

# Pharmaceuticals and Medical Devices Safety Information

No. 277 February 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/>, Japanese only).

**Published by**  
**Pharmaceutical and Food Safety Bureau,**  
**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](mailto:safety.info@pmda.go.jp)

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# Pharmaceuticals and Medical Devices Safety Information No. 277 February 2011

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

## [ Outline of Information ]

No.	Subject	Measures	Outline of Information	Page
1	<b>Safety Measures for Gemtuzumab Ozogamicin (Genetical Recombination)</b>		On June 21, 2010, it was published that gemtuzumab ozogamicin (Genetical Recombination), a therapeutic agent for acute myeloid leukaemia, was voluntarily withdrawn from the U.S. market. On the basis of the above, the MHLW reviewed the safety measures for gemtuzumab ozogamicin to be taken in Japan, and an expert discussion was held at the meeting of the Subcommittee of the Drug Safety, part of the Committee on Drug Safety, under the Pharmaceutical Affairs and Food Sanitation Council, on November 2, 2010. As a result, additional safety measures for the use of this drug have been taken. The details are described in the following section.	6
2	<b>Imatinib Mesilate, Nilotinib Hydrochloride Hydrate (and 2 others)</b>	<i>P</i> <i>C</i>	This section presents the contents of the revisions and a case summary 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 Notifications dated January 11, 2011.	11
3	<b>Ciclosporin (oral and injectable dosage forms) (and 13 others)</b>		Revision of Precautions (No. 223)	20
4	<b>List of Products Subject to Early Post-marketing Phase Vigilance</b>		Lists products subject to Early Post-marketing Phase Vigilance as of February 1, 2011.	25

*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 (Japanese only), 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, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

## Abbreviations

ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AML	Acute myeloid leukaemia
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CHDF	Continuous hemodiafiltration
CR	Complete remission
CRp	Complete remission with incomplete platelet recovery
DA	Combination therapy of daunorubicin hydrochloride and cytarabine
DIC	Disseminated intravascular coagulation
DLST	Drug lymphocyte stimulation test
ECG	Electrocardiogram
EPPV	Early Post-marketing Phase Vigilance
FAB classification	French-American-British classification
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GIST	Gastrointestinal stromal tumor
K	Potassium
LDH	Lactate dehydrogenase
M0	Undifferentiated acute myeloblastic leukaemia
M1	Acute myeloblastic leukaemia with minimal maturation
M2	Acute myeloblastic leukaemia with maturation
M3	Acute promyelocytic leukaemia
M4	Acute myelomonocytic leukaemia
M5	Acute monocytic leukaemia
M6	Acute erythroid leukaemia
M7	Acute megakaryoblastic leukaemia
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
NR	No response
PLT	Platelet
PS	Performance status
RBC	Red blood cell count
SWOG	Southwest Oncology Group
US	United States
VOD	Veno-Occlusive Disease
WBC	White blood cell count
$\gamma$ -GTP	gamma-glutamyl transpeptidase

# Safety Measures for Gemtuzumab Ozogamicin (Genetical Recombination)

Active Ingredient Brand Name (name of company)	Active Ingredient	Brand Name (name of company)
	Gemtuzumab Ozogamicin (Genetical Recombination)	MYLOTARG Injection 5mg (Pfizer Japan Inc.)
Therapeutic Category	Antineoplastics-Antibiotics	
Indications	Relapsed or refractory CD33 positive acute myeloid leukaemia	

## 1. Introduction

Gemtuzumab Ozogamicin (Genetical Recombination) is an antineoplastic agent composed of humanized anti-CD33 antibody gemtuzumab conjugated with a calicheamicin derivative. In Japan, this drug was approved in July 2005 as a monotherapy indicated for the treatment of patients with relapsed or refractory CD33 positive acute myeloid leukaemia (AML) and for whom no other reinduction therapies were indicated. Gemtuzumab ozogamicin had been used in approximately 3,000 patients between the launch in September 2005 and June 2010<sup>1)</sup>.

In the United States (U.S.), gemtuzumab ozogamicin was approved in May 2000 under the Food and Drug Administration (FDA)'s accelerated approval program as a monotherapy for "patients with CD33 positive AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy." Under accelerated approval, the FDA had required the manufacturer to conduct an additional clinical trial after approval to confirm the clinical benefit of this drug.

Accordingly, the Southwest Oncology Group (SWOG) conducted a clinical study (Study S0106) in patients with untreated CD33 positive AML to evaluate the clinical benefit of addition of gemtuzumab ozogamicin to the standard induction therapy and post-consolidation therapy with gemtuzumab ozogamicin. In December 2009, it was announced that the result of the study failed to demonstrate the clinical benefit of gemtuzumab ozogamicin.<sup>2)</sup>

At first, U.S. Pfizer had intended to use the results of the Study S0106 as the data for the post-marketing clinical study to confirm the clinical benefit required by FDA. However, since the study failed to demonstrate the clinical benefit of gemtuzumab ozogamicin, Pfizer announced on June 21, 2010 that gemtuzumab ozogamicin would be voluntarily withdrawn from the market<sup>3)</sup>, and sales of the drug were discontinued on October 15, 2010. In the U.S., gemtuzumab ozogamicin can be supplied only if it is used as an investigational drug.

Considering the above, an expert discussion was held at the meeting of the Subcommittee of the Drug Safety, part of the Committee on Drug Safety, under the Pharmaceutical Affairs and Food Sanitation Council, on November 2, 2010. As a result, additional safety measures for the use of the drug have been taken. The details are described below.<sup>1)</sup>

## 2. Process to approval in Japan

In Japan, gemtuzumab ozogamicin was assessed for approval based on the evaluation of monotherapy data in patients with CD33 positive relapsed AML : (i) results of the phase I study in the Japanese phase I/II study, (ii) results of the overseas phase I study, and (iii) results of 3 overseas phase II studies. The following findings were shown from the review:

(i) In Japan, high-dose cytarabine therapy is used as the standard reinduction therapy in patients

under the age of 60 with AML in first relapse other than acute promyelocytic leukaemia. Therefore, the clinical positioning of gemtuzumab ozogamicin in patients aged under age of 60 with AML in first relapse cannot be evaluated unless data of a randomized controlled study are available.

- (ii) In contrast, gemtuzumab ozogamicin is considered to be well positioned clinically in patients for whom reinduction therapies including high-dose cytarabine therapy are not indicated, because complete remission was achieved in some of these cases in clinical studies.

On the basis of the above, gemtuzumab ozogamicin was approved as a monotherapy of patients with relapsed or refractory CD33 positive AML for whom other reinduction therapies are not indicated. At the time of the approval, the PMDA required that the following alerts were described in “Precautions of Indications” of the package insert.

[Precautions of Indications]

When administrating this drug, the necessity of using this drug should be carefully considered. This drug should be used in patients for whom no other reinduction therapies are indicated and who meet one of the following criteria.

- (1) Refractory patients expected to be unresponsive or resistant to reinduction therapies (e.g., high-dose cytarabine therapy)
- (2) Elderly patients (patients in first relapse who are 60 years or older)
- (3) Patients in second or subsequent relapse
- (4) Patients in relapse after hematopoietic stem cell transplantation (see “Warnings”)
- (5) Patients with acute promyelocytic leukaemia who are expected to be unresponsive or resistant to reinduction therapies (e.g., tretinoin therapy)

### 3. Post-marketing surveillance in Japan

Because of the limited number of subjects treated in Japanese clinical studies and cases of serious adverse reactions including hepatic dysfunction observed in Japanese and overseas clinical studies, a use-results survey for all treated patients (number of enrolled patients: 852) was conducted from the launch to the end of December 2009.

In this survey, complete remission rates and response rates in 528 patients evaluable for efficacy were 9.8% and 18.0%, respectively. (Table 1). Although there were limitations to the direct comparison of the efficacy, the above values were lower than those obtained in studies conducted before the approval (Japanese phase I/II study); this may have been attributed to the difference in distribution of the patient baseline characteristics between the pre-approval studies and the post-marketing surveillance. Table 2 shows the complete remission rate and response rate by patient baseline characteristics. The Complete remission was achieved even in patients with second or subsequent relapses, i.e. those who are unlikely to respond to chemotherapy. It was noted that gemtuzumab ozogamicin showed effectiveness.

Table 1 Complete remission rate and response rate in pre-approval studies and in use-results survey

Study/survey	Number of cases	Number of CR cases	Number of CRp cases	Number of NR cases	Complete remission rate*	Response rate**
Pre-approval studies	20	5	1	14	25.0%	30.0%
Use-results survey	528	52	43	433	9.8%	18.0%

\* Complete remission rate (%) = Number of patients who are in complete remission (CR) / Number of efficacy-evaluable patients (CR + CRp + NR) × 100

\*\* Response rate (%) = Number of patients with response (CR + CRp) / Number of patients evaluable for efficacy (CR + CRp + NR) × 100

Table 2 Complete remission rate and response rate by patient baseline characteristics

Patient baseline characteristics		Number of cases	Number of CR cases*	Number of CRp cases*	Number of NR* cases	Complete remission rate	Response rate**	
Sex	Male	312	28	23	261	9.0%	16.3%	
	Female	216	24	20	172	11.1%	20.4%	
Age (years)	Under age of 60	186	21	14	151	11.3%	18.8%	
	Aged 60-75	255	23	20	212	9.0%	16.9%	
	Aged 75 or older	87	8	9	70	9.2%	19.5%	
PS before treatment	0	127	22	19	86	17.3%	32.3%	
	1	160	14	12	134	8.8%	16.3%	
	2	83	4	4	75	4.8%	9.6%	
	3	64	6	0	58	9.4%	9.4%	
	4	11	0	0	11	0.0%	0.0%	
	Unknown, unlisted	83	6	8	69	7.2%	16.9%	
FAB classification	M0	41	3	4	34	7.3%	17.1%	
	M1	74	4	7	63	5.4%	14.9%	
	M2	220	23	15	182	10.5%	17.3%	
	M3	16	8	1	7	50.0%	56.3%	
	M4	71	5	12	54	7.0%	23.9%	
	M5	42	6	3	33	14.3%	21.4%	
	M6	20	1	1	18	5.0%	10.0%	
	M7	11	2	0	9	18.2%	18.2%	
	Undefined	31	0	0	31	0.0%	0.0%	
Unknown, unlisted	2	0	0	2	0.0%	0.0%		
Prognosis classification by chromosome abnormality (n=528)	Good prognosis	100	18	9	73	18.0%	27.0%	
	Intermediate	251	23	24	204	9.2%	18.7%	
	Poor prognosis	135	9	9	117	6.7%	13.3%	
	Unknown, unlisted	42	2	1	39	4.8%	7.1%	
Number of relapse (n=357)	1	222	23	18	181	10.4%	18.5%	
	2	92	10	9	73	10.9%	20.7%	
	3	27	3	2	22	11.1%	18.5%	
	4 and more	15	1	2	12	6.7%	20.0%	
	Unknown, unlisted	1	0	0	1	0.0%	0.0%	
Duration of initial remission (n=357)	Under 1 year	248	17	18	213	6.9%	14.1%	
	1 year and longer	93	17	13	63	18.3%	32.3%	
	Unknown, unlisted	16	3	0	13	18.8%	18.8%	
Past treatment for target disease	Transplant	No	437	46	36	355	10.5%	18.8%
		Yes	91	6	7	78	6.6%	14.3%

\* CR: Cases that meet all of the following criteria 1 to 5:

1. No blast cells are in peripheral blood.
2. Percentage of blast cells in the bone marrow is  $\leq 5\%$  according to morphological evaluation
3. The peripheral blood picture meets the following criteria: hemoglobin  $\geq 9\text{g/dL}$ , platelet count  $\geq 100,000/\text{mm}^3$ , and neutrophil count  $\geq 1,500/\text{mm}^3$
4. Red blood cell or platelet transfusion is not required (Definition: Red blood cell or platelet transfusion should not be performed within 2 and 1 week before judgment, respectively)
5. No extramedullary leukaemia is detected.

CRp: Patients who meet all the criteria for CR except the criterion for platelet count

NR: Other than CR and CRp

\* Complete remission rate (%) = Number of patients who are in complete remission (CR) / Number of patients evaluable for efficacy (CR + CRp + NR)  $\times 100$

\*\* Response rate (%) = Number of patients with response (CR + CRp) / Number of patients evaluable for efficacy (CR + CRp + NR) × 100

Tables 3 to 5 show the results obtained from 753 patients evaluable for safety together with those obtained in pre-approval studies. Of the 753 patients evaluable for safety, 88.1% experienced adverse reactions. The incidence of grade 3 or higher adverse reactions was 78.9% (**Table 3**), and the treatment-related mortality was 9.8% (**Table 4**). The most common adverse reactions included bone marrow depression, infection associated with bone marrow depression, anemia or haemorrhage, infusion reactions during the administration or within 24 hours after administration (e.g., chilliness, pyrexia, difficulty in breathing or allergic symptoms), and hepatic disorder with decreased hepatic function caused by a hepatic vein occlusion (veno-occlusive disease [VOD]) (**Table 5**).

The mortality due to adverse reactions (for which a causality to gemtuzumab ozogamicin could not be denied) in this survey was higher than that observed in the pre-approval studies (**Table 4**). However, because of the limited number of patients enrolled in the pre-approval studies, it is difficult to determine the possible increase in the risk of death caused by gemtuzumab ozogamicin based solely on the numerical value of the mortality. Since patients who died during the present survey had background factors predicative of possible aggravated general condition such as advanced age, frequent relapses, and poor PS, the possibility cannot be ruled out that these factors contributed to the death of the patients; thus there were limitations to direct comparison between the results of the present survey and those of the pre-approval clinical studies. On the basis of these considerations, it does not suggest that any emerging safety concerns have been raised after approval of the drug.<sup>1)</sup>

**Table 3** Incidence of adverse reactions in pre-approval studies and in use-results survey

Type of ADRs	Study/survey	Number of cases	ADRs		
			Number of ADRs cases	Number of events	Incidence
All ADRs	Pre-approval studies	40	40	1,072	100.0%
	Use-results survey	753	663	3,291	88.1%
ADRs ≥Grade 3	Pre-approval studies	40	39	210	97.5%
	Use-results survey	753	594	1,804	78.9%

**Table 4** Fatal cases for which a causality to the drug could not be denied in pre-approval studies and in use-results survey

Study/survey	Number of cases	Number of deaths	Mortality
Pre-approval studies	40	2	5.0%
Use-results survey	652 <sup>Note)</sup>	64	9.8%

Note: 101 patients whose life or death status was unknown because of change of hospital were excluded from the 753 patients evaluable for safety.



**Table 5 Incidence of adverse reactions handled as priority survey items\* in pre-approval studies and in use-results survey**

Type of ADR	Study/survey	Number of cases	Number of ADRs cases	Number of events	Incidence
All VODs	Pre-approval studies	40	1	1	2.5%
	Use-results survey	753	42	42	5.6%
VODs $\geq$ Grade 3	Pre-approval studies	40	0	0	0.0%
	Use-results survey	753	33	33	4.4%
All infections	Pre-approval studies	40	26	33	65.0%
	Use-results survey	753	257	331	34.1%
Infections $\geq$ Grade 3	Pre-approval studies	40	5	5	12.5%
	Use-results survey	753	206	255	27.4%
All hemorrhages	Pre-approval studies	40	29	61	72.5%
	Use-results survey	753	106	143	14.1%
Hemorrhages $\geq$ Grade 3	Pre-approval studies	40	3	3	7.5%
	Use-results survey	753	65	81	8.6%
All infusion reactions**	Pre-approval studies	40	40	316	100.0%
	Use-results survey	753	340	716	45.2%
Infusion reactions $\geq$ Grade 3	Pre-approval studies	40	23	49	57.5%
	Use-results survey	753	166	285	22.1%
All lung disorders	Pre-approval studies	40	1	2	2.5%
	Use-results survey	753	27	30	3.6%
Lung disorders $\geq$ Grade 3	Pre-approval studies	40	1	1	2.5%
	Use-results survey	753	23	24	3.1%
All tumor lysis syndromes	Pre-approval studies	40	0	0	0.0%
	Use-results survey	753	17	17	2.3%

\* VODs, infections, hemorrhages, infusion reactions, lung disorders, and tumor lysis syndromes that were observed characteristically with the drug in Japanese and overseas clinical studies.

\*\* All infusion reactions were defined as adverse reactions that occurred on the day or the next day of administration of the drug, as was the case with pre-approval studies.

#### 4. Overseas clinical studies

Major clinical studies conducted overseas include SWOG Study S0106<sup>2)</sup> and AML15 Trial.<sup>4)</sup> Both clinical trials investigated the benefit of gemtuzumab ozogamicin as an addition to other antineoplastic agents, and not as a monotherapy, the indication approved in Japan. The outlines of these trials are as follows.

##### (1) Study S0106

The SWOG in the U.S. conducted the study to evaluate the efficacy of addition of gemtuzumab ozogamicin to standard initial induction therapy with daunorubicin hydrochloride and cytarabine (DA), and the efficacy of addition of this drug after consolidation chemotherapy with high-dose cytarabine therapy, in patients aged 18 to 60 with untreated AML.<sup>2)</sup> The interim analysis of the study did not

show any improvement in the complete remission rate in patients treated with gemtuzumab ozogamicin in combination with the standard induction therapy (75% in DA + gemtuzumab ozogamicin, 73% in DA group), nor in the disease-free survival period in patients who received post-consolidation therapy with gemtuzumab ozogamicin (2 year disease-free survival rate: 39% in additional gemtuzumab ozogamicin group, 50% in control observation group). Moreover, the incidence of fatal adverse reactions during the induction period for which a causality to the treatment could not be denied was significantly higher in DA + gemtuzumab ozogamicin group (5.7% [16/283] in DA + gemtuzumab ozogamicin group, 1.4% [4/281] in DA group,  $p=0.01$ ).

## (2) AML15 Trial

The Medical Research Council in the United Kingdom conducted a randomized study to evaluate the efficacy of addition of gemtuzumab ozogamicin to the standard induction therapy (daunorubicin/cytarabine, cytarabine/daunorubicin/etoposide, or fludarabine/cytarabine/idarubicin/granulocyte colony-stimulating factor [G-CSF]) and/or consolidation therapy (amsacrine/etoposide or high dose cytarabine) in patients under the age of 60 with AML. In a preliminary analysis on 1,115 patients enrolled in the study, it was reported that addition of gemtuzumab ozogamicin to the induction therapy reduced the risk of relapse without evidence of increase in toxicity<sup>4)</sup>, whereas the results of subsequent analysis showed that addition of this drug improved neither relapse-free survival nor overall survival period.<sup>5)</sup>

## 5. Details and implementation of safety measures

In light of the results of Japanese and overseas clinical studies described above, the risk-benefit balance was assessed for gemtuzumab ozogamicin as a monotherapy for patients with relapsed or refractory CD33 positive AML for whom other reinduction therapies are not indicated, which is the approved indication in Japan. As a result, it was concluded that the risk-benefit balance of gemtuzumab ozogamicin has not changed from its state at the time of approval.

- (1) The “Indications” and “Dosage and Administration” approved for gemtuzumab ozogamicin is a monotherapy for patients with relapsed or refractory AML for whom other reinduction therapies are not indicated. In contrast, Study S0106, which led to voluntary withdrawal from the U.S. market of gemtuzumab ozogamicin, was conducted in a different patient group (patients under the age of 60 with initial occurrence) using a different treatment method (addition to other standard therapies or post-consolidation therapy). Thus, it is inappropriate to evaluate the benefit of gemtuzumab ozogamicin in Japan based solely on the results of this study.
- (2) Given the information obtained from the use-results survey, the assessment on the efficacy of gemtuzumab ozogamicin remains unchanged from that made at the time of approval, and no additional safety problems have been found.

On the basis of the above, it has been concluded that it is appropriate to continue marketing gemtuzumab ozogamicin provided that the drug is used alone in an appropriate manner by physicians with extensive experience in the treatment of acute leukaemia by selecting appropriate patients as specified in the package insert, in medical institutions well-equipped for monitoring and treating leukaemia patients, by continuously paying attention to occurrence of adverse reactions including VODs identified at the approval.

In response to the above conclusion, the MHLW required the marketing authorization holder (MAH) to take the appropriate safety measures listed in (1) to (5) below in addition to the current safety measures, to continue collecting safety and efficacy information, and to take additional measures for the proper use of the drug, as necessary. The MHLW is currently developing measures for further promoting the proper use of gemtuzumab ozogamicin, with cooperation of relevant organizations including the Japanese Society of Medical Oncology and the Japanese Society of Hematology.

The MHLW asked that healthcare professionals would cooperate with the effort for the

promotion of proper use of gemtuzumab ozogamicin by selecting patients appropriately based not only on the “Indications” section but on the sections of “Warnings,” “Contraindications,” “Careful Administration,” and “Precautions of Indications,” by avoiding concomitant therapy with other neoplastic agents, by fully explaining to the patient about the current situations in and outside Japan before administering the drug, and by obtaining informed consent in an appropriate manner.

- (1) Information on the results of the use-results survey, the results of Study S0106 and AML15 Trial, and regulatory actions taken in the U.S. and Europe should be provided to health professionals via the package insert or other materials.
- (2) Before gemtuzumab ozogamicin is delivered to a medical institution without prior experience of using the drug, MAH should confirm that the drug can be used in an appropriate manner by checking whether the institution has sufficient equipment for monitoring and treating leukaemia patients and checking whether a physician with extensive experience in the treatment of acute leukaemia is prescribing the drug.
- (3) A “patient checklist” to be used before administration of gemtuzumab ozogamicin to allow appropriate selection of patients, “supplementary material for obtaining informed consent” to be used in obtaining informed consent from patients, and an “informed consent form” should be prepared and distributed to medical institutions to promote the use of the drug in an appropriate manner in appropriate patients.
- (4) It should be investigated approximately once every year whether the safety measures listed in (3) are taken in an appropriate manner, and the measures should be improved as necessary.
- (5) In order to promote the compliance with the alerts included in the package insert, healthcare professionals should be reminded, at least once every year using appropriate materials.

#### <References>

- 1) Materials of the 7th meeting of 2010 the Subcommittee of the Drug Safety, part of the Committee on Drug Safety, under the Pharmaceutical Affairs and Food Sanitation Council (on the safety measures for Gemtuzumab Ozogamicin (Genetical Recombination))  
<http://www.mhlw.go.jp/stf/shingi/2r985200000vrz2.html> (in Japanese only)
- 2) Petersdorf S, Kopecky K, Stuart R et al., Preliminary Results of Southwest Oncology Group Study S0106 : An International Intergroup Phase 3 Randomized Trial Comparing the Addition of Gemtuzumab Ozogamicin to Standard Induction Therapy Versus Standard Induction Therapy Followed by a Second Randomization to Post-Consolidation Gemtuzumab Ozogamicin Versus No Additional Therapy for Previously Untreated Acute Myeloid Leukemia. *Blood*. 2009; 114: Abstract790.
- 3) FDA News Release (June 21, 2010 FDA)  
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm216448.htm>
- 4) Burnett AK, Kell WJ, Goldstone AH et al., The Addition of Gemtuzumab Ozogamicin to Induction Chemotherapy for AML Improves Disease Free Survival without Extra Toxicity: Preliminary Analysis of 1115 Patients in the MRC AML15 Trial. *Blood*. 2006; 108: Abstract13.
- 5) Burnett AK, Hills RK, Milligan D et al., Identification of Patients With Acute Myeloblastic Leukemia Who Benefit From the Addition of Gemtuzumab Ozogamicin : Results of the MRC AML15 Trial. *J Clin Oncol*. 2011; 29: 369-377.

## 2

# Important Safety Information

This section presents the contents of revisions and a case summary 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 January 11, 2011.

[Brand Name]: Major product names are showed.

### 1 Imatinib Mesilate, Nilotinib Hydrochloride Hydrate

<b>Brand Name (name of company)</b>	<b>Imatinib Mesilate</b> Glivec Tablets 100 mg (Novartis Pharma K.K.) <b>Nilotinib Hydrochloride Hydrate</b> Tasigna Capsules 150 mg, 200 mg (Novartis Pharma K.K.)
<b>Therapeutic Category</b>	Antineoplastics-Miscellaneous
<b>Indications</b>	<b>Imatinib Mesilate</b> 1. Chronic myeloid leukaemia 2. KIT (CD117)-positive gastrointestinal stromal tumors 3. Philadelphia chromosome positive acute lymphocytic leukaemia <b>Nilotinib Hydrochloride Hydrate</b> Chronic myeloid leukaemia in chronic or accelerated phase

#### «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 recovery from such symptoms.

#### <Reference Information>

Imatinib Mesilate

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, 2007 to November 19, 2010)

- Tumour lysis syndrome: 3 cases (1 fatal case)

The number of patients using this drug per year estimated by the marketing authorization holders (MAH(s)): approximately 12,000 (January to December 2010)

Launched in Japan: July 2005 (Glivec Tablets 100 mg)

\* December 2001 to March 2007 (Glivec Capsules 100 mg)

Nilotinib Hydrochloride Hydrate

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years (from initial marketing to November 30, 2010)

- Tumour lysis syndrome: 1 case (no fatal cases)

The number of patients using this drug per year estimated by the MAH(s): approximately 930 (January to December 2010)

Launched in Japan in: March 2009 (compassionate use: February, 2009)

## Case Summary <Imatinib Mesilate>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Gastrointestinal stromal tumour [GIST] (Diabetes insipidus)	400 mg for 4 days	<p><b>Tumour lysis syndrome, acute renal failure</b></p> <p>Day 1 of administration: The patient started receiving imatinib mesilate 400 mg for peritoneal GIST.</p> <p>Day 2 of administration: Urine output decreased to 484 mL.</p> <p>Day 3 of administration (day of onset): Blood urea nitrogen (BUN), creatinine, and uric acid were elevated to 47 mg/dL, 2.19 mg/dL, and 8.9 mg/dL, respectively. Tumour lysis syndrome and acute renal failure associated with the use of imatinib mesilate were suspected. Urine output was 103 mL.</p> <p>Day 4 of administration (day of discontinuation): Administration of imatinib mesilate was discontinued. Transfusion loading and administration of a diuretic (furosemide) were started. Urine output was 214 mL.</p> <p>2 days after discontinuation: The dose of the diuretic was increased and administration of a vasopressor (dopamine hydrochloride) was initiated to maintain renal blood flow.</p> <p>6 days after discontinuation: Administration of allopurinol was started for hyperuricaemia. Creatinine level worsened to 5.15 mg/dL. The patient was followed up with transfusion loading and treatment with the diuretic and vasopressor.</p> <p>11 days after discontinuation: Administration of the diuretic and vasopressor was discontinued.</p> <p>13 days after discontinuation: Administration of allopurinol was discontinued.</p> <p>16 days after discontinuation: Creatinine level improved to 2.57 mg/dL.</p> <p>27 days after discontinuation: Uric acid level improved to 6.9 mg/dL.</p> <p>59 days after discontinuation: Creatinine level improved to 0.82 mg/dL. Outcome: ameliorated</p>
Concomitant medication: desmopressin acetate hydrate				

## Laboratory Examination

	Day 1 of administration	Day 3 of administration (day of onset)	Day 4 of administration (day of discontinuation)	6 days after discontinuation	27 days after discontinuation	49 days after discontinuation	59 days after discontinuation
BUN (mg/dL)	21	47	80	78	-	26	31
Creatinine (mg/dL)	0.95	2.19	3.34	5.15	-	0.94	0.82
Blood glucose (mg/dL)	81	165	171	158	-	97	145
Serum potassium (mEq/L)	3.5	4.7	5.3	3.4	-	4.7	3.7
Serum sodium (mEq/L)	139	136	125	126	-	129	115
Uric acid (mg/dL)	5.7	8.9	9.0	12.3	6.9	-	-
Serum calcium (mg/dL)	8.4	7.8	7.3	5.7	-	-	8.3

<Nilotinib Hydrochloride Hydrate>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Chronic phase chronic myeloid leukaemia (Third degree atrioventricular block, cardiac pacemaker insertion, urinary calculus, diabetes mellitus)	800 mg for 10 days	<p><b>Tumour lysis syndrome, renal disorder, cardiac failure, pleural effusion, atrial fibrillation, hepatic dysfunction, anaemia</b></p> <p>Day 1 of administration: The patient was intolerant to imatinib, and administration of nilotinib hydrochloride hydrate was started at 800 mg/day.</p> <p>Day 7 of administration: Tumour lysis syndrome and renal disorder occurred. BUN and creatinine were elevated to 23.4 mg/dL and 1.3 mg/dL, respectively.</p> <p>Day 8 of administration: Administration of allopurinol was started at 300 mg/day.</p> <p>Day 9 of administration: BUN and creatinine were further elevated to 49.4 mg/dL and 2.5 mg/dL, respectively, and uric acid also elevated to 10.2 mg/dL. Sodium bicarbonate and allopurinol were administered for tumour lysis syndrome.</p> <p>Day 10 of administration (day of discontinuation): Cardiac failure occurred. Administration of nilotinib hydrochloride hydrate was discontinued. Administration of D-mannitol was started for tumour lysis syndrome.</p> <p>3 days after discontinuation: Pleural effusion developed. Administration of D-mannitol was discontinued.</p> <p>4 days after discontinuation: Atrial fibrillation developed and resolved on the same day. Fluid replacement was initiated, and breathing difficulty and bilateral pleural effusion occurred, suggesting cardiac failure. Cardiac failure and/or heart strain possibly caused atrial fibrillation. Hepatic dysfunction and anaemia developed. Administration of sodium bicarbonate was discontinued.</p> <p>6 days after discontinuation: Anaemia resolved.</p> <p>7 days after discontinuation: Atrial fibrillation developed and resolved on the same day. Administration of metoprolol tartrate and pilsicainide hydrochloride hydrate was started.</p> <p>11 days after discontinuation: Administration of naftopidil and a combination drug of potassium citrate/sodium citrate hydrate was started for tumour lysis syndrome.</p> <p>13 days after discontinuation: Hepatic dysfunction resolved.</p> <p>15 days after discontinuation: Pleural effusion resolved.</p> <p>18 days after discontinuation: Cardiac failure resolved.</p> <p>20 days after discontinuation: Renal disorder resolved. Tumour lysis syndrome resolved.</p> <p>77 days after discontinuation: Administration of naftopidil and a combination drug of potassium citrate/sodium citrate hydrate was discontinued.</p>
Concomitant medications: glimepiride, pioglitazone hydrochloride, voglibose, valsartan, carvedilol				

## Laboratory Examination

	4 days before administration	Day 1 of administration	Day 3 of administration	Day 7 of administration	Day 9 of administration	Day 10 of administration (day of discontinuation)	4 days after discontinuation	7 days after discontinuation	18 days after discontinuation
RBC ( $\times 10^4/\text{mm}^3$ )	-	477	-	422	-	387	371	-	430
Hemoglobin (g/dL)	-	14.2	-	12.3	-	11.1	10.6	-	12.2
Hematocrit (%)	-	44.8	-	38.2	-	33.7	33.5	-	40.2
WBC (/mm <sup>3</sup> )	-	50600	-	29570	-	19090	18540	-	10980
Neutrophils (%)	-	52	-	66	-	71	78	-	23
Lymphocytes (%)	-	16	-	6	-	6	3	-	15
Eosinophils (%)	-	7	-	7	-	4	15	-	31
Basophils (%)	-	4	-	2	-	1	4	-	13
Monocytes (%)	-	0	-	0	-	2	0	-	0
Blast (%)	-	0	-	0	-	0	0	-	0
Promyelocyte (%)	-	1	-	0	-	1	0	-	2
Myelocyte (%)	-	13	-	14	-	10	1	-	14
Metamyelocyte (%)	-	7	-	5	-	3	0	-	1
PLT ( $\times 10^4/\text{mm}^3$ )	-	115.2	-	98.9	-	82.5	63.2	-	30.3
Serum potassium (mEq/L)	-	4.5	-	4.4	-	4.7	4.2	-	3.6
AST (GOT) (IU/L)	-	42	-	26	-	36	58	-	26
ALT (GPT) (IU/L)	-	21	-	29	-	37	60	-	21
$\gamma$ -GTP (IU/L)	-	90	-	150	-	177	153	-	45
LDH (IU/L)	-	858	-	427	-	338	362	-	284
Total bilirubin (mg/dL)	-	0.3	-	1.9	-	2.1	1.5	-	0.7
Direct bilirubin (mg/dL)	-	0.1	-	0.5	-	0.9	0.7	-	0.3
BUN (mg/dL)	-	15.2	-	23.4	49.4	61.9	25.4	-	14.1
Creatinine (mg/dL)	-	1.1	-	1.3	2.5	2.9	0.9	-	1.2
Uric acid (mg/dL)	-	5.8	-	10.2	10.2	-	-	-	-
Body weight (kg)	-	69.5	-	-	-	-	-	-	64.0
QTc (sec)	0.48	-	0.487	-	-	-	-	0.449	-

## 2 Sunitinib Malate

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

### «PRECAUTIONS (underlined parts are revised)»

#### [Adverse Reactions (clinically significant adverse reactions)]

**Haemorrhage:** Epistaxis, subcutaneous haemorrhage, mouth haemorrhage, genital haemorrhage, haemoptysis, conjunctival haemorrhage, tumour haemorrhage, haemorrhage of digestive tract, or cerebral haemorrhage may occur. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, the dose of this drug should be reduced, or administration should be temporarily or permanently discontinued and appropriate measures should be taken.

**Transient ischaemic attack, cerebral infarction:** Transient ischaemic attack or cerebral infarction may occur. Patients should be carefully monitored, and if any

abnormalities are observed, the dose of this drug should be reduced, or administration should be temporarily or permanently 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 2 years (from initial marketing to November 11, 2010)

- Cerebral infarction: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAH(s): approximately 1,800 (for FY 2009)

Marketed in Japan in: June 2008

**Case Summary**

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Renal cell carcinoma stage IV (Metastases to bone, hypertension, abnormal hepatic function, renal impairment)	50 mg for 10 days ↓ (administration suspended for 9 days) ↓ 37.5 mg for 4 days	<p><b>Lacunar infarction</b></p> <p>&lt;History of prior treatment&gt; Surgery: nephrectomy Medications: Interferon Alfa</p> <p>6 days before administration: The patient's performance status (PS) was 0.</p> <p>Day 1 of administration: The patient started receiving sunitinib malate at 50 mg/day for renal cell carcinoma (stage IV) (first course).</p> <p>Day 11 of administration (day of discontinuation): Pyrexia and gingivitis developed, and sunitinib malate was temporarily discontinued.</p> <p>10 days after discontinuation (day of readministration): Administration of sunitinib malate was resumed at 37.5 mg/day.</p> <p>Day 4 of readministration (day of discontinuation of readministration): The patient experienced sensory disturbance on the right side of his body and atonic seizures on the right upper- and lower-limbs. He underwent a head MRI, which showed lacunar infarction. Administration of sunitinib malate was temporarily discontinued.</p> <p>Drip infusion of ozagrel sodium and edaravone was started, and he also began rehabilitation. No aggravation of symptoms was noted.</p> <p>7 days after discontinuation: Drip infusion of ozagrel sodium and edaravone was discontinued. For prevention of relapse, administration of aspirin was initiated.</p> <p>95 days after discontinuation: Lacunar infarction resolved with sequelae. The patient had no problem in his daily life and was able to walk. The muscles of his right upper- and lower-limbs were still weak.</p>
Concomitant medications: amlodipine besilate, candesartan cilexetil, loxoprofen sodium hydrate, teprenone, sodium gualeinate hydrate				

**Laboratory Examination**

	Day 1 of administration	Day 11 of administration (Day of discontinuation)
Body temperature (°C)	35.7	39.2
Heart rate (/min)	60	95
Systolic blood pressure (mmHg)	143	149
Diastolic blood pressure (mmHg)	90	91



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 lymph nodes)	50 mg for 21 days	<p><b>Cerebral infarction</b></p> <p>&lt;History of prior treatment&gt; None</p> <p>5 days before administration: The patient's PS was 0.</p> <p>Day 1 of administration: Administration of sunitinib malate was started at 50 mg/day for renal cell carcinoma (stage IV) (first course). The patient complained of blurry vision and an unclear head early in the treatment.</p> <p>Day 21 of administration (day of discontinuation): In the morning, the patient complained of sudden flash vision. Oral administration of sunitinib malate was discontinued. Since the symptoms were not severe and not markedly worsened, only oral sunitinib malate was discontinued, and the patient was followed up.</p> <p>6 days after discontinuation: The symptoms improved considerably but remained. A head CT was performed, which showed widespread infarction. Hemianopia symptoms were noted. After a consultation with the department of neurosurgery, an MRI was performed. The patient was followed up as symptoms persisted, and he began rehabilitation.</p> <p>7 days after discontinuation: Holter monitoring showed ventricular arrhythmia and supraventricular arrhythmia. Cerebral infarction had not resolved.</p>
Concomitant medications: loxoprofen sodium hydrate, famotidine				

### Laboratory Examination

	5 days before administration	Day 21 of administration (day of discontinuation)	6 days after discontinuation	9 days after discontinuation
Body temperature (°C)	38.8	37.2	36.8	37.1
Heart rate (/min)	84	86	93	93
Systolic blood pressure (mmHg)	107	125	123	136
Diastolic blood pressure (mmHg)	84	84	75	92

## 3 Pilsicainide Hydrochloride Hydrate

### (1) Pilsicainide Hydrochloride Hydrate (oral dosage form)

<b>Brand Name (name of company)</b>	SUNRYTHM CAPSULES 25 mg, 50 mg (Daiichi-Sankyo Company, Limited)
<b>Therapeutic Category</b>	Antiarrhythmic agents
<b>Indications</b>	Patients with the following disease who cannot use or do not respond to other antiarrhythmic agents Tachyarrhythmia

«**PRECAUTIONS (underlined parts are revised)**»

**[Adverse Reactions (clinically significant adverse reactions)]** **Ventricular fibrillation, ventricular tachycardia (including torsades de pointes), sinus arrest, complete atrioventricular block, syncope, cardiac failure:** These adverse reactions may occur and lead to shock or cardiac arrest. Frequent examinations including electrocardiogram (ECG) and chest X-ray should be performed, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.  
**Acute renal failure:** Acute renal failure due to shock, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

**[Overdose]** **Signs and Symptoms:** If blood concentrations of this drug increased due to overdose of this drug or severe renal impairment, cardiovascular disorders including conduction disorder (markedly widened QRS, etc.), cardiac arrest, cardiac failure, ventricular fibrillation, ventricular tachycardia (including torsades de pointes), sinus arrest, bradycardia, shock, syncope, and decreased blood pressure, or psychiatric/neurological disorders including dysarthria may occur.

**(2) Pilsicainide Hydrochloride Hydrate (injectable dosage form)**

<b>Brand Name (name of company)</b>	SUNRYTHM INJECTION 50 (Daiichi-Sankyo Company, Limited) PILSICAINIDE HYDROCHLORIDE IV INJECTION 50 mg "YD" (Yoshindo Inc.) PILSICAINIDE HYDROCHLORIDE i.v. 50 mg "Isei" (Isei Co., Inc.)
<b>Therapeutic Category</b>	Antiarrhythmic agents
<b>Indications</b>	Tachyarrhythmia (supraventricular and ventricular) requiring emergency treatment

«**PRECAUTIONS (underlined parts are revised)**»

**[Adverse Reactions (clinically significant adverse reactions)]** **Ventricular fibrillation, ventricular tachycardia (including torsades de pointes), sinus arrest, complete atrioventricular block, syncope, cardiac failure:** These adverse reactions may occur and lead to shock or cardiac arrest. Patients should be continuously monitored with an electrocardiogram (ECG), etc., and if any abnormal findings are observed, administration of this drug should be discontinued and appropriate measures should be taken.  
**Acute Renal failure:** Acute renal failure due to shock, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

**[Overdose]** **Signs and Symptoms:** If blood concentrations of this drug increased due to overdose of this drug or severe renal impairment, cardiovascular disorders including conduction disorder (markedly widened QRS, etc.), cardiac arrest, cardiac failure, ventricular fibrillation, ventricular tachycardia (including torsades de pointes), sinus arrest, bradycardia, shock, syncope, and decreased blood pressure, or psychiatric/neurological disorders including dysarthria may occur.

**<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, 2007 to November 26, 2010)

- Cardiac arrest: 8 cases (1 fatal case)
- Cardiac failure: 1 case (no fatal cases)
- Shock: 4 cases (no fatal cases)
- Torsades de pointes: 1 case (no fatal cases)
- Acute renal failure: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAH(s):  
 approximately 110,000 for [1]

approximately 60,000 for [2]  
(FY 2009)

Marketed in Japan in: May 1991 for [1]  
April 2000 for [2]

### Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Arrhythmia (Renal failure, diabetes mellitus, hyperlipidaemia, hypertension, hyperphosphataemia, hyperuricaemia, haemodialysis)	50 mg for approx. 3 months	<p><b>Cardiac failure</b></p> <p>Day 1 of administration: The patient started receiving pilsicainide hydrochloride hydrate at 50 mg/day for arrhythmia.</p> <p>1 month after administration: The patient experienced a white visual field once or twice per month.</p> <p>1 day before discontinuation: The patient underwent dialysis.</p> <p>Approximately 3 months after administration (day of discontinuation): The patient began to have difficulty moving his legs at around noon, and pain developed in from his neck through to the shoulder on his left side at night. He suffered chest pain for 1 to 2 minutes and visited a nearby hospital for palpitations, tremblousness of hands, and weakness of limbs.</p> <p>Hypotension was noted and acute myocardial infarction was suspected after an ECG. The patient was admitted to the reporting medical institution.</p> <p>During hospitalization, the patient was fully conscious with blood pressure of 89/37 mmHg. He had an irregular heart rates, weak heart sounds, and no murmur or rales. His abdomen was slightly swollen. No oedema in extremities was observed, although examinations on the liver, spleen, and kidneys were unable to be performed.</p> <p>The patient was diagnosed with cardiac failure and abnormal left ventricular contraction based on cardiac catheterization and angiography.</p> <p>1 day after discontinuation: The patient's condition improved with dialysis.</p> <p>2 days after discontinuation: The patient recovered.</p>
Concomitant medications: allopurinol, sodium rabeprazole, atorvastatin calcium hydrate, precipitated calcium carbonate, amezinium metilsulfate, droxidopa				

### Laboratory Examination

	Approx. 3 months after administration (day of discontinuation)
BUN (mg/dL)	64
Creatinine (mg/dL)	13.0
K (mEq/L)	6.5

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Paroxysmal atrial fibrillation (Hypertension, chronic renal failure)	150 mg for 54 days	<p><b>Renal impairment, shock</b></p> <p>Day 1 of administration: The patient started receiving pilsicainide hydrochloride hydrate for paroxysmal atrial fibrillation. Thereafter, the patient experienced no arrhythmia.</p> <p>Day 54 of administration: The patient visited the emergency outpatient department for queasy in the evening. The patient experienced bradycardia (heart rate of 30s), renal impairment, and hepatic function disorder, and was admitted to the hospital. (blood concentration of pilsicainide hydrochloride hydrate, 2.3 µg/mL; blood pressure, 100/80 mmHg)</p> <p>1 day after discontinuation: Renal and hepatic functions aggravated. Bradycardia persisted. Continuous hemodialysis-filtration (CHDF) was started because the patient had almost no urination during hospitalization. Disseminated intravascular coagulation (DIC, score of 4) also occurred and anticoagulant therapy was started. Drug lymphocyte stimulation test (DLST) was negative for both pilsicainide hydrochloride hydrate and bisoprolol fumarate, and weakly-positive for valsartan.</p> <p>2 days after discontinuation: Spontaneous urination recovered and CHDF was terminated. (blood concentration of pilsicainide hydrochloride hydrate 0.9 µg/mL) Renal failure, hepatic failure, and DIC remitted gradually.</p> <p>34 days after discontinuation: The patient was discharged from the hospital.</p>
Concomitant medications: bisoprolol fumarate, valsartan				

### Laboratory Examination

	Day 54 of administration (day of discontinuation)	1 day after administration	2 days after discontinuation	32 days after discontinuation
Blood pressure (mmHg)	100/80	140/80	-	140/100
Pulse rate (/min)	30	50	-	80
BUN (mg/dL)	58.8	69.4	48.8	23.4
Creatinine (mg/dL)	4.95	5.92	3.68	1.36
AST (GOT) (IU/L)	1570	9990	4380	26
ALT (GPT) (IU/L)	752	3770	2910	17
Total bilirubin (mg/dL)	0.9	0.9	1.3	0.6
LDH (IU/L)	1674	10370	3010	252
K (mEq/L)	6.0	5.8	3.7	3.5
Blood concentration of pilsicainide hydrochloride hydrate (µg/mL)	2.3	-	0.9	-

## 3

## Revision of Precautions (No. 223)

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 January 11, 2011 (excluding those presented in “2. Important Safety Information” of this Bulletin).

[Brand Name]: Major product names are showed.

1

<Miscellaneous metabolism agents-Miscellaneous>

### Ciclosporin (oral and injectable dosage forms)

**[Brand Name]** Sandimmun Capsules 25 mg, Sandimmun Oral Solution 10%, Sandimmun for i.v. infusion 250 mg, Neoral 10 mg Capsules, Neoral Oral Solution 10 % (Novartis Pharma K.K.)

**[Adverse Reactions (clinically significant adverse reactions)]** **Liver injury, hepatic failure:** Hepatic disorder including hepatic dysfunction and jaundice, or hepatic failure may occur. If any abnormalities including increased AST (GOT), ALT (GPT), Al-P, LDH, and bilirubin are observed, appropriate measures such as dose reduction or discontinuation of administration should be taken.

2

<Psychotropics>

### Mianserin Hydrochloride

**[Brand Name]** Tetramide Tablets 10 mg, 30 mg (MSD K.K.)

**[Contraindications]** Patients with a history of hypersensitivity to ingredients of this drug

**[Adverse Reactions (clinically significant adverse reactions)]** **Hepatic dysfunction, jaundice:** Hepatic dysfunction with significantly increased AST (GOT), ALT (GPT),  $\gamma$ -GTP, Al-P, and total bilirubin, or jaundice 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.  
**Convulsion:** Convulsion may occur. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

3

<Diuretics, antihypertensives>

### Trichlormethiazide Hydrochlorothiazide Benzylhydrochlorothiazide Indapamide Benzylhydrochlorothiazide/Reserpine/Carbazochrome Meticrane

**[Brand Name]** Fluitran Tablet 1 mg, 2 mg (Shionogi & Co., Ltd.)

NEWTOLIDE TABLETS 25 mg (Towa Pharmaceutical Co., Ltd.)  
BEHYD Tablets 4 mg (Kyorin Pharmaceutical Co., Ltd.)  
NATRIX Tablet 1, 2 (Kyoto Pharmaceutical Industries, Ltd.)  
BEHYD-RA Combination Tablets (Kyorin Pharmaceutical Co., Ltd.)  
Arresten Tablets 150 mg (Nippon Shinyaku Co., Ltd.)

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

**Hyponatraemia:** Hyponatraemia may occur accompanied by malaise, anorexia, queasy, vomiting, convulsion, disturbed consciousness, and other symptoms. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken immediately.  
**Hypokalaemia:** Hypokalaemia may occur accompanied by malaise, feelings of weakness, arrhythmia, and other symptoms. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken immediately.

4

<Diuretics, antihypertensives>

**Mefruside  
Triпамide**

**[Brand Name]**

BAYCARON TABLETS 25 mg (Mitsubishi Tanabe Pharma Corporation)  
Normonal Tablet 15 mg (Eisai Co., Ltd.)

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

**Hyponatraemia:** Hyponatraemia may occur accompanied by malaise, anorexia, queasy, vomiting, convulsion, disturbed consciousness, and other symptoms. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken immediately.  
**Hypokalaemia:** Hypokalaemia may occur accompanied by malaise, feelings of weakness, arrhythmia, and other symptoms. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken immediately.

5

<Antihypertensives>

**Losartan potassium/Hydrochlorothiazide**

**[Brand Name]**

PREMINENT Tablets (MSD K.K.)

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

**Hypokalaemia, hyperkalaemia:** Serious hypokalaemia or hyperkalaemia may occur. Malaise, feelings of weakness, arrhythmia, and other symptoms may occur associated with abnormal variations in serum potassium. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken immediately.

6

<Enzyme preparations>

**Agalsidase Alfa (Genetical Recombination)**

**[Brand Name]**

REPLAGAL Intravenous Infusion 3.5 mg (Dainippon Sumitomo Pharma Co., Ltd.)

**[Important  
Precautions]**

In overseas countries, it has been reported that atrial fibrillation, ventricular extrasystoles, tachyarrhythmia, myocardial ischaemia, cardiac failure, and other symptoms occurred in association with infusion related reactions in patients with cardiac lesions of Fabry's disease during or within 24 hours after administration of this drug. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

7

&lt;Antidiabetic agents&gt;

**Sitagliptin Phosphate Hydrate**

<b>[Brand Name]</b>	GLACTIV Tablets 25 mg(Ono Pharmaceutical Co., Ltd.), JANUVIA Tablets 25 mg (MSD K.K.)
<b>[Important Precautions]</b>	<u>Acute pancreatitis may occur. Patients should be instructed to immediately consult a doctor if initial symptoms including persistent intense abdominal pain and vomiting occur.</u>
<b>[Adverse Reactions (clinically significant adverse reactions)]</b>	<u><b>Acute pancreatitis:</b> Acute pancreatitis may occur. Patients should be carefully monitored, and if initial symptoms including persistent intense abdominal pain and vomiting occur, administration of this drug should be discontinued, and appropriate measures should be taken. Haemorrhagic pancreatitis and necrotising pancreatitis have been reported as overseas spontaneous reports.</u>

8

&lt;Alkylating agents&gt;

**Temozolomide**

<b>[Brand Name]</b>	TEMODAL Capsules 20 mg, 100 mg, TEMODAL Infusion 100 mg (MSD K.K.)
<b>[Adverse Reactions (clinically significant adverse reactions)]</b>	<u><b>Hepatic dysfunction, jaundice:</b> Hepatic dysfunction with significantly increased AST (GOT), ALT (GPT), Al-P and <math>\gamma</math>-GTP, or jaundice 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.</u>

9

&lt;Antineoplastics-Miscellaneous&gt;

**Miriplitin Hydrate**

<b>[Brand Name]</b>	MIRIPLA for Intra-arterial Injection 70 mg (Dainippon Sumitomo Pharma Co., Ltd.)
<b>[Adverse Reactions (clinically significant adverse reactions)]</b>	<u><b>Hepatic dysfunction, jaundice, hepatic failure:</b> Hepatic dysfunction with increased AST (GOT), ALT (GPT), bilirubin, Al-P and <math>\gamma</math>-GTP, or jaundice may occur immediately after administration of this drug, and some of the cases may result in hepatic failure. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.</u> <u><b>Shock, anaphylactoid symptoms:</b> Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored, and if any abnormalities such as dyspnoea and decreased blood pressure are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.</u>

10

&lt;Antivirals&gt;

**Entecavir Hydrate**

<b>[Brand Name]</b>	Baraclude Tablets 0.5 mg (Bristol-Myers K.K.)
<b>[Adverse Reactions (clinically significant adverse reactions)]</b>	<u><b>Lactic acidosis:</b> Lactic acidosis may occur, and some fatal cases have been reported. If clinical symptoms or abnormal laboratory values of suspected lactic acidosis were observed, appropriate measures such as discontinuing administration should be taken.</u>

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&lt;Vaccines&gt;

## Freeze-dried, Cell Culture-derived Japanese Encephalitis Vaccine (Inactivated)

**[Brand Name]** JEBIK V (The Research Foundation for Microbial Diseases of Osaka University)

**[Adverse Reactions (clinically significant adverse reactions)]** Thrombocytopenic purpura: Thrombocytopenic purpura may occur. Symptoms including Purpura, epistaxis, and oral mucosa bleeding generally occur several days to approximately 3 weeks after vaccination. If thrombocytopenia purpura is suspected, examinations including blood tests should be performed, and appropriate measures should be taken.

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&lt;Diagnostic Agents-Miscellaneous&gt;

## Perflubutane

**[Brand Name]** SONAZOID FOR INJECTION 16 µL (Daiichi-Sankyo Company, Limited)

**[Adverse Reactions (clinically significant adverse reactions)]** Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored, and if any abnormalities including dyspnoea, decreased blood pressure, and rash are observed, appropriate measures should be taken.

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&lt;Non-main therapeutic purpose agents-Miscellaneous&gt;

## Iodine Addition Products of the Ethylesters of the Fatty Acids obtained from Poppseed Oil (MIRIPLA suspension vehicle)

**[Brand Name]** MIRIPLA suspension vehicle 4 mL (Dainippon Sumitomo Pharma Co., Ltd.)

**[Adverse Reactions (clinically significant adverse reactions)]** Hepatic dysfunction, jaundice, hepatic failure: Hepatic dysfunction with increased AST (GOT), ALT (GPT), bilirubin, Al-P and γ-GTP, or jaundice may occur immediately after administration of miriplatin suspension, and some of the cases may result in hepatic failure. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur after administration of miriplatin suspension. Patients should be carefully monitored, and if any abnormalities including dyspnoea and decreased blood pressure are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

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&lt;Synthetic narcotics&gt;

## Remifentanil Hydrochloride

**[Brand Name]** Ultiva Intravenous 2 mg, 5 mg (Janssen Pharmaceutical K.K.)

**[Adverse Reactions (clinically significant adverse reactions)]** Muscle stiffness: Muscle stiffness may occur. A single intravenous administration of this drug should be given over 30 seconds because the occurrence of muscle stiffness is related to the dose level and infusion rate. Excessive muscle stiffness occurring at the time of induction of anaesthesia should be treated with additional administration of muscle relaxants such as vecuronium bromide. In addition, appropriate measures including reduced infusion rate and discontinuing administration should be taken as necessary.

Difficulty in ventilation: Muscle stiffness and laryngospasm may lead to difficulty in ventilation. If any abnormalities are observed, appropriate measures such as the use of muscle relaxants should be taken. It has been reported that laryngospasm



occurred in patients using laryngeal masks, resulting in difficulty in ventilation. Caution should be exercised against the occurrence of such symptoms.

**Respiratory arrest, respiratory depression:** Respiratory arrest and respiratory depression may occur. Patients being treated with this drug should undergo assisted ventilation, and appropriate respiratory care such as the use of muscle relaxants or narcotic antagonists (naloxone hydrochloride, levallorphan tartrate, etc.) should be given as necessary.

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## 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 collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of February 1, 2011)

Nonproprietary name Brand name on	Name of the marketing authorization holder	Date of EPPV initiate
Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg	Pfizer Japan Inc.	June 22, 2010* <sup>1</sup> October 27, 2010* <sup>2</sup>
Lenalidomide Hydrate Revlimid Capsules 5 mg	Celgene K.K.	July 20, 2010* <sup>3</sup> August 20, 2010* <sup>4</sup>
Lansoprazole Takepron capsules 15, Takepron OD Tablets 15* <sup>5</sup>	Takeda Pharmaceutical Company Limited	August 20, 2010
Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 10 µg/1 mL PLASTIC SYRINGE, NESP INJECTION 15 µg/1 mL PLASTIC SYRINGE, NESP 20 µg/1 mL PLASTIC SYRINGE, NESP INJECTION 30 µg/1 mL PLASTIC SYRINGE, NESP INJECTION 40 µg/1 mL PLASTIC SYRINGE, NESP INJECTION 60 µg/0.6 mL PLASTIC SYRINGE, NESP 120 µg/0.6 mL PLASTIC SYRINGE, NESP INJECTION 180 µg/0.9 mL PLASTIC SYRINGE	Kyowa Hakko Kirin Co., Ltd.	August 26, 2010
Ambrisentan Volibris Tablets 2.5 mg	GlaxoSmithKline K.K.	September 17, 2010
Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg	Nippon Shinyaku Co., Ltd.	September 17, 2010
Levetiracetam E Keppra Tablets 250 mg, 500 mg	UCB Japan Co., Ltd.	September 17, 2010
Abatacept (Genetical Recombination) ORENCIA FOR I.V. INFUSION 250 mg	Bristol-Myers K.K.	September 21, 2010
Temsirolimus TORISEL Injection 25 mg	Pfizer Japan Inc.	September 22, 2010
Paclitaxel Abraxane I.V. Infusion 100 mg	Taiho Pharmaceutical Co., Ltd.	September 24, 2010
Teriparatide (Genetical Recombination) FORTEO s.c. injection kit 600 µg	Eli Lilly Japan K.K.	October 1, 2010
Telmisartan/Amlodipine Besilate Micamlo Combination Tablets AP	Nippon Boehringer Ingelheim Co., Ltd.	October 7, 2010

Bazedoxifene Acetate Viviant Tablets 20 mg	Pfizer Japan Inc.	October 13, 2010
Laninamivir Octanoate Hydrate INAVIR DRY POWDER INHALER 20 mg	Daiichi Sankyo Company, Limited	October 19, 2010
Botulinum Toxin Type A BOTOX for injection 50 Unit, 100 Unit* <sup>6</sup>	GlaxoSmithKline K.K.	October 27, 2010
Adalimumab (Genetical Recombination) HUMIRA Subcutaneous Injection 40 mg Syringe 0.8 mL* <sup>7</sup>	Abbott Japan Co., Ltd.	October 27, 2010
Olanzapine Zyprexa Tablet 2.5 mg, 5 mg, 10 mg, Zyprexa Fine Granule 1 %, Zyprexa Zydis Tablet 5 mg, 10 mg* <sup>8</sup>	Eli Lilly Japan K.K.	October 27, 2010
Peramivir Hydrate RAPIACTA Bag for Intravenous Drip Infusion 300 mg, RAPIACTA Vial for Intravenous Drip Infusion 150 mg* <sup>9</sup>	Shionogi & Co., Ltd.	October 27, 2010
Polyethylene Glycol Treated Human Normal Immunoglobulin Venoglobulin IH 5% I.V. 0.5 g/10 mL, 1 g/20 mL, 2.5 g/50 mL, 5 g/100 mL* <sup>10</sup>	Benesis Corporation	October 27, 2010
Drospirenone/Ethinylestradiol YAZ Combination Tablet	Bayer Yakuhin, Ltd.	November 16, 2010
Eltrombopag Olamine REVOLADE Tablets 12.5 mg, 25 mg	GlaxoSmithKline K.K.	December 10, 2010
Nepafenac Nevanac Ophthalmic Suspension 0.1%	Alcon Japan Ltd.	December 10, 2010
Bendamustine Hydrochloride TREAKISYM Injection 100 mg	Symbio Pharmaceuticals Limited	December 10, 2010
Levocetirizine Hydrochloride Xyzal Tablets 5 mg	GlaxoSmithKline K.K.	December 10, 2010
Diquafosol Sodium DIQUAS ophthalmic solution 3%	Santen Pharmaceutical Co., Ltd.	December 13, 2010
Tolvaptan Samsca tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	December 14, 2010
Sodium Hyaluronate Crosslinked Polymer/Sodium Hyaluronate Crosslinked Polymer Crosslinked with Vinylsulfone SYNVISC 2 mL (intra-articular injection)	Genzyme Japan K.K.	December 14, 2010
Exenatide Byetta Subcutaneous Injection 5 µg Pen 300, 10 µg Pen 300	Eli Lilly Japan K.K.	December 17, 2010
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg	Wakamoto Co., Ltd.	December 24, 2010
l-Menthol MINCLEA catapasm for internal use 0.8%	Nippon Pharmaceutical Co., Ltd.	January 11, 2011
Levofloxacin Hydrate CRAVIT INTRAVENOUS DRIP INFUSION BAG 500 mg/100 mL, CRAVIT INTRAVENOUS DRIP INFUSION 500 mg/20 mL	Daiichi Sankyo Company, Limited	January 11, 2011
Paliperidone Invega Tablets 3 mg, 6 mg, 9 mg	Janssen Pharmaceutical K.K.	January 17, 2011

Ciclesonide Alvesco 50 µg Inhaler 112 puffs, Alvesco 100 µg Inhaler 112 puffs, Alvesco 200 µg Inhaler 56 puffs* <sup>9</sup>	Teijin Pharma Limited.	January 21, 2011
Roxatidine Acetate Hydrochloride ALTAT CAPSULES 37.5, 75* <sup>9</sup>	ASKA Pharmaceutical Co., Ltd.	January 21, 2011

- \*1 The originally approved indication for “post herpetic neuralgia”
- \*2 An additional indication for "treatment of patients with peripheral neuropathic pain"
- \*3 The originally approved indication for “treatment of patients with relapsed or refractory multiple myeloma”
- \*4 An additional indication for “treatment of patients with myelodysplastic syndrome associated with a chromosome 5q deletion”
- \*5 An additional indication for “treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of non-steroidal anti-inflammatory drugs”
- \*6 An additional indication for "treatment of patients with upper limb spasms or lower limb spasms"
- \*7 An additional indication for "remission induction or maintenance therapy for moderate or severe active Crohn's disease (limited to patients who are not adequately responsive to conventional therapy)"
- \*8 An additional indication for "treatment of manic symptoms in patients with bipolar disorder"
- \*9 An additional administration for “pediatrics”
- \*10 An additional indication for “improvement of muscular weakness associated with polymyositis or dermatomyositis (limited to patients who are not adequately responsive to steroids)”