation could be difficult in the small eyes of children under 2 years of age, and there are also some growth-related risks. The child's guardian should be thoroughly informed of these possible risks in advance.
- In patients with active uveitis or children with uveitis, surgical invasion may aggravate uveitis or induce other complications. IOL implantation should be performed after suppression of inflammation by medication.

Based on the review of the Subcommittee on Medical Device Safety, MHLW issued a notification on July 20, 2011 and required MAHs of IOL to revise the package insert. Healthcare professionals are encouraged to cooperate to ensure patients' safety through the proper use of IOL.

Before revision (crossed-out parts to be deleted)	After revision (underlined parts to be added)
[Contraindications]	[Contraindications]
~~1. IOL is contraindicated in the following patients:.~~	1. (deleted)
~~(1) Children~~	(1) (deleted)
~~(2) Patients with uncontrolled glaucoma~~	(2) (deleted)
~~(3) Patients with proliferative diabetic retinopathy~~	(3) (deleted)
~~(4) Patients with active uveitis~~	(4) (deleted)
~~(5) Patients with iris neovascularization~~	(5) (deleted)
~~(6) Patients with retinal detachment~~	(6) (deleted)
~~(7) Patients who have previous history of serious adverse events during surgery~~	(7) (deleted)
~~(8) Other cases for which use of this lens is determined to be inappropriate by a doctor due to potential systemic or ocular complications~~	(8) (deleted)
(N/A)	<u>[Relative Contraindications (As a general rule, IOL is contraindicated in the following patients. If the use of IOL is considered essential, it should be used carefully.)]</u> <u>• Children under 2 years of age (See "Important Precautions.")</u>
[Precautions]	[Precautions]
1. Precautions (IOL should be used carefully in the following patients.)	1. Precautions (IOL should be used carefully in the following patients.)
(1) ~~Young patients~~	(1) <u>Children aged 2 or older</u>
(2) Patients with disorder of corneal endothelium	(2) Same as on the left

(3) Patients with glaucoma	(3) Same as on the left
(4) Patients with ~~previous history of~~ uveitis	(4) Patients with uveitis
(5) Patients with diabetic retinopathy	(5) Same as on the left
(6) Patients with ~~previous history of~~ retinal detachment	(6) Patients with retinal detachment
~~(7) Patients with excessive myopia~~	(7) (deleted)
(8) Patients with congenital ocular abnormalities	(8) Same as on the left
The rest is omitted.	The rest is omitted.
(N/A)	(○) Patient with iris neovascularization
	(○) Patients who have previous history of serious adverse events during surgery
2. Important Precautions	2. Important Precautions
(○) ~~As a high level of surgical skill is required for IOL implantation, the surgeon should have observed and/or assisted in numerous cataract surgeries and IOL implantations before attempting to implant an IOL.~~	(○) IOL may increase the incidence of complications or impair visual acuity in patients listed in the "Precautions" section. IOL implantation should be performed appropriately including postoperative follow-up under the supervision of an ophthalmologist with adequate experience at an appropriate medical institution.
~~(○) Since long-term safety and effectiveness of IOL implantation have not been established, surgeons should continue to monitor implant patients postoperatively on a regular basis.~~	(○) (deleted)
(N/A)	(○) IOL implantation should be performed in children under the supervision of ophthalmologists with adequate knowledge and experience of characteristics of children. Especially, IOL implantation and manipulation could be difficult in the small eyes of children under 2 years of age, and it has been reported that additional surgery may be required due to axial length growth. The child's guardian should be thoroughly informed of these possible risks in advance.
	(○) In patients with active uveitis or children with uveitis, surgical invasion may aggravate uveitis or induce other complications. IOL implantation should be performed after suppression of inflammation by medication.

<Reference>

1) Documents of the first meeting of the Subcommittee on Medical Device Safety of Committee on Medical Device Safety in 2011 (Revision of “Contraindications” section in the package insert of intraocular lens) (only available in Japanese language)
http://www.mhlw.go.jp/stf/shingi/2r9852000001g8ac-att/2r9852000001g8g3.pdf#search

3

Important Safety Information

This section presents the contents of revisions and case summaries that served as the basis for these revisions to important adverse reactions included under the Precautions section of the package inserts of drugs that have been revised in accordance with the Notification dated July 5, 2011.

1 Oxaliplatin

Brand Name (name of company)	ELPLAT FOR INJECTION 50 mg, 100 mg, ELPLAT I. V. INFUSION SOLUTION 50 mg, 100 mg (Yakult Honsha Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Incurable, unresectable, advanced/recurrent colorectal cancer Postoperative adjuvant chemotherapy for colon cancer

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Drug-induced thrombocytopenia: Thrombocytopenia may occur through immunological mechanisms. Patients should be carefully monitored for changes in their symptoms including purpura, epistaxis, and oral mucosal bleeding. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Haemolytic anaemia: Coombs test-positive haemolytic anaemia may occur through an immunological mechanism. Patients should be carefully monitored for changes in their symptoms including jaundice. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Leukoencephalopathy (including reversible posterior leukoencephalopathy syndrome): Leukoencephalopathy (including reversible posterior leukoencephalopathy syndrome) may occur. If symptoms including staggering gait, lisp, convulsion, headache, confusion, or visual disturbance are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Hyperammonaemia: Hyperammonaemia with disturbed consciousness may occur. Patients should be carefully monitored. 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

[April 1, 2008 to May 23, 2011]

- Drug-induced thrombocytopenia: 7 cases (no fatal cases)
- Haemolytic anaemia: 4 cases (no fatal cases)

[April 1, 2008 to April 9, 2011]

- Leukoencephalopathy: 4 cases (no fatal cases)
- Hyperammonaemia: 7 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 35,000 (2010).

Launched in Japan: April 2005

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Colon cancer (diabetes mellitus)	73 mg/m^2 × 16 (Day 1, 24, 36, 59, 73, 87, 101, 115, 129, 164, 178, 192, 206, 234, 248, and 276)	**Decreased platelets** Day 1 of administration: The patient who had colon cancer (primary cancer with metastases to the liver, peritoneum and lymph nodes) complicated with diabetes mellitus (Performance Status [PS]: 0) was treated with oxaliplatin 73 mg/m^2, levofolinate calcium 195 mg/m^2, bolus intravenous infusion of fluorouracil 366 mg/m^2, continuous intravenous infusion of fluorouracil 1951 mg/m^2/2 days (FOLFOX 6). Day 24 of administration: FOLFOX 6 was performed. Day 36 of administration: FOLFOX 6 and bevacizumab (genetical recombination) 525 mg/body were concomitantly administered. Day 59 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 73 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 87 of administration: FOLFOX 6 was performed. Day 101 of administration: FOLFOX 6 was performed. Day 115 of administration: FOLFOX 6 and bevacizumab (genetical recombination) 525 mg/body were concomitantly administered. Day 129 of administration: FOLFOX 6 (bolus intravenous infusion of fluorouracil 244 mg/m2) and bevacizumab (genetical recombination) were concomitantly administered. Day 136 of administration: Platelets decreased (7.3 × 10^4/mm^3). Day 164 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 178 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 192 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 206 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 234 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 248 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. Day 276 of administration: FOLFOX 6 and bevacizumab (genetical recombination) were concomitantly administered. The patient developed gingival bleeding and petechiae in the left upper limb after she went home (about 6 and half hours after starting the administration of this drug) and visited the emergency department. Platelet decrease associated with platelet antibody was suspected based

				on the decreased platelet count ($11.9 \times 10^4/mm^3$ at baseline to $0.4 \times 10^4/mm^3$ after treatment) and the elevated platelet-associated immunoglobulin G (PAIgG) (272 ng/10^7 cells). The patient was admitted to the hospital to receive platelet transfusion and steroid pulse therapy. Day 283 of administration: Drug lymphocyte stimulation test (DLST) was positive for oxaliplatin and negative for levofolinate calcium. The patient was discharged from the hospital on the same day. Day 285 of administration: Decreased platelets remitted. Day 288 of administration: PAIgG was 74 ng/10^7 cells.
	Concomitant medications: fluorouracil, levofolinate calcium, bevacizumab (genetical recombination), granisetron hydrochloride, dexamethasone sodium phosphate, pioglitazone hydrochloride, glibenclamide, voglibose			

Laboratory Examination

	Day 136 of administration:	Day 164 of administration:	Day 178 of administration:	Day 192 of administration:	Day 206 of administration:	Day 276 of administration:		Day 277 of administration	Day 278 of administration	Day 280 of administration	Day 282 of administration	Day 285 of administration:
						Before administration	After administration					
CRP (mg/dL)	-	0.28	0.19	0.33	0.44	0.26	0.31	0.49	-	0.07	-	-
Hemoglobin (g/dL)	10.8	11.6	11.1	11.8	11.3	11.6	12.7	11.3	12.0	13.1	12.0	11.9
PLT ($\times 10^4/mm^3$)	7.3	13.5	8.4	9.2	12.2	11.9	0.4	2.8	5.4	7.7	7.6	9.3
WBC ($/mm^3$)	2830	4470	3770	3960	4640	4050	5000	4630	9060	7420	5700	5850
Neutrophil count ($/mm^3$)	792	1770	1847	1703	2134	1924	-	4213	7610	4081	2679	2568
PT (sec)	11.6	11.1	11.5	10.7	11.3	11.4	12.0	12.0	-	-	-	-
APTT (sec)	26.6	27.0	26.7	26.8	27.4	29.3	31.9	39.8	-	-	-	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Large intestine carcinoma (none)	71 mg/m^2 once (Day 1) 57 mg/m^2 3 times (Day 25, 39 and 53) 67 mg/m^2 4 times (Day 67, 91, 116 and 137)	**Haemolytic anaemia, acute renal failure** Approximately 2 years before administration: The patient completed prior treatment (FOLFOX 6; concomitant use with oxaliplatin, levofolinate calcium, and fluorouracil, 26 cycles). Approximately 1 years and 8 months before administration: Prior treatment (concomitant use with fluorouracil and calcium folinate, 8 cycles) was completed. Approximately 10 months before administration: Prior treatment (concomitant use with fluorouracil, calcium folinate, and bevacizumab [genetical recombination], 21 cycles) was completed. 39 days before administration: Prior treatment (irinotecan hydrochloride hydrate monotherapy, 18 cycles) was completed. Day 1 of administration: Oxaliplatin 71 mg/m^2, levofolinate calcium 168 mg/m^2, and continuous intravenous infusion of fluorouracil 1980 mg/m^2/2days were concomitantly administered to patients with large intestine cancer (post-resection relapse with metastases to the peritoneum and ovary; PS 0). Day 25 of administration: Oxaliplatin 57 mg/m^2, levofolinate calcium 134 mg/m^2, and continuous intravenous infusion of fluorouracil 1577

				mg/m^2/2days were concomitantly administered. Day 39 of administration: Oxaliplatin, levofolinate calcium, and continuous intravenous infusion of fluorouracil (2days) were concomitantly administered. Day 53 of administration: Oxaliplatin, levofolinate calcium, and continuous intravenous infusion of fluorouracil (2days) were concomitantly administered. Day 67 of administration: Oxaliplatin 67 mg/m^2 and capecitabine 3600 mg/day (XELOX, daily administration until Day 80) were concomitantly administered. Day 91 of administration: Oxaliplatin and capecitabine (XELOX, daily administration until Day 104) were concomitantly administered. Day 116 of administration: Oxaliplatin and capecitabine (XELOX, daily administration until Day 129) were concomitantly administered. Day 137 of administration: Oxaliplatin and capecitabine (XELOX, daily administration until Day 141) were concomitantly administered. Day 143 of administration: A blood test showed BUN 93 mg/dL and creatinine 8.80 mg/dL, and the patient was diagnosed with acute renal failure. Since platelet count 5.1 × 104/mm3, hemoglobin 5.6 g/dL, and LDH 613 IU/L was noted, and direct Coombs test was positive in the cross-match test for blood transfusion (no transfusion was performed), haemolytic anaemia (autoimmune haemolytic anaemia [AIHA]) was suspected. Haemodialysis (until Day 148) and plasma exchange were started. Indirect bilirubin 0.5 mg/dL, haptogloblin < 10 mg/dL Day 144 of administration: Administration of prednisolone was started. Day 162 of administration: The patient recovered from acute renal failure. Haemolytic anaemia remitted.
	Concomitant medications: fluorouracil, levofolinate calcium, capecitabine			

Laboratory Examination

	Day 39 of administration	Day 53 of administration	Day 67 of administration	Day 91 of administration	Day 116 of administration	Day 137 of administration	Day 143 of administration	Day 162 of administration
CRP (mg/dL)	-	-	-	-	-	-	-	0.33
Hemoglobin (g/dL)	11.8	11.0	12.4	-	-	8.2	5.6	7.4
RBC (× 10^4/mm^3)	394	369	414	-	-	245	165	232
PLT (× 10^4/mm^3)	10.7	9.4	11.8	7.8	9.1	10.8	5.1	9.8
WBC (/mm^3)	2960	1160	6170	2250	3200	2850	5340	5990
Neutrophil count (/mm^3)	1968	539	5047	-	-	2052	4518	5229
AST (GOT) (IU/L)	27	25	26	-	-	23	15	16
ALT (GPT) (IU/L)	22	19	16	-	-	13	12	10
LDH (IU/L)	211	212	242	-	-	301	613	289
Al-P (IU/L)	205	214	185	-	-	196	181	145
Total bilirubin (mg/dL)	1.0	0.7	0.7	-	-	0.8	0.8	0.4
Indirect bilirubin (mg/dL)	-	-	-	-	-	-	0.5	-
Haptogloblin (mg/dL)	-	-	-	-	-	-	<10	-
Reticulocyte (%)	-	-	-	-	-	-	-	8
BUN (mg/dL)	18	17	17	-	-	13	93	18

Creatinine (mg/dL)	0.60	0.60	0.63	-	-	0.65	8.80	1.07
Na (mEq/L)	143	142	141	-	-	140	134	136
K (mEq/L)	4.0	3.8	4.0	-	-	3.8	4.4	3.5
Cl (mEq/L)	104	104	103	-	-	103	89	98

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 60s	Colon cancer (hypertension)	85 mg/m^2 once (Day 1)	**Leukoencephalopathy** 44 days before administration: The patient received ileocecal resection. Day 1 of administration: Oxaliplatin 85 mg/m^2, levofolinate calcium 200 mg/m^2, bolus intravenous infusion of fluorouracil 400 mg/m^2, and continuous intravenous infusion of fluorouracil 2400 mg/m^2/2days (FOLFOX 6) as postoperative adjuvant chemotherapy were concomitantly administered in patients with colon cancer (post-resection; PS 0) and hypertension. Day 4 of administration: The patient experienced staggering gait in the evening. Day 5 of administration: The patient had inarticulateness after he got up. His staggering gait increased. Moderate dyslalia was noted. Bilateral finger-to-nose test was positive. Cranial CT and Magnetic resonance imaging (MRI) showed no apparent cerebrovascular disorder or metastases to brain. Diffusion MRI showed high intensity areas in bilateral deep hemispheric white matter and corpus callosum. The patient was diagnosed with leukoencephalopathy (grade 3). The symptoms remitted without further treatment. Day 9 of administration: Diffusion MRI showed a marked decrease of abnormal high intensity areas. Day 13 of administration: Leukoencephalopathy remitted.
	Concomitant medications: fluorouracil, levofolinate calcium, irbesartan, olmesartan medoxomil, metoclopramide, amlodipine besilate			

Laboratory Examination

	10 days before administration	Day 14 of administration
Hemoglobin (g/dL)	12.9	13.0
PLT (× 10^4/mm^3)	20.4	20.2
WBC (/mm^3)	5690	3960
Neutrophil count (/mm^3)	3260	1972
AST (GOT) (IU/L)	18	21
ALT (GPT) (IU/L)	16	28
Al-P (IU/L)	168	195
Total bilirubin (mg/dL)	0.6	0.4
BUN (mg/dL)	19.4	14.8
Creatinine (mg/dL)	0.83	0.92

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 70s	Rectal cancer (none)	86 mg/m^2 once (Day 1)	**Hyperammonaemia** Day 1 of administration: The patient with (relapsed) rectal cancer concomitantly received oxaliplatin 86 mg/m^2, levofolinate calcium 197 mg/m^2, bolus intravenous infusion of fluorouracil 395 mg/m^2, and continuous intravenous infusion of fluorouracil 2434 mg/m^2/2days). Day 3 of administration: Continuous intravenous infusion of fluorouracil was being performed. The patient vomited early in the morning and subsequently had disturbed consciousness (Japan Coma Scale [JCS] - 100). He was taken to the hospital in the afternoon. The patient was diagnosed with hyperammonaemia (NH_3 773 μg/dL), metabolic acidosis (pH, 7.264; HCO_3-, 8.4 mEq/L; BE, -16.6 mmol/L) and renal impairment (creatinine 2.85 mg/dL) and admitted to the Intensive Care Unit (ICU). Massive fluid replacement was given to maintain urinary output. Metabolic acidosis improved, and consciousness returned at night. Day 6 of administration: Hyperammonaemia improved.
	Concomitant medications: fluorouracil, levofolinate calcium, azasetron hydrochloride, dexamethasone sodium phosphate			

Laboratory Examination

	Day 3 of administration	Day 4 of administration	Day 5 of administration	Day 6 of administration
Maximum body temperature (°C)	35.6	37.4	36.3	-
CRP (mg/dL)	0.1	0.5	0.8	1.3
Hemoglobin (g/dL)	10.3	8.9	9.1	9.1
PLT (× 10^4/mm^3)	14.6	14.7	12.0	12.1
WBC (/mm^3)	10800	14500	9000	6200
AST (GOT) (IU/L)	85	57	46	36
ALT (GPT) (IU/L)	37	-	-	15
Al-P (IU/L)	261	-	-	224
LDH (IU/L)	245	-	-	207
Total bilirubin (mg/dL)	0.8	0.9	1.1	0.9
BUN (mg/dL)	52.2	64.3	54.3	53.1
Creatinine (mg/dL)	2.85	2.73	2.30	1.89
Na (mEq/L)	141	144	136	137
K (mEq/L)	5.3	4.1	3.6	3.8
Cl (mEq/L)	102	111	106	106
NH_3 (μg/dL)	773	34	26	28
pH	7.264	7.495	7.426	7.415
$PaCO_2$ (mmHg)	18.9	26.3	31.4	32.7
PaO_2 (mmHg)	130.2	106.5	102.2	111.3
HCO_3^- (mEq/L)	8.4	19.8	20.2	20.5
BE (mmol/L)	-16.6	-2.6	-3.5	-3.4

2 **Recombinant Adsorbed Hepatitis B Vaccine** (yeast-derived) (Bimmugen)

Brand Name (name of company)	Bimmugen (The Chemo-Sero-Therapeutic Research Institute)
Therapeutic Category	Vaccines
Indications	Prevention of hepatitis B Prevention of fetomaternal infection of hepatitis B virus (Concomitant use with anti-Hepatitis B surface [HBs] human immunoglobulin) Prevention of hepatitis B after contamination with HBs antigen- and Hepatitis B envelope (HBe) antigen-positive blood (Concomitant use with anti-HBs human immunoglobulin)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Multiple sclerosis, acute disseminated encephalomyelitis, Guillain-Barre syndrome: If any symptoms are observed, 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 (April 1, 2008 to April 26, 2011)

- Guillain-Barre syndrome: 1 case (no fatal case)

The number of patients using this drug per year estimated by the MAHs: Approximately 290,000 (FY 2010)

Launched in Japan: June 1988

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Prevention of hepatitis B (none)	0.5 mL once	**Guillain-Barre syndrome** The patient had pollinosis, allergic history to shrimp and crab (mild allergies). No problems occurred after she received the first vaccination of recombinant adsorbed hepatitis B vaccine 0.5 mL about 7 months earlier and second vaccination about 6 months earlier. Day of vaccination: Third vaccination of recombinant adsorbed hepatitis B vaccine 0.5 mL. (the patient reported that her menstruation had just finished) 12 days after vaccination: Sharp prickling pain occurred in the right thigh. 20 days after vaccination: The pain disappeared. Numbness in both hands occurred. 21 days after vaccination: General malaise worsened. 25 days after vaccination: Decreased grip strength in both hands occurred. 27 days after vaccination: The patient visited Hospital A. The patient was diagnosed with suspected Guillain-Barre syndrome. The patient was referred and admitted to Hospital B. Definite diagnosis of Guillain-Barre syndrome was made. Since she was found to be pregnant, immunoglobulin therapy or plasma exchange was not performed.

				63 days after vaccination: The patient was transferred to the convalescence rehabilitation ward at Hospital A. The axonal form of Guillain-Barre syndrome is acute motor sensory axonal neuropathy. The patient still had gait disturbance associated with impaired vibratory sense due to poor recovery from sensory impairment. 87 days after vaccination: Guillain-Barre syndrome was not resolved. Anti-gangrioside antibody was negative (test date unknown).
	Concomitant medications: none			

3 Sunitinib Malate

Brand Name (name of company)	SUTENT Capsule 12.5 mg (Pfizer Japan Inc.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Imatinib-resistant gastrointestinal stromal tumors Radically unresectable or metastatic renal cell carcinoma

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Tumour lysis syndrome: Tumour lysis syndrome may occur. Patients should be carefully monitored, checking serum electrolyte levels and 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 they have recovered from such symptoms.

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 (from initial marketing to May 30, 2011)

- Tumour lysis syndrome: 4 cases (1 fatal case)

The number of patients using this drug per year estimated by the MAHs: Approximately 2,300 (FY 2010)
Launched in Japan: June 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Renal cell carcinoma stage IV (metastases to bone, metastases to lung)	37.5 mg for 9 days	**Tumour lysis syndrome** <History of prior treatment> None 12 days before administration: A CT showed the primary lesion of renal cell carcinoma (stage IV, T4N2M1) with the size of 131.43 mm and the volume of 1210 mL. PS: 1. Day 1 of administration: Administration of sunitinib malate 37.5 mg/day was started for treatment of renal cell carcinoma. Day 7 of administration: Hepatic dysfunction (grade 2) developed. Palpitation found apparent softening of primary lesion of tumor. Day 8 of administration: Malaise (grade 3) developed.

				Day 9 of administration (day of discontinuation): Hepatic dysfunction (grade 4), hyperuricaemia (grade 4), anorexia (grade 3), decreased platelets (grade 2), and decreased estimated Glomerular Filtration Rate (eGFR) (grade 1) developed. Administration of sunitinib malate was discontinued. 1 day after discontinuation: Decreased eGFR (grade 2), hyperkalaemia (grade 1), and acidosis (grade 1) developed. 2 days after discontinuation: Decreased platelets (grade 3), hyperkalaemia (grade 2), and acidosis (grade 3) developed. 4 days after discontinuation: Hypocalcaemia (grade 2) developed. 5 days after discontinuation: Decreased platelets (grade 4) developed. 6 days after discontinuation: Hyperkalaemia (grade 3) developed. Despite the liver supporting therapy, administration of diuretics, electrolyte correction, treatment of acidosis, and nutritional support, the patient suddenly had bradycardia followed by cardio-respiratory arrest on this day. The patient was resuscitated and monitored in the ICU. 7 days after discontinuation: A CT showed the size of primary tumor was 123.54 mm. The tumor volume was reduced by 160 mL (13% reduction). 44 days after discontinuation: The patient died of multiorgan failure.
	Concomitant medications: carbocisteine, dimemorfan phosphate, levofloxacin hydrate, codeine phosphate hydrate, ursodeoxycholic acid, domperidone			

Laboratory Examination

	8 days before administration	Day 9 of administration (day of discontinuation)	2 days after discontinuation:	6 days after discontinuation:
WBC (/mm^3)	5930	5560	9930	20740
AST (GOT) (IU/L)	24	1237	11760	1519
ALT (GPT) (IU/L)	19	368	3281	892
Al-P (IU/L)	298	322	592	533
LDH (IU/L)	155	2277	15651	1740
γ-GTP (IU/L)	-	43	89	-
Total bilirubin (mg/dL)	0.6	1.9	2.2	3.5
BUN (mg/dL)	9.5	22.5	33.9	34.5
Creatinine (mg/dL)	0.5	0.7	1.2	1.5
Uric acid (mg/dL)	-	10.1	12.6	-
Na (mEq/L)	137	134	128	142
K (mEq/L)	4.3	4.6	5.9	6.8
Cl (mEq/L)	100	96	92	100
Ca (mEq/L)	8.8	8.9	8.3	7.6
CRP (mg/dL)	12.38	-	12.74	31.1

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Renal cell carcinoma stage IV (metastases to lung, metastases to liver, metastases to bone, and metastases to adrenals)	50 mg for 14 days	**Tumour lysis syndrome** <History of prior treatment> None 9 days before administration: The patient visited the emergency outpatient department with a chief complaint of severe back pain due to which he was unable to move. Based on detailed examinations, the patient was diagnosed with left renal cell carcinoma (T2N0M1) with multiple metastases (lung, bone, liver, and adrenals) and referred to the urology department. Lumbar vertebral fracture also occurred. PS: 1. Day 1 of administration: Administration of sumitinib malate 50 mg/day was started for treatment of renal cell carcinoma. Day 12 of administration: Vomiting occurred. Day 14 of administration (day of discontinuation): The patient had dark brown urine. Biochemical test showed increase of BUN, creatinine, uric acid, and inorganic phosphorus. This met the diagnostic criteria for tumour lysis syndrome. Administration of sunitinib malate was immediately discontinued. A CT showed mild enlargement of the tumor. Pleural effusion also increased. Forced diuresis with transfusion and conservative therapy with administration of allopurinol were started. 1 day after discontinuation: Urine output was maintained at least 2000 mL. BUN, creatinine, uric acid, and inorganic phosphorus decreased. 3 days after discontinuation: BUN, creatinine, uric acid, and inorganic phosphorus decreased to the normal range. The patient recovered from tumour lysis syndrome. 5 days after discontinuation (day of readministration): Administration of sumitinib malate 50 mg/day was resumed. After treatment resumption: Based on determination of therapeutic efficacy after first cycle of sumitinib malate, the tumor was considered to be aggravated. The general condition worsened. Palliative care was performed. Day 54 of administration: The patient died of cancer.
	Concomitant medications: rebamipide, loxoprofen sodium hydrate, urea, zopiclone, diclofenac sodium, valsartan, isosorbide dinitrate, magnesium oxide, pentazocine hydrochloride, clindamycin hydrochloride, domperidone			

Laboratory Examination

	9 days before administration	Day 7 of administration	Day 14 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	5 days after discontinuation (day of readministration)
WBC (/mm^3)	7650	5740	4460	-	3730	3490
AST (GOT) (IU/L)	138	156	161	-	-	-
ALT (GPT) (IU/L)	32	84	39	-	-	-
LDH (IU/L)	1510	1671	3244	-	-	-
BUN (mg/dL)	21.8	21.5	61.0	49.3	16.9	12.1

Creatinine (mg/dL)	1.0	1.1	2.6	2.3	1.3	1.1
Uric acid (mg/dL)	6.6	-	9.5	7.6	3.2	2.0
Na (mEq/L)	129	-	136	134	136	134
K (mEq/L)	4.1	-	4.9	4.3	4.1	4.1
Cl (mEq/L)	89	-	99	99	102	101
Ca (mEq/L)	9.8	-	8.8	7.9	8.0	8.0
P (mEq/L)	-	-	5.4	3.8	2.9	3.2
CRP (mg/dL)	9.3	-	-	-	-	-

4 Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed)

Brand Name (name of company)	Prevenar Suspension Liquid for S.C. Injection (Pfizer Japan Inc.)
Therapeutic Category	Vaccines
Indications	Prevention of invasive infection with pneumococcus (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Thrombocytopenic purpura: Thrombocytopenic purpura may occur. If any abnormalities including purpura, epistaxis, and oral mucosal bleeding are observed, a blood test should be performed, 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 year (from initial marketing to April 15, 2011)

- Thrombocytopenic purpura: 7 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs: approximately 1.80 million (July 1, 2010 to June 30, 2011)

Launched in Japan: February 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male Under age of 10	Infection prophylaxis (none)	0.5 mL for 1 day	**Idiopathic thrombocytopenic purpura** Day of vaccination: The patient received pneumococcal polysaccharide conjugate vaccine. Day 18 of vaccination (day of onset): The patient had epistaxis everyday. It took as long as 40 minutes to stop the bleeding. Idiopathic thrombocytopenic purpura occurred. Day 20 of vaccination: Subcutaneous haemorrhage occurred on both elbows and knees. Petechiae appeared around the eye. Day 24 of vaccination: The patient visited the pediatric department of a hospital where he had received the vaccination because of expanded subcutaneous haemorrhage, newly occurred subcutaneous haemorrhage in the legs, and purpura in the buttocks and back. The patient visited and was admitted to the hospital to receive detailed examinations. Leukaemia was rejected based on platelet count $0.8 \times 10^4/mm^3$, no abnormal hemocyte in

				peripheral blood smear, and no pancytopenia. Idiopathic thrombocytopenic purpura was most strongly suspected. Administration of polyethylene glycol treated human normal immunoglobulin injection 20 g (1 g/kg) was started. Day 25 of vaccination: Platelet count increased in response to human normal immunoglobulin ($4.2 \times 10^4/mm^3$). However, since sufficient recovery was not confirmed, polyethylene glycol treated human normal immunoglobulin injection 20 g (1 g/kg) was administered again. Day 27 of vaccination: Purpura appeared on the left upper arm. Purpura in the other areas was disappearing. Day 29 of vaccination: Platelet count increased to $25.3 \times 10^4/mm^3$. Idiopathic thrombocytopenic purpura improved. Day 32 of vaccination: The patient was discharged from the hospital since decreased platelets had not been confirmed. He was to be followed up on an outpatient basis (platelet count $30.7 \times 10^4/mm^3$). Test date unknown: influenza (-), rotavirus (-)
	Concomitant medications: none			

Laboratory Examination

	Day 24 of vaccination		Days 25 of vaccination	Day 29 of vaccination	Day 32 of vaccination
	On admission	Second test during hospitalization			
RBC ($\times 10^4/mm^3$)	390	401	375	399	399
Hemoglobin (g/dL)	11.3	11.4	10.8	11.6	11.5
WBC ($/mm^3$)	8020	8400	4470	4900	8240
PLT ($\times 10^4/mm^3$)	0.8	0.6	4.2	25.3	30.7

5 Varenicline Tartrate

Brand Name (name of company)	CHAMPIX Tablets 0.5 mg, 1 mg (Pfizer Japan Inc.)
Therapeutic Category	Non-main therapeutic purpose agents-Miscellaneous
Indications	Aid to smoking cessation in nicotine-dependent smokers

PRECAUTIONS (underlined parts are revised)

Important Precautions

Some cases of dizziness, somnolence, and disturbed consciousness leading to automobile accidents have been reported. Patients should be advised to refrain from engaging in potentially hazardous operations including driving.

Adverse Reactions (clinically significant adverse reactions)

Disturbed consciousness: Disturbed consciousness including decreased level of consciousness, and loss of consciousness may occur. Patients should be carefully monitored. 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 (from initial marketing to April 21, 2011)

- Disturbed consciousness occurring while driving: 3 cases (no fatal cases)
- Disturbed consciousness-related events: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs: approximately 414,000 (July 1, 2010 to June 30, 2011)
Launched in Japan: May 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Smoking cessation therapy (chronic obstructive pulmonary disease, bullous lung disease)	0.5 mg for 3 days ↓ 1 mg for 4 days ↓ 2 mg for 1 day	**Loss of consciousness, tremor, salivary hypersecretion** Smoking status: details unknown 10 years before administration: The patient was cured of bullous lung disease in the left lung. 4 months before administration: The patient developed chronic obstructive pulmonary disease. Administration of tiotropium bromide hydrate was started. Day 1 of administration: Administration of varenicline tartrate 0.5 mg/day was started for smoking cessation therapy. Day 4 of administration: The dose of varenicline tartrate was increased to 1 mg/day. The patient had no symptoms. Administration of varenicline tartrate was continued. Day 8 of administration (day of discontinuation): The dose of varenicline tartrate was increased to 2 mg/day. The patient took varenicline tartrate 1 mg after breakfast. About 20 minutes later, the patient had salivation, tremulousness in the whole body, and loss of consciousness while driving. When the patient came to, the car was in a roadside ditch. The patient took varenicline tartrate 1 mg after dinner. About 20 minutes later, the patient had salivation, tremulousness in the whole body, and loss of consciousness while driving again. He almost drove into an electric pole. The symptoms improved without treatment. Administration of varenicline tartrate was discontinued. The patient has never had the symptoms.
	Concomitant medication: tiotropium bromide hydrate			

6 Lenalidomide Hydrate

Brand Name (name of company)	Revlimid Capsules 5 mg (Celgene K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Relapsed or refractory multiple myeloma Myelodysplastic syndrome associated with a chromosome 5q deletion

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Serious renal disorder: Serious renal disorder including renal failure may occur. Patients should be carefully monitored through periodic tests. If any abnormalities are observed, appropriate measures including dose reduction, drug suspension, and drug discontinuation 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 year (from initial marketing to May 29, 2011)

- Serious renal disorder: 23 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs: approximately 4,100 (July 20, 2010 to July 19, 2011)
Launched in Japan: July 2010

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Multiple myeloma (chronic renal failure, cardiac failure, post herpetic neuralgia)	15 mg (alternate day) for 5 days ↓ (administration suspended for 7 days) ↓ 10 mg (once every 3 days) for 4 days ↓ (administration suspended for 5 days)	**Renal failure** Approximately 2 months before administration: The patient had multiple myeloma. Day 1 of administration: Administration of lenalidomide hydrate was started. (creatinine clearance at the start of treatment administration < 30 mL/min) Day 7 of administration (day of onset): Renal failure worsened. Day 13 of administration: Renal failure resolved. Administration of lenalidomide hydrate was resumed at 10 mg once every 3 days. Day 15 of administration (day of recurrence): Renal failure and rash occurred. The patient received olopatadine hydrochloride for treatment of rash. Day 17 of administration: The patient received prednisolone for treatment of rash. Day 20 of administration: Renal failure resolved. Day 21 of administration: Rash resolved.
	Concomitant medications: dexamethasone, azosemide, candesartan cilexetil, sulfamethoxazole/trimethoprim, gabapentin, aspirin			

Laboratory Examination

	2 days before administration	Day 2 of administration	Day 7 of administration (day of onset)	Day 10 of administration	Day 13 of administration	Day 15 of administration (day of recurrence)	Day 20 of administration
Creatinine (mg/dL)	2.54	1.91	3.65	2.47	1.87	3.39	1.45
BUN (mg/dL)	76.2	59.0	89.2	75.1	58.1	58.0	54.4

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Multiple myeloma (peripheral neuropathy, diabetes mellitus, neurogenic bladder)	25 mg for 8 days ↓ (administration suspended for 1 day) ↓ 10 mg for 5 days	**Acute renal failure** Approximately 5 years before administration: The patient had multiple myeloma. Day 1 of administration: Administration of lenalidomide hydrate was started. Day 4 of administration: Hypercalcaemia occurred. The patient was treated with elcatonin. Day 8 of administration (day of onset): Acute renal failure, hyperuricaemia and

			↓ 15 mg for 1 day ↓ (administration suspended for 1 day) ↓ 15 mg for 1 day	thrombocytopenia occurred. Administration of lenalidomide hydrate was suspended. The patient received allopurinol for treatment of hyperuricaemia. Day 10 of administration: Administration of lenalidomide hydrate was resumed at 10 mg. Day 15 of administration: The dose of lenalidomide hydrate was increased to 15 mg. Day 17 of administration: Lenalidomide hydrate 15 mg was administered. Day 18 of administration: Hypercalcaemia remitted. Administration of furosemide and transfusion were started for treatment of acute renal failure. Day 21 of administration: Hyperuricaemia remitted. Day 23 of administration: Thrombocytopenia improved. Day 35 of administration: Acute renal failure remitted.
	Concomitant medications: dexamethasone, aspirin, tamsulosin hydrochloride, sodium rabeprazole, sulfamethoxazole/trimethoprim, valaciclovir hydrochloride, imidafenacin, celecoxib, pregabalin			

Laboratory Examination

	6 days before administration	Day 4 of administration	Day 8 of administration (day of onset)	Day 14 of administration	Day 18 of administration	Day 21 of administration	Day 23 of administration	Day 35 of administration
Calcium (mg/dL)	10.2	12.2	-	15.3	10.0	-	-	-
Creatinine (mg/dL)	0.83	-	1.85	3.07	-	-	2.47	1.04
BUN (mg/dL)	19.1	-	20.7	-	99.9	65.7	-	-
Uric acid (mg/dL)	7.5	-	9.5	-	8.0	5.7	-	-
PLT ($\times 10^4/\mu L$)	13.7	-	13.0	11.3	-	-	14.7	12.4

4

Revision of Precautions (No. 228)

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 June 24 and July 5, 2011 (excluding those presented in 3. Important Safety Information of this Bulletin).

1

Antidiabetic agents

Pioglitazone Hydrochloride

Brand Name

ACTOS Tablets 15, 30, ACTOS OD Tablets 15, 30 (Takeda Pharmaceutical Company Limited)

Important Precautions

Overseas epidemiological studies in patients with diabetes mellitus suggested that the risk of bladder cancer may increase in patients treated with this drug, and that the risk may increase with the treatment duration. Attention should be paid to the following points. (See "Other Precautions.")

- This drug should not be administered to patients who are currently being treated for bladder cancer. The use of this drug should be carefully determined in patients with a history of bladder cancer after due consideration of the benefits of treatment and potential risks.
- Prior to initiation of the treatment with this drug, patients and their families should be thoroughly informed of the risk of bladder cancer. Patients should be instructed to immediately consult a doctor if symptoms including haematuria, pollakiuria, or painful micturition are observed.
- Urine analysis etc. should be periodically performed during the administration of this drug. If any abnormalities are observed, appropriate measures should be taken. Patients should be carefully monitored after completion of this drug.

Other Precautions

In an overseas epidemiological study in patients with diabetes mellitus, the interim analysis showed that the bladder cancer risk significantly increased in patients treated with this drug for more than 2 years (hazard ratio, 1.4 [95% CI, 1.03 - 2.0]) in the stratified analysis, although no significant difference was shown in the overall analysis (hazard ratio, 1.2 [95% CI, 0.9 – 1.5])
Another epidemiological study showed the bladder cancer risk significantly increased in patients treated with this drug (hazard ratio, 1.22 [95% CI, 1.05 - 1.43]) as well as in patients treated for more than one year (hazard ratio, 1.34 [95% CI, 1.02 - 1.75]).

2

Antidiabetic agents

Pioglitazone Hydrochloride/Glimepiride
Pioglitazone Hydrochloride/Metformin Hydrochloride

Brand Name

SONIAS Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
METACT Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)

Important Precautions	Overseas epidemiological studies in patients with diabetes mellitus suggested that the risk of bladder cancer may increase in patients treated with pioglitazone hydrochloride, and that the risk may increase with the treatment duration. Attention should be paid to the following points. (See "Other Precautions.") • This drug should not be administered to patients who are currently being treated for bladder cancer. The use of this drug should be carefully determined in patients with a history of bladder cancer after due consideration of the benefits of treatment and potential risks. • Prior to initiation of the treatment with this drug, patients and their families should be thoroughly informed of the risk of bladder cancer. Patients should be instructed to immediately consult a doctor if symptoms including haematuria, pollakiuria, or painful micturition are observed. • Urine analysis etc. should be periodically performed during the administration of this drug. If any abnormalities are observed, appropriate measures should be taken. Patients should be carefully monitored after completion of this drug.
Other Precautions	In an overseas epidemiological study in patients with diabetes mellitus, the interim analysis showed that the bladder cancer risk significantly increased in patients treated with this drug for more than 2 years (hazard ratio, 1.4 [95% CI, 1.03 - 2.0]) in the stratified analysis, although no significant difference was shown in the overall analysis (hazard ratio, 1.2 [95% CI, 0.9 – 1.5]) Another epidemiological study showed the bladder cancer risk significantly increased in patients treated with this drug (hazard ratio, 1.22 [95% CI, 1.05 - 1.43]) as well as in patients treated for more than one year (hazard ratio, 1.34 [95% CI, 1.02 - 1.75]).

3 **Antipyretics and analgesics, anti-inflammatory agents**

Ergotamine Tartrate/Anhydrous Caffeine/Isopropylantipyrine

Brand Name	CLEAMINE Combination Tablets A 1.0, S 0.5 (Nichi-Iko Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), etc. or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

4 **Antiepileptics**

Gabapentin

Brand Name	GABAPEN Tablets 200 mg, 300 mg, 400 mg (Pfizer Japan Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Drug-induced hypersensitivity syndrome**: Rash and pyrexia may occur as the initial symptoms followed by serious late-onset hypersensitivity symptoms with organ damage such as hepatic dysfunction, swollen lymph nodes, leukocytosis, eosinophilia and atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. In addition, attention should be paid to recurrence or prolongation of symptoms including rash, pyrexia, and hepatic dysfunction.

5 **Respiratory organ agents-Bronchodilators**

Terbutaline Sulfate

Brand Name	Bricanyl Tablets 2 mg, Bricanyl Syrup 0.5 mg/mL, Bricanyl Injection 0.2 mg (AstraZeneca K.K.)

Other Precautions

In the off-label use of this drug, serious adverse reactions in the cardiovascular system and death have been reported in overseas mothers treated with this drug for threatened premature labour.

6

Antineoplastics-Miscellaneous

Bevacizumab (Genetical Recombination)

Brand Name

AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Bone marrow depression: Pancytopenia, neutropenia, decreased white blood cell, anaemia, and decreased platelets may occur in patients treated with this drug and other antineoplastic agents. Patients should be carefully monitored through periodical blood tests etc. If any abnormalities are observed, appropriate measures should be taken. In some clinical studies, increased incidences of severe neutropenia, febrile neutropenia, infection with neutropenia (e.g., sepsis) and fatal cases have been reported in patients treated with this drug and other antineoplastic agents compared with those without this drug.

7

Allergic agents-Miscellaneous

Fexofenadine Hydrochloride

Brand Name

allegra 30 mg Tablets, allegra 60 mg Tablets, allegra OD 60 mg Tablets (Sanofi-aventis K.K.)

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored. If any abnormalities including dyspnoea, decreased blood pressure, loss of consciousness, angioedema, chest pain, and flushing are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Agranulocytosis, decreased white blood cell, decreased neutropenia: Agranulocytosis, decreased white blood cell, or neutropenia may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

8

Vaccines

Recombinant Adsorbed Hepatitis B Vaccine (Yeast-derived) (HEPTAVAX)

Brand Name

HEPTAVAX-II (MSD K.K.)

Important Precautions

The rubber cap of the vial of this drug contains dried natural rubber (latex). Careful attention should be made since allergic reactions may occur in patients sensitive to latex.

9

Biological preparations-Miscellaneous

Tocilizumab (Genetical Recombination)

Brand Name

ACTEMRA 80 mg for Intravenous Infusion, ACTEMRA 200 mg for Intravenous Infusion, ACTEMRA 400 mg for Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)

Contraindications

Patients with active tuberculosis

Important Precautions	Prior to treatment, a sufficient interview regarding tuberculosis (e.g., history of tuberculosis and past close contact with infected persons), chest X-ray, and tuberculin test should be performed. Chest CT and interferon-gamma response assay (QuantiFERON) also should be performed to check for, tuberculosis infection, if necessary. If the patient has history of tuberculosis or suspected tuberculosis, the patients should be referred to a physician who has clinical experience with tuberculosis. The following patients should be treated with an antitubercular agent before starting the treatment with this drug in principle. (1) Patients whose chest image confirms or suggests old tuberculosis (2) Patients who have been treated for tuberculosis (including extrapulmonary tuberculosis) (3) Patients with strongly suspected infection based on a tuberculin test or interferon-gamma response assay (QuantiFERON) (4) Patients who have had close contact with patients with tuberculosis Patients should be carefully monitored for tuberculous infection by performing periodic chest such as X-rays during administration of this drug. Additionally, patients should be instructed to contact a physician immediately if symptoms suggesting tuberculosis (e.g., persistent cough and pyrexia) are observed. Also, if active tuberculosis is confirmed, this drug should not be administered and treatment for tuberculosis should be performed first.

5

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 Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of the drug in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of August 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg	Janssen Pharmaceutical K.K.	February 4, 2011
Azacitidine Vidaza for Injection 100 mg	Nippon Shinyaku Co., Ltd.	March 11, 2011
Fondaparinux Sodium Arixtra Injection 5 mg, 7.5 mg	GlaxoSmithKline K.K.	March 11, 2011
Ustekinumab (Genetical Recombination) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	March 14, 2011
Dabigatran Etexilate Methanesulfonate Prazaxa Capsules 75 mg, 110 mg	Nippon Boehringer Ingelheim Co., Ltd.	March 14, 2011
Galantamine Hydrobromide REMINYL Tablets 4 mg, 8 mg, 12 mg, REMINYL OD Tablets 4 mg, 8 mg, 12 mg, REMINYL Oral Solution 4 mg/mL	Janssen Pharmaceutical K.K.	March 22, 2011
Eldecalcitol EDIROL Capsule 0.5 μg, 0.75 μg	Chugai Pharmaceutical Co., Ltd.	April 11, 2011
Freeze-dried, Cell Culture-Derived Japanese Encephalitis Vaccine (Inactivated) ENCEVAC Subcutaneous Injection	The Chemo-Sero-Therapeutic Research Institute	April 11, 2011
Romiplostim (Genetical Recombination) Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Ltd.	April 13, 2011
Anti-human Thymocyte Immunoglobulin, Rabbit Thymoglobuline for Intravenous Infusion 25 mg*[1]	Genzyme Japan K.K.	April 22, 2011
Doripenem Hydrate FINIBAX for Drip Infusion 0.25 g, FINIBAX Kit for Drip Infusion 0.25 g*[2]	Shionogi & Co., Ltd.	April 22, 2011
Levobupivacaine Hydrochloride POPSCAINE 0.25% inj. 25 mg/10mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL*[3]	Maruishi Pharmaceutical Co., Ltd.	April 22, 2011
Repaglinide SUREPOST Tablets 0.25 mg, 0.5 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 16, 2011

Febuxostat Feburic Tablet 10 mg, 20 mg, 40 mg	Teijin Pharma Limited	May 17, 2011
Levonorgestrel NORLEVO 0.75 mg Tablet	Sosei Co. Ltd.	May 24, 2011
Pioglitazone Hydrochloride/Glimepiride SONIAS Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	June 6, 2011
Memantine Hydrochloride MEMARY TABLETS 5 mg, 10 mg, 20 mg	Daiichi Sankyo Company, Limited	June 8, 2011
Adalimumab (Genetical Recombination) HUMIRA for s.c. injection syringe 40 mg/0.8 mL, HUMIRA for s.c. injection syringe 20 mg/0.4 mL*4	Abbott Japan Co., Ltd.	July 1, 2011
Erlotinib Hydrochloride TARCEVA Tablets 25 mg, 100 mg*5	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Gabapentin GABAPEN Tablets 200 mg, 300 mg, 400 mg*6	Pizer Japan Inc.	July 1, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 μg, 180 μg*7	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Lamotrigine Lamictal Tablets 25 mg, 100 mg*8	GlaxoSmithKline K.K.	July 1, 2011
Ribavirin COPEGUS Tablet 200 mg*9	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Edoxaban Tosilate Hydrate LIXIANA TABLETS 15 mg, 30 mg	Daiichi Sankyo Company, Limited	July 19, 2011
Eribulin Mesilate Halaven injection 1 mg	Eisai Co., Ltd.	July 19, 2011
Tramadol Hydrochloride/Acetaminophen TRAMCET Combination Tablets	Janssen Pharmaceutical K.K.	July 19, 2011
Rivastigmine EXELON PATCH 4.5 mg, 9 mg, 13.5 mg, 18 mg	Novartis Pharma K.K.	July 19, 2011
Rivastigmine RIVASTACH Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Ono Pharmaceutical Co., Ltd.	July 19, 2011
Epoetin Beta Pegol (Genetical Recombination) MIRCERA Injection Syringe 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg	Chugai Pharmaceutical Co., Ltd.	July 20, 2011
Pramipexole Hydrochloride Hydrate Mirapex-LA Tablets 0.375 mg, 1.5 mg	Nippon Boehringer Ingelheim Co., Ltd.	July 20, 2011
Mitiglinide Calcium Hydrate/Voglibose GLUBES Combination Tab.	Kissei Pharmaceutical Co., Ltd.	July 22, 2011
Desflurane Suprane Inhalational Anesthetic Solution	Baxter Limited	July 29, 2011

*1 An additional indication for “treatment of acute rejection after renal transplantation”

*2 An additional dosage and administration for “maximum daily dose, 3 g”

*3 An additional indication for “conduction anesthesia”

*4 An additional indication for “treatment of patients with polyarticular-course juvenile idiopathic arthritis”

*5 An additional indication for “treatment of patients with unresectable pancreatic cancer”

*6 An additional administration for “pediatrics”

*7 An additional indication for “improvement of viraemia in compensated cirrhosis type C in combination therapy with ribavirin”

*8 An additional indication for “suppression of recurrent/relapsed mood episodes in patients with bipolar disorder”

*9 An additional indication for “improvement of viraemia in compensated cirrhosis type C in combination therapy with peginterferon alfa-2a (genetical recombination)”