Pharmaceuticals and Medical Devices Safety Information

No. 289 March 2012

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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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Pharmaceutical and Food Safety Bureau,
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[Outline of Information]

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

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

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

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

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

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ADRs	Adverse drug reactions
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BP	Blood pressure
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CMV-IgG	Cytomegalovirus immunoglobulin G
CMV-IgM	Cytomegalovirus immunoglobulin M
CRP	C-reactive protein
Cr	Creatinine
CT	Computed tomography
DIC	Disseminated intravascular coagulation
d.i.v.	Intravenous drip
DLST	Drug lymphocyte stimulation test
EASL	European Association for the Study of the Liver
EB-IgG	Epstein-Barr immunoglobulin G
EB-IgM	Epstein-Barr immunoglobulin M
eGFR	estimated glomerular filtration rate
EIA	Enzyme immunoassay
EPPV	Early Post-marketing Phase Vigilance
HBc	Hepatitis B core
HBe	Hepatitis B envelope
HBs	Hepatitis B surface
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
ICU	Intensive care unit
IgM-HBc	Immunoglobulin M hepatitis B core
IU	International unit
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
NSAID	Nonsteroidal antiinflammatory drug
PCR	Polymerase chain reaction
PLT	Platelet
PO	Per oral
PT	Prothrombin Time
RBC	Red blood cell count
S.I.	Stimulation index
TEN	Toxic epidermal necrolysis
UA	Uric acid
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Reactivation of Hepatitis B Virus Associated with Antineoplastic Agent Everolimus

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Everolimus	AFINITOR tablets 5 mg (Novartis Pharma K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous	
Indications	Radically unresectable or metastatic renal cell carcinoma Pancreatic neuroendocrine tumor	

1. Introduction

Everolimus (AFINITOR tablets 5 mg) is a sirolimus derivative developed as a macrolide immunosuppressant. In Japan, everolimus was approved as a treatment for "radically unresectable or metastatic renal cell carcinoma" in January 2010, and the additional indication for the treatment of "pancreatic neuroendocrine tumor" was approved in December 2011.

Alerts against reactivation of hepatitis B virus (HBV) associated with everolimus have been included in the package insert, etc., since the marketing authorization. Since a fatal case due to reactivation of HBV after being treated with everolimus was reported in Japan, reactivation of HBV associated with the use of immunosuppressive drugs is presented. In addition, the safety measures and summary of reported cases are also included to provide information for proper use of everolimus.

2. HBV reactivation related to immunosuppressive therapy

With the advancement of chemotherapy, liver transplantation, hematopoietic stem-cell transplantation, and immunosuppressive therapy for rheumatic diseases, reactivation of hepatitis B is becoming a clinical problem requiring special attention.

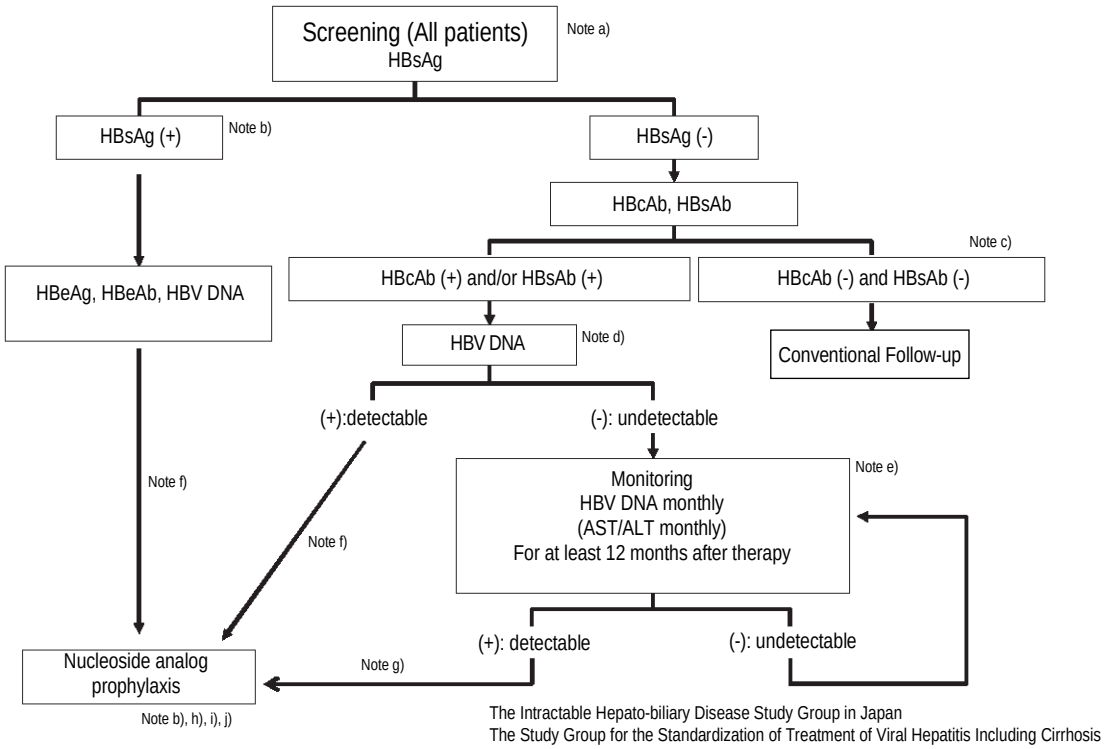
Reactivation of HBV is a well-recognized complication in Hepatitis B surface antigen (HBsAg) positive patients who are undergoing immunosuppressive chemotherapy for cancer. Clearance of HBsAg and appearance of antibody to hepatitis B core antigen (HBcAb) with or without HBsAb provides evidence of resolved infection in patients. However, it has been shown that HBV DNA remains at a low level in such patients, and that the intensive chemotherapy or immunosuppressive therapy can cause HBV reactivation and subsequent severe hepatitis. [1)-4)]

In 2009, the "Intractable Hepato-biliary Disease Study Group in Japan" and the "Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis" in the Health and Labour Sciences Research developed "Guideline for preventing hepatitis B due to immunosuppressive therapy or chemotherapy".[1)] This guideline describes that patients receiving rituximab-plus-steroid combination therapy or hematopoietic stem cell transplantation are particularly at risk of HBV reactivation and deserve careful attention. Patients receiving intensive immunosuppressive therapy are also at risk of HBV reactivation.

The Health and Labour Sciences Research Group for "Clarification of current status for reactivation of hepatitis B virus associated with immunosuppressants and antineoplastics and establishment of the preventive measures" conducted a survey on reactivation of HBV associated with antineoplastics other than rituximab and immunosuppressants, and published the 2010 study report in March 2011.[2)] In September 2011, the Japan College of Rheumatology issued "The proposal for management of rheumatic disease patients with hepatitis B virus infection receiving

immunosuppressive therapy." [5] In the same month, "Guideline for preventing hepatitis B due to immunosuppressive therapy or chemotherapy" were revised minorly.[6] These guidelines were publicized by the Japan Society of Hepatology.

Figure 1. Guideline for preventing hepatitis B due to immunosuppressive therapy or chemotherapy (revised version)



Reactivation of hepatitis B virus can occur not only in HBsAg-positive patients, but also in a proportion of HBsAg-negative patients during and after intensive immunosuppressive therapy or chemotherapy of hematological malignancy. HBV reactivation deserves special attention because it can cause flare-up of hepatitis resulting in fulminant hepatitis. Appropriate measures are also necessary in patients receiving immunosuppressive therapy or chemotherapy for non-hematological malignancy in consideration of the risk of HBV reactivation. Because of a lack of evidence, there is no guarantee that prophylactic administration of nucleoside analog on this guidelines can prevent acute hepatic failure due to HBV reactivation.

Notes

a) HBV carriers and patients who have apparently recovered from HBV infection receiving immunosuppressive therapy or cytotoxic chemotherapy are at a risk of HBV reactivation. All patients should be screened for being HBV carriers by HBsAg. If results for HBsAg are negative, patients should be screened for evidence of previous infection by HBcAb and HBsAb. Highly sensitive detection methods for HBsAg, HBcAb, and HBsAb are desirable.

b) HBsAg-positive cases are subject to consultation of a hepatologist. Consultation of a hepatologist is desirable in all patients subject to administration of nucleoside analogs.

c) Detection of HBV DNA is desirable in those patients who have previously received immunosuppressive therapy or cytotoxic chemotherapy, and HBcAb and HBsAb are undermined before the start of the therapy.

d) Detection by PCR or real-time PCR is recommended. The sensitive real-time PCR method is desirable.

e) Patients receiving rituximab-plus- steroid combination therapy or hematopoietic stem cell transplantation are particularly at risk of HBV reactivation and deserve careful attention. Although there is a lack of evidence regarding the risk of HBV reactivation in patients receiving fludarabine, an intensive immunosuppressive agent, this still deserves careful attention in the future.

f) Prophylactic nucleoside analogs should be started as soon as possible before the start of immunosuppressive therapy or chemotherapy.

g) Nucleoside analogs should be administered immediately when HBV DNA becomes positive during and after immunosuppressive therapy or chemotherapy.

h) Entecavir is recommended as the nucleoside analog. HBV DNA is monitored monthly during administration of nucleoside analogs.

i) Termination of nucleoside analog treatment is considered when the timing is as follows:,
If HBsAg is positive at screening, the timing of termination of nucleoside analog treatment will be determined in accordance to the treatment for type B chronic hepatitis. If HBcAb and/or HBsAb is positive at screening, nucleoside analog treatment will be discontinued when (1) nucleoside analogs are administered for 12 months after the completion of immunosuppressive therapy or chemotherapy, (2) ALT levels are normal during the administration period, and (3) HBV DNA is negative during the administration period.

j) Patients should be closely observed for 12 months after treatment with nucleoside analogs. The follow-up is according to the instruction method of each nucleoside analogs. Nucleoside analogs should be re-administered immediately when HBV DNA becomes positive during the observation period.

(Revised on September 26, 2011)

The PMDA posted "PMDA Alert for Proper Use of Drugs – Hepatitis B viral growth associated with the use of drugs with immunosuppressive effects" on the PMDA website to alert healthcare professionals to pay attention to occurrence of signs or symptoms related to hepatitis B viral growth by monitoring results of liver function tests or hepatitis viral markers, when administrating immunosuppressive drugs, such as antineoplastics, immunosuppressants, and antirheumatic agents.[7)]

The conventional treatments with antineoplastics for cancer patients, especially for patients with haematological malignancy, are therapies with a high level of immunosuppressive effect, which include chemotherapies in concomitant with corticosteroids and hematopoietic stem cell transplantation. As the concomitant use with rituximab and corticosteroids has become a common treatment for malignant lymphoma, the importance of raising the level of caution against reactivation of HBV in not only HBV carriers but HBs antigen-negative patients is now recognized.[2-4)] Since a wide variety of antineoplastics became recently available and potent immunosuppressive drugs, including everolimus, are being used in patients with solid tumor as well as in those with hematological malignancy, some cautions have become necessary in solid tumor patients.

3. Safety measures to be taken when using everolimus

During the regulatory review of the indication of everolimus for the treatment of "radically unresectable or metastatic renal cell carcinoma," an overseas clinical study in patients with pancreatic neuroendocrine tumour reported that hepatitis due to reactivation of HBV occurred in HBV carriers treated with everolimus, resulting in a fatal outcome.[8)] (See Case 1) Based on this fatal case, cautions against reactivation of HBV were included in the "WARNINGS," "Careful Administration," "Important Precautions," and "Clinically Significant Adverse Reactions" sections of the package insert since the initial marketing. (See Table 1)

Table 1

Warning	It has been reported that a hepatitis virus carrier patient developed hepatic failure due to reactivation of hepatitis virus during treatment with this drug and resulted in death. Fulminant hepatitis, aggravation of hepatitis, or hepatic failure may occur during or after treatment with this drug. Attention should be paid to the occurrence of signs and symptoms related to reactivation of hepatitis virus through periodic liver function tests.
Careful Administration	Patients previously infected with hepatitis virus, tuberculosis, etc. [Reactivation may occur.]
Important Precautions	Infections from bacteria, fungi, viruses, or protozoa or opportunistic infections may occur or worsen due to the immunosuppressive effect of this drug. In addition, hepatitis virus, tuberculosis, etc. may be reactivated in association with administration of this drug. Patients should be checked for infection prior to treatment with this drug. If patients have an infection, appropriate measures should be taken before treatment with this drug. Careful attention should be paid to the occurrence or exacerbation of infection during the administration of this drug.
Adverse reactions (Clinically significant adverse reactions)	Infection: Serious infections from bacteria, fungi, viruses, or protozoa (pneumonia, aspergillosis, candidiasis, sepsis, etc.) or opportunistic infections may occur or worsen, and fatal cases have been reported. In addition, it has been reported that a patient developed hepatic failure due to reactivation of hepatitis B virus and resulted in death. If a patient is diagnosed with any of these infections, administration of this drug should be suspended or discontinued immediately, and appropriate measures should be taken. If a patient is diagnosed with invasive systemic fungal infection, administration of this drug should be discontinued immediately, and appropriate antifungals should be administered. In this case, administration of this drug should not be resumed.

In addition to the alerts included in the package insert, "The Guide to Proper Use of Everolimus" prepared by the marketing authorization holders (MAHs) also introduces the Health and Labour Sciences Research Group's "Guideline for prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection" and provides information on an overseas fatal case associated with reactivation of HBV.

As described above, alerts have been issued against reactivation of HBV associated with everolimus, including the "WARNINGS" section of the package insert. However, 3 cases of hepatitis B associated with reactivation of HBV, including a fatal case, have been reported to the PMDA as serious adverse reactions as of February 21, 2012. Two of the cases in which the patients were positive for HBs antigen are presented below to further promote proper use of everolimus. (See Case 2 and 3)

The post-marketing surveillance for all the patients treated with everolimus is ongoing, and 2002 patients have been enrolled as of February 10, 2012.[9)]

4. Conclusion

As recommended in the "WARNINGS" section, everolimus should "only be administered to patients who are considered to be suitable, at a medical institution capable of appropriately handling emergencies and under the supervision of a physician with substantial expertise and experience in chemotherapy." Thorough reading of the package insert and "the Guide for Proper Use of Everolimus" is recommended. In addition, careful use of everolimus based on the information from the latest guidelines for prevention and treatment of hepatitis B, monitoring of reactivation of HBV, and appropriate consultation with a hepatologist, according to the test results of pre- and post-treatment and the patient's condition, is requested.

Everolimus may possibly cause a variety of adverse reactions other than hepatitis B. Healthcare professionals are encouraged to cooperate the proper use of everolimus based on a thorough understanding of its safety profile.

Case 1) Overseas fatal case reported until the time of drug approval review

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Pancreatic neuroendocrine tumour (HBV carrier, type 2 diabetes mellitus, hyperglycaemic hyperosmolar nonketotic syndrome, mucositis, gastritis, peptic ulcer, calculus renal)	Unknown for 167 days	**Hepatitis B reactivation, hepatic necrosis** 34 days before administration: The patient was positive for HBs antigen and negative for immunoglobulin M (IgM)-HBc antibody. Day 1 of administration: Administration of everolimus was started. Day 113 of administration: Liver function test values began to increase (ALT 42 IU/L, AST 53 IU/L, total bilirubin 6 μmol/L [0.35 mg/dL]). Day 141 of administration: Liver function test values further increased (ALT 74I U/L, AST 97 IU/L, total bilirubin 6 μmol/L [0.35 mg/dL]). Day 167 of administration (day of discontinuation): Administration of everolimus was discontinued. 2 days after discontinuation: ALT 263 IU/L, AST 698 IU/L, total bilirubin 28 μmol/L (1.64 mg/dL). Acute hepatic necrosis was confirmed. 16 days after discontinuation: HBV load was >100,000,000 IU/mL. 24 days after discontinuation: The patient dropped out from the study. ALT 210 IU/L, AST 548 IU/L, total bilirubin 32 μmol/L (1.87 mg/dL). 40 days after discontinuation: The patient developed hepatic encephalopathy due to reactivation of HBV associated with acute hepatic failure, and was admitted to the hospital. Concomitant hepatic encephalopathy occurred. Acute decompensated hepatic failure was suspected, and treatment with entecavir hydrate, lactulose, and lamivudine was performed. 45 days after discontinuation: ALT 552 IU/L, AST 1730 IU/L. 56 days after discontinuation: Ammonia 211 μg/dL. 61 days after discontinuation: The patient was transported to the intensive care unit (ICU) since his condition worsened. 63 days after discontinuation: The patient died. An autopsy was not performed.
	Concomitant medications: insulin, lansoprazole			

Case 2) Post-marketing case in Japan

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Metastatic renal cell carcinoma (intrathoracic metastasis, metastases to lymph nodes,	10 mg for 42 days ↓ 5 mg for 128 days	**Hepatitis B** 154 days before administration: HBs antigen > 250.00 IU/mL (normal range: < 0.05 IU/mL), HBs antibody, HBc antigen, HBc antibody, HBe antigen, HBe antibody, HBV-DNA quantitative: Not measured. 14 days before administration: The patient discontinued interferon alfa.

		hypertension, HBV carrier)		1 day before administration: Administration of sorafenib tosilate was discontinued. Day 1 of administration: Administration of everolimus was started at 10 mg/day. Day 15 of administration: Stomatitis (G1) occurred. The patient was treated with sodium gualenate hydrate gargle 4% (5 times/day) (for 28 days). Day 29 of administration: Urticaria (G1) occurred. Stomatitis remitted. Day 43 of administration: Due to urticaria, the dose of everolimus was reduced to 5 mg/day. Day 71 of administration: [Chest/abdominal computed tomography (CT)] Liver: Metastasis was not found. Size of the nodules under the hepatic dome did not change (with possibility of disseminated nodules). Gallbladder, pancreas, and spleen: No abnormalities. Day 154 of administration: The patient recovered from urticaria. Day 165 of administration: Hepatitis B (G3) reactivated. Day 168 of administration: As symptoms of hepatitis B reactivation, the patient had anorexia and chilliness, and was admitted to the hospital. The patient was referred to the department of gastroenterology. The patient was treated with vitamin drip infusion alone. [Chest/abdominal CT] Liver: No marked change was seen in nodules (suspected dissemination) on the liver surface. Apparent metastases to liver were not confirmed. Enlarged lymph nodes in the abdomen were not found. Ascites was not found. HBs antigen: positive, IgM-HBc antibody: negative, HBe antigen: negative, HBe antibody: positive, HBV-DNA quantitative: 8.3 copies/mL. Day 170 of administration (day of discontinuation): Administration of everolimus was discontinued. 2 days after discontinuation: Entecavir hydrate (per oral [PO] 0.5 mg/day) was administered. (No therapy other than administration of nucleotide analogue was performed.) 13 days after discontinuation: Hepatitis B remitted. HBV-DNA quantitative: 5.3 copies/mL 31 days after discontinuation: The patient was discharged from the hospital. Administration of entecavir hydrate was continued. 34 days after discontinuation: HBV-DNA quantitative: 3.9 copies/mL 69 days after discontinuation: HBV-DNA quantitative: 3.0 copies/mL
	Concomitant medications: valsartan, sodium gualenate hydrate			

Laboratory Examination

	154 days before administration	14 days before administration	Day 168 of administration	4 days after discontinuation	6 days after discontinuation	10 days after discontinuation	13 days after discontinuation	34 days after discontinuation	69 days after discontinuation
Total bilirubin (mg/dL)	—	0.8	0.4	—	—	—	0.9	—	—
Direct bilirubin (mg/dL)	—	—	—	0.3	0.3	0.3	0.4	—	—

Al-P (IU/L)	—	209	512	750	726	583	482	—	—
AST (GOT) (IU/L)	—	33	1402	1421	464	115	107	—	—
ALT (GPT) (IU/L)	—	26	1375	1515	911	320	181	—	—
γ-GTP (IU/L)	—	30	265	575	547	415	332	—	—
BUN (mg/dL)	—	8	11	—	—	—	9	—	—
Creatinine (mg/dL)	—	0.76	0.83	—	—	—	0.66	—	—
CRP (mg/dL)	—	0.3	0.7	—	—	—	1.3	—	—
WBC (/mm^3)	—	2800	3600	—	—	—	7500	—	—
RBC ($\times 10^4/mm^3$)	—	462	460	—	—	—	408	—	—
PLT ($\times 10^4/mm^3$)	26.8	10.1	10.7	—	—	—	27.7	—	—
PT activity (%)	91	—	104	—	—	—	—	—	—
HC: HCV antibody	(-)	—	(-)	—	—	—	—	—	—

Case 3) Post-marketing case in Japan

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 50s	Right metastatic renal cell carcinoma (intrathoracic metastasis, HBV carrier, tumour associated fever)	10 mg for 154 days ↓ Drug withdrawal for 18 days ↓ 10 mg for 8 days	**Hepatitis B** 532 days before administration: HBs antigen: Positive HBs antibody, HBc antigen, HBc antibody, HBe antigen, HBe antibody, HBV-DNA quantitative: Not measured. 331 days before administration: The patient discontinued interferon alfa. 86 days before administration: Administration of sorafenib tosilate was discontinued. 14 days before administration: Administration of sunitinib malate was discontinued. Day 1 of administration: Administration of everolimus was started at 10 mg/day. Day 56 of administration: Stomatitis (G1) occurred. Treatment with dexamethasone was started (for 43 days). Day 84 of administration: Hepatic dysfunction (G2) was confirmed. Treatment with glycyrrhizin/glycine/DL-methionine and ursodeoxycholic acid was started. Day 98 of administration: The patient recovered from stomatitis. Day 154 of administration (day of discontinuation): General malaise (G3) occurred. Administration of everolimus was discontinued due to general malaise. The patient did not recover from hepatic dysfunction. A chest CT showed reticular and linear opacities in the middle lung field. The patient was diagnosed with atelectasis (G1). 19 days after discontinuation (day of readministration): General malaise remitted. Administration of everolimus was resumed at 10 mg/day. Day 7 of readministration: The patient urgently visited the hospital with the chief complaint of faeces pale. The blood biochemical test showed a serious liver disorder, and the patient was diagnosed with acute aggravation of hepatitis B (G4). Day 8 of readministration (day of discontinuation of readministration): The patient was urgently admitted to the hospital.

				Administration of everolimus was discontinued and treatment with entecavir hydrate 0.5 mg/day and lactulose 30 mL/day was performed, but no improvement was noted. The echography showed no apparent abnormality in the hepatic parenchyma. Ascites was found around the spleen (+). HBs antigen: positive, HBs antibody: negative, HBc antibody: positive, HBe antigen: negative, HBe antibody: positive, HBV-DNA quantitative: ≥ 9.1 copies/mL 1 day after discontinuation: Transfusion of 6 units of fresh frozen plasma was performed. 2 days after discontinuation: Transfusion of 6 units of fresh frozen plasma was performed. 4 days after discontinuation: Administration of maintenance solution (glucose-added) (2) 500 mL × 4 intravenous drip (d.i.v.), famotidine 20 mg 1A + saline 20 mL × 2, saline 100 mL + ampicillin sodium 1A × 2 was started (for 4 days). Transfusion of 6 units of fresh frozen plasma was performed. 5 days after discontinuation: Transfusion of 6 units of fresh frozen plasma was performed. 6 days after discontinuation: Transfusion of 6 units of fresh frozen plasma was performed. 7 days after discontinuation: The patient did not recover from atelectasis. The patient was transferred and admitted to another hospital. The patient did not develop encephalopathy and was able to walk. Disseminated intravascular coagulation (DIC) was suspected because platelet (PLT) level had been low from before hospital transfer. Prothrombin Time (PT) activity 29%. To suppress inflammation of the liver, corticosteroid pulse therapy (methylprednisolone sodium succinate 1000 mg/day) was started (for 3 days). Administration of entecavir hydrate prescribed by the previous physician was continued. [Abdominal CT] Shrinkage of the liver and a low density area around the portal tracts (periportal collar) were noted. Shrinkage of the gall bladder and oedematous thickening of the wall were also noted. These findings were consistent with fulminant hepatitis. Ascites was also noted. HBs antigen: positive, HBs antibody: negative, HBe antigen: negative, HBe antibody: positive, HBV-DNA quantitative: 7.2 copies/mL. 10 days after discontinuation: The dose of methylprednisolone sodium succinate was reduced to 500 mg/day (for 3 days). 13 days after discontinuation: The dose of methylprednisolone sodium succinate was reduced to 250 mg/day (for 3 days). 15 days after discontinuation: [Abdominal CT] Shrinkage of the liver and a low density area around the portal tracts (periportal collar) were noted. Shrinkage of the gall bladder and oedematous thickening of gall bladder fluid were observed (+). 16 days after discontinuation: The dose of methylprednisolone sodium succinate was reduced to 125 mg/day (for 3 days). 19 days after discontinuation:

				The dose of prednisolone (oral) was changed to 60 mg/day. Administration of sulfamethoxazole/trimethoprim was started. 22 days after discontinuation: [Abdominal CT] Liver generally slightly shrunk. No apparent abnormality was noted in the parenchyma. Some hepatic cysts were noted, but no apparent tumor was found. Biliary dilatation was not found (-). Ascites and generalised oedema were noted. Date unknown: Delirium associated with corticosteroids was confirmed. 26 days after discontinuation: From nighttime onwards, the patient had a feeling of somewhat unrest. 27 days after discontinuation: The patient got into a state of excitement in the morning. A chest CT showed pneumonia. Administration of micafungin sodium was started. [Abdominal CT] Shrinkage of the liver and a low density area around the portal tracts (periportal collar) were noted. Shrinkage of the gall bladder and oedematous thickening of gall bladder fluid were observed (+). Ascites increased from the last level. 29 days after discontinuation: Micafungin sodium was switched to ampiroxicam. 30 days after discontinuation: As HBV-DNA continuously increased, interferon beta was administered every day. 33 days after discontinuation: The dose of prednisolone (oral) was changed to 50 mg/day. Total bilirubin 29.6 mg/dL. Plasma exchange and dialysis were performed. 35 days after discontinuation: Plasma exchange was performed. 37 days after discontinuation: [Abdominal CT] Shrinkage of the liver and a low density area around the portal tracts (periportal collar) were noted. Shrinkage of the gall bladder and oedematous thickening of gall bladder fluid were observed (+). 38 days after discontinuation: Plasma exchange was performed. 41 days after discontinuation: Plasma exchange was performed. 42 days after discontinuation: The dose of prednisolone (oral) was changed to 40 mg/day. Immediately before death, dialysis cannot be performed due to a low blood pressure reading. 44 days after discontinuation: The patient died from hepatorenal syndrome due to hepatic failure caused by acute aggravation of hepatitis B. [Autopsy] Fungi were noted between the parietal pleura and visceral pleura. The liver shrunk, and there were almost no normal parts of the liver. Metastases were noted in adrenals and lung. No apparent metastases to liver were found.
	Concomitant medications: loxoprofen sodium hydrate, rebamipide, naproxen, d-chlorpheniramine maleate, hydrocortisone acetate/fradiomycin sulfate/diphenhydramine hydrochloride, sodium ferrous citrate, diclofenac sodium, lansoprazole, levofloxacin hydrate			

Laboratory Examination

	532 days before administration	1 day before administration	Day 84 of administration	Day 112 of administration	Day 154 of administration (day of discontinuation)	Day 7 of readministration	Day 8 of readministration (day of discontinuation of readministration)	7 days after discontinuation	22 days after discontinuation	38 days after discontinuation	43 days after discontinuation
WBC ($\times 10^3/\mu L$)	7.6	4.4	6.6	7.4	7.1	6.6	6.2	6.8	21.5	14.5	14.2
RBC ($\times 10^4/mm^3$)	480	389	482	449	507	574	519	541	511	436	402
PLT ($\times 10^4/mm^3$)	34.2	19.3	16.4	19.4	14.3	6.7	9.4	5.4	5.7	2.5	4.3
Prothrombin time (%)	68.0	—	—	—	—	—	37.1	29	47	37	31
Prothrombin ratio	1.32	—	—	—	—	—	1.83	1.98	1.48	1.70	1.89
Prothrombin time (sec)	12.3	—	—	—	—	—	19.9	22.6	16.3	19.1	21.5
Fibrin or Fibrinogen degradation products (μg/mL)	—	—	—	—	—	—	21.0	22.4	—	—	—
D-dimer (μg/mL)	—	—	—	—	—	—	14.10	9.0	—	—	—
Serum albumin (g/dL)	3.2	2.9	3.5	3.5	2.8	2.9	2.6	3.3	—	2.6	—
Total bilirubin (mg/dL)	0.3	0.4	0.4	0.4	0.3	6.8	6.4	11.0	18.1	19.6	19.9
BUN (mg/dL)	14	16	14	16	14	11	12	6.1	22.2	81.5	77.6
Creatinine (mg/dL)	0.6	0.8	1.0	1.0	1.0	1.1	0.9	1.03	0.97	4.10	3.98
Ammonia (μg/dL)	—	—	—	—	—	—	105	46	36	23	42
CRP (mg/dL)	11.0	10.24	2.98	3.95	2.56	1.15	1.26	2.09	2.31	3.95	7.27
AST (GOT) (IU/L)	40	21	63	129	83	2572	1874	1920	101	141	154
ALT (GPT) (IU/L)	43	20	71	198	106	1331	1082	878	112	67	67
Al-P (IU/L)	367	254	258	317	295	935	839	632	647	513	658
γ-GTP (IU/L)	76	—	—	—	—	—	249	149	159	96	148
Cholinesterase (IU/L)	198	—	—	—	—	—	—	243	—	—	—
HC: HCV antibody	(-)	—	—	—	—	—	(-)	(-)	—	—	—
CMV-IgG antibody	—	—	—	—	—	—	(+)	(+)	—	—	—
CMV-IgM antibody	—	—	—	—	—	—	(-)	(-)	—	—	—
EB-IgG antibody	—	—	—	—	—	—	(+)	(+)	—	—	—
EB-IgM antibody	—	—	—	—	—	—	(-)	(-)	—	—	—

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2

Use of the “PMDA medi-navi” and “My Drug List for Safety Update”

* “PMDA medi-navi” and “My Drug List for Safety Update” are only available in Japanese language.

The PMDA medi-navi is a free e-mail service which informs of release of very important safety information regarding pharmaceuticals and medical devices as soon as it is available. Subscriptions to the PMDA medi-navi are encouraged to enhance pharmaceuticals and medical devices safety measures.

1. Introduction

The “PMDA medi-navi” (official name, Pharmaceuticals and Medical Devices Information E-mail Alert Service) is a free e-mail service provided by the PMDA to help healthcare professionals to enhance pharmaceutical and medical device safety measures. It provides important safety information regarding pharmaceuticals and medical devices, such as Dear Healthcare Professional Letters, Revisions of Precautions, recall information, and regulatory approval information (e.g., review reports of new drugs) when such information is issued.

The PMDA medi-navi was previously introduced in the Pharmaceuticals and Medical Devices Safety Information No. 278. This section presents an additional function of PMDA medi-navi called My Drug List for Safety Update and the latest information on the service.

Not only pharmaceutical and medical device safety management supervisors but also healthcare professionals are encouraged to use the PMDA medi-navi and My Drug List for Safety Update to collect prompt and efficient information for the aim of promoting safe use of drugs and medical devices.

2. My Drug List for Safety Update

Users of My Drug List for Safety Update can create their customized drug list on the web. Links to the safety-related websites including package inserts, Interview Forms, and Drug Guide for Patients of pre-selected products by the user will be shown in a list. The functions of My Drug List for Safety Update include caution signs displayed when safety information (e.g., Dear Healthcare Professional Letters) of a pre-selected product is issued. (Figure 1)

Information offered by the My Drug List for Safety Update is updated daily with other contents of the PMDA website. The customized drug list will be updated on the following day of posting of information including package inserts on the PMDA website. Important information posted on the PMDA website will be distributed to the PMDA medi-navi users immediately. The PMDA medi-navi combined with My Drug List for Safety Update will enable more efficient collection and management of drug safety information.

The My Drug List for Safety Update will be renewed shortly for improved usability and convenience. The renewed display of My Drug List for Safety Update is shown below (still under development and subject to change).

Figure 1. Renewed display of My Drug List for Safety Update

3. How to subscribe to My Drug List for Safety Update

My Drug List for Safety Update is an additional function of the PMDA medi-navi. To receive the service, you need to subscribe to both the PMDA medi-navi and My Drug List for Safety Update. Anyone can subscribe to this service, free of charge.

If you have not subscribed to the PMDA medi-navi, please visit the PMDA medi-navi website (http://www.info.pmda.go.jp/info/idx-push.html) to subscribe.

If you are a subscriber to the PMDA medi-navi, please search “マイ医薬品集” (My Drug List) and subscribe to the service on the website (http://www.info.pmda.go.jp/info/idx-myiyaku.html).

4. Current status and encouragement to use the PMDA medi-navi for enhancement of safety measures

At present, the number of hospitals, clinics, and pharmacies in Japan is estimated to be approximately 230,000. As of February 20, 2012, the PMDA medi-navi subscribers count has reached 51,107 (12,277 staff at hospitals, 6372 staff at general clinics, 3665 staff at dental clinics, 11,580 staff at pharmacies, and 17,213 staff elsewhere [the staff of MAHs of drug or medical device and wholesale distributor]; a single institution may have multiple subscribers). Those working at clinics and pharmacies are especially encouraged to subscribe.

The PMDA medi-navi was included as the means for information collection in the facility criteria for additional dispensing fees for standard operation and the precautions for additional fees for pharmacist ward operation (part of the medical service fees) in the FY 2012 revision of health insurance medical fees.

Facility criteria for additional dispensing fees for standard operation (excerpt)

Installing computer terminal(s) at the pharmacy to collect up-to-date medical information including Dear Healthcare Professional Letters and Pharmaceuticals and Medical devices Safety Information via the Internet, e.g., the Pharmaceuticals and Medical Devices Information E-mail Alert Service (PMDA medi-navi), and keeping the staff health insurance pharmacists thoroughly informed.

Precautions for additional fees for pharmacist ward operation (excerpt)

Collecting up-to-date medical information including Dear Healthcare Professional Letters and Pharmaceuticals and Medical Devices Safety Information via the Internet, e.g., the Pharmaceuticals and Medical Devices Information E-mail Alert Service (PMDA medi-navi), and keeping the healthcare professionals thoroughly informed of important drug information.

In order to have the PMDA medi-navi used by more healthcare providers, the password requirement was removed in January 2012. The PMDA medi-navi was improved so that users can register more easily. The PMDA is making efforts to improve the PMDA medi-navi to provide more usable and easier to understand services.

The MHLW and the PMDA hope the PMDA medi-navi and My Drug List for Safety Updates will be used by more healthcare professionals including, not only pharmaceutical and medical device safety management supervisors, but also physicians, dentists, pharmacists, nurses, and clinical engineers. The active use of the services is encouraged to enhance pharmaceutical and medical device safety measures.

3
Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated February 14, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Montelukast Sodium

Brand Name (name of company)	KIPRES Tablets 5 mg, 10 mg, KIPRES Fine Granules 4 mg, KIPRES Chewable Tablets 5 mg (Kyorin Pharmaceutical Co., Ltd.), SINGULAIR Tablets 5 mg, 10 mg, SINGULAIR Fine Granules 4 mg, SINGULAIR Chewable Tablets 5 mg (MSD K.K.)
Therapeutic Category	Allergic agents-Miscellaneous
Indications	Bronchial asthma Allergic rhinitis (except fine granules and chewable tablets)

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome, or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to December 4, 2011)

- Toxic epidermal necrolysis: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 6,340,000 (2011)

Launched in Japan: August 2001 (tablets 10 mg. chewable tablets 5 mg)
October 2007 (fine granules 4 mg)
April 2008 (tablets 5 mg)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Bronchial asthma (retinal pigment degeneration)	10 mg for 24 days	**Toxic epidermal necrolysis** 14 days before administration: The patient visited a nearby hospital with the chief complaints of cough, sputum, and nasal discharge. Auscultation showed no abnormalities. X-ray showed no abnormalities. Treatment was started based on the diagnosis of acute bronchitis. Day 1 of administration: Common cold symptoms improved, but cough was severe. Auscultation showed wheezing. The patient was diagnosed

				with bronchial asthma. Administration of montelukast sodium, budesonide, prednisolone, irsogladine maleate, and clarithromycin was started. Day 5 of administration: Administration of only clarithromycin was discontinued. Day 8 of administration: Because the cough did not completely disappear, administration of codeine phosphate hydrate, prochlorperazine maleate, and magnesium oxide was added. Day 14 of administration: Administration of irsogladine maleate, codeine phosphate hydrate, prochlorperazine maleate, and magnesium oxide was discontinued. Day 22 of administration: Cough substantially improved. Skin eruption occurred and spread. Administration of cetirizine hydrochloride and difluprednate was started. Day 23 of administration: Administration of prednisolone was discontinued. Day 24 of administration (day of discontinuation): Administration of montelukast sodium, budesonide, cetirizine hydrochloride, and difluprednate was discontinued. 3 days after discontinuation: The patient visited the dermatology departments and was admitted to the hospital. Oral administration of prednisolone 50 mg/day was started. Skin biopsy was performed. Epidermal necrosis was found. Date unknown: The patient had pyrexia of ≥ 38°C . Dermatological findings: erythema multiforme of ≥ 10%, blister/erosion, Nikolsky's sign were observed. Mucosal findings: Conjunctival hyperaemia, eye discharge, lip erosion, and genital erosion were confirmed. Herpes simplex virus infection was unknown. Mycoplasma infection was not found. Herpes simplex virus type 2-IgG antibody (Enzyme immunoassay [EIA]): 46.7. Multi-organ failure was not found. 9 days after discontinuation: Because the symptoms did not remit, double membrane filtration plasma exchange was performed (for 2 days). Date unknown: After that, the symptoms slowly remitted. 86 days after discontinuation: The patient was discharged from the hospital. Date unknown: Drug lymphocyte stimulation test (DLST) was performed. DLST showed negative results for montelukast sodium with stimulation index (S.I.) of 114%.
	Concomitant medications: budesonide, prednisolone, irsogladine maleate, clarithromycin, codeine phosphate hydrate, prochlorperazine maleate, magnesium oxide, cetirizine hydrochloride, difluprednate			

2 Monobasic Sodium Phosphate Monohydrate/Dibasic Sodium Phosphate Anhydrous

Brand Name (name of company)	Visiclear Combination Tablets (Zeria Pharmaceutical Co., Ltd.)
Therapeutic Category	Non-main therapeutic purpose agents-Miscellaneous
Indications	Elimination of intestinal contents as pretreatment prior to colonoscopy

PRECAUTIONS (underlined parts are revised)

Warnings

WARNINGS

Acute renal failure or acute phosphate nephropathy (nephrocalcinosis) may occur as serious adverse events associated with this drug. Such events often result in persistent renal impairment, which may require dialysis for a long period. Before administration, patients should be carefully interviewed and monitored. Additionally, this drug should be carefully administered to the following high-risk patients. In particular, this drug should not be administered to elderly patients with hypertension.

- Elderly patients
- Patients with hypertension
- Patients with decreased circulatory blood volume, renal disease, or active colitis
- Patients treated with drugs (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, Nonsteroidal antiinflammatory drugs [NSAIDs], etc.) that affect renal blood flow or renal function

Contraindications

Elderly patients with hypertension

Careful Administration

Patients with hypertension

Use in the Elderly

Serious renal diseases such as acute renal failure may occur in the elderly. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken. In particular, this drug should not be administered to elderly patients with hypertension.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 8 months (March 28, 2011 to November 25, 2011)

- Acute renal failure-related cases: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 60,000 (February 2011 to January 2012)

Launched in Japan: June 2007

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Pretreatment prior to colonoscopy (hypertension,	50 g for 1 day	**Renal failure (oliguria, malaise), urticaria (generalised), decreased blood pressure, difficulty in walking.** Medical history: Reflux oesophagitis, uterine myoma, cataract, cholelithiasis, cholecystectomy, hypertension, hyperlipidaemia

		hyperlipidaemia, insomnia, chronic gastritis, gastric ulcer, sholder muscle stiffness, allergic rhinitis, headaches, dizziness)		1 day before administration: The patient took magnesium citrate 50 g and sennoside 36 mg in the evening since colonoscopy was scheduled for a detailed examination of intestinal gas retention. Day of administration: As a pretreatment, 5 tablets of monobasic sodium phosphate monohydrate/dibasic sodium phosphate anhydrous × 10 times/day + water 2 L and metoclopramide 50 mg were administered, and then colonoscopy was performed. Decreased blood pressure (blood pressure [BP] 74/56 mmHg) was noted immediately after the examination, but BP immediately returned (106/59 mmHg). Thus, she returned home. After returning home, severe malaise developed and she had difficulty in walking. The patient also developed generalised urticaria. 2 days after administration: The patient recovered from difficulty in walking without treatment. 3 days after administration: The patient visited an outpatient department. The patient was admitted to the hospital due to renal failure (oliguria and malaise) and generalised urticaria. The blood test at admission showed blood urea nitrogen (BUN) 47.1 mg/dL, creatinine (Cr) 4.79 mg/dL, and estimated glomerular filtration rate (eGFR) 7mL/min. Regarding oliguria, a detailed urine output volume is unknown, but almost no urine was excreted. For urticaria, oral administration of prednisolone 10 mg × twice/day, d-chlorpheniramine maleate preparation 6 mg × twice/day and topical administration of difluprednate cream were performed. For renal failure, fluid replacement (acetated Ringer solution 500 mL × 5 times/day) was started. 7 days after administration: The patient was considered to have recovered from generalised urticaria. 58 days after administration: Renal function gradually improved, and administration of fluid replacement (acetated Ringer solution) was discontinued. 71 days after administration: The blood test showed improvement: BUN 25.7mg/dL, Cr 1.60 mg/dL, and eGFR 25mL/min. 72 days after administration: Based on the blood test results of the previous day, the patient was discharged from the hospital and was followed up on an outpatient basis. 118 days after administration: The blood test showed BUN 28.3 mg/dL and Cr 1.59 mg/dL. eGFR reached a peak at 25 mL/min. The patient was considered to have chronic renal failure.
	Concomitant medications: perindopril erbumine, telmisartan, carvedilol, amlodipine besilate, sennoside, magnesium citrate, metoclopramide, tofisopam, triazolam, itopride hydrochloride, lansoprazole, pravastatin sodium, tizanidine hydrochloride, betahistine mesilate, fexofenadine hydrochloride, ketoprofen			

Laboratory Examination

	4 days before administration	3 days after administration	7 after administration	17 after administration	32 after administration	46 after administration	71 after administration	118 after administration
BUN (mg/dL)	15.2	47.1	57.3	37.1	21.1	21.2	25.7	28.3
Cr (mg/dL)	0.66	4.79	3.90	2.88	1.94	1.67	1.60	1.59
UA (mg/dL)	3.5	6.2	5.7	4.4	2.8	3.4	4.6	6.8
LDH (IU/L)	206	252	270	221	173	173	155	179
Na (mEq/L)	144	142	142	141	143	145	143	145
K (mEq/L)	4.6	3.5	3.9	4.0	3.5	4.0	4.5	4.2
Cl (mEq/L)	103	101	105	103	105	108	109	106
Ca (mg/dL)	9.6	7.7	8.1	8.3	9.0	8.9	9.1	9.4
P (mg/dL)	4.3	5.0	4.6	4.1	4.1	4.5	4.7	4.1
eGFR (mL/min)	—	7	—	—	—	24	25	25

4

Revision of Precautions (No. 234)

(1) Drugs

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated February 14, 2012 (excluding those presented in 3. Important Safety Information of this Bulletin).

1

Miscellaneous metabolism agents-Miscellaneous

Leflunomide

Brand Name	Arava 10 mg Tablets, Arava 20 mg Tablets, Arava 100 mg Tablets (sanofi-aventis K.K.)
Contraindications	Patients with active tuberculosis
Careful Administration	Patients previously infected with tuberculosis (particularly patients with a history of tuberculosis and patients with a finding of tuberculosis healing on chest X-ray)
Important Precautions	Hepatitis may occur due to reactivation of hepatitis B virus in hepatitis B virus carriers. Hepatitis C may be exacerbated in hepatitis C virus carriers. If this drug is administered to hepatitis virus carriers, attention should be paid for the occurrence of signs or symptoms related to reactivation of hepatitis B virus and hepatitis C aggravation, by monitoring results of liver function tests or hepatitis viral markers, etc. Prior to treatment, a sufficient interview regarding tuberculosis, 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 a 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 prior to 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 previous 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 also carefully monitored for tuberculous infection through periodic tests such as chest X-rays during administration of this drug. In addition, patients should be instructed to contact their physician immediately if symptoms suspicious of tuberculosis (e.g., persistent cough and pyrexia) are observed. If active tuberculosis is confirmed, this drug should not be administered.
Adverse Reactions (clinically significant adverse reactions)	**Infection**: Serious infections (pneumonia [including carinii pneumonia], sepsis, etc.) may occur. Fatal infections, sepsis, and opportunistic infections have been reported, and hepatitis due to reactivation of hepatitis B virus or exacerbation of hepatitis C has

also been reported. Patient's general conditions should be carefully monitored, and if any abnormalities are observed, administration of the drug should be discontinued, and appropriate measures should be taken. When a drug removal method is used, the absorption of oral antibiotics may be inhibited, and therefore an injectable dosage form should be used.
Tuberculosis: Tuberculosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

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

Extract from Inflamed Cutaneous Tissue of Rabbits Inoculated with Vaccine Virus (oral dosage form)

Brand Name

Neurotropin tab. 4 N.U. (Nippon Zoki Pharmaceutical Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Hepatic dysfunction, jaundice: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), and γ-GTP or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
Shock or anaphylactoid symptoms associated with the injectable dosage form of this drug have been reported. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

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

Extract from Inflamed Cutaneous Tissue of Rabbits Inoculated with Vaccine Virus (injectable dosage form)

Brand Name

Neurotropin 1.2 N.U. injection, Neurotropin 3.6 N.U. injection
(Nippon Zoki Pharmaceutical Co., Ltd.) and the others

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored. If abnormalities such as abnormal pulse, chest pain, dyspnoea, decreased blood pressure, loss of consciousness, redness, or pruritus are observed, administration of the drug should be discontinued immediately, and appropriate measures should be taken.
Hepatic dysfunction, jaundice: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), and γ-GTP or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

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4 **Stomachics and digestives**

FK Powder
HM Powder
KM Powder
NIM Combination Powder
OM Powder Mix

Brand Name

FK Powder (Fuso Pharmaceutical Industries, Ltd.)
HM Powder (Konishi Pharmaceutical Co., Ltd.)
KM POWDER (Towa Pharmaceutical Co., Ltd.)
NIM Combination Powder (Nichi-Iko Pharmaceutical Co., Ltd.)
OM POWDER MIX (Nichi-Iko Pharmaceutical Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylactoid symptoms**: Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored, and if abnormalities are observed, administration of the drug should be discontinued, and appropriate measures should be taken.

5 Antidotes

Deferasirox

Brand Name	EXJADE Dispersible Tablets 125 mg, 500 mg (Novartis Pharma K.K.)
Precautions of Dosage and Administration	It is preferable to avoid administration of this drug to patients with severe hepatic dysfunction (Child-Pugh Class C). The starting dose should be reduced by about half in patients with moderate hepatic dysfunction (Child-Pugh Class B).

6 Antivirals

Ritonavir

Brand Name	Norvir Tablets 100 mg, Norvir Oral Solution 8%, Norvir Soft Capsules 100 mg (Abbott Japan Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Hypersensitivity**: Hypersensitivity symptoms including anaphylaxis, urticaria, skin eruption, bronchospasm, and angioedema, may occur. **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome)**: Toxic epidermal necrolysis or oculomucocutaneous syndrome may occur.

(2) Medical Devices

This section presents details of revisions to the Precautions section of package inserts and brand names of medical devices that have been revised in accordance with the Notification dated February 29, 2012.

1 **Radiation Therapy Equipment** (X-ray/CT combined linear accelerator system, X-ray/CT combined particle radiotherapy, Living tissue radiotherapy system, Linear accelerator system, Stereotactic radiotherapy accelerator system, Stereotactic radiotherapy radionuclide system, Non-linear accelerator system, Particle radiotherapy equipment)

Brand Name	ONCOR Impression (Siemens Japan K.K.), Particle Beam Treatment System (Carbon and Proton Type) (Mitsubishi Electric Corporation), ONCOR high-energy system ONCR-K (Toshiba Medical Systems Corporation), Proton Therapy System (Sumitomo Heavy Industries, Ltd.), CyberKnife II (Accuray Japan K.K.), Novalis Shaped Beam Surgery System (Brainlab), Mobetron (Chiyoda Technol Corporation), CLINAC 600C Medical Linear Accelerator (Varian Medical Systems K.K.), MHI-TM2000 Linear Accelerator System (Mitsubishi Heavy Industries, Ltd.), Precise Treatment System (Elekta K.K.), Hi-ART System (Hitachi Medical Corporation), PROBEAT PROTON BEAM THERAPY SYSTEM (Hitachi, Ltd.)

Important Precautions

Radiation (electromagnetic wave or particle beam) therapy with this device may affect medical electronic devices (mechanical ventilator, transfusion pump, electrocardiogram monitor, pulse oximeter, etc.) that are brought into the treatment room. (Refer to the Interactions section)

Interactions (precautions for concomitant use)

Name etc. of medical device	Clinical symptoms and measures to be taken	Mechanism and risk factors
Medical electronic devices (mechanical ventilator, transfusion pump, electrocardiogram monitor, pulse oximeter, etc.)	• When these devices are brought into the radiation treatment room, malfunction may occur. • When these devices are brought into the treatment room by necessity, the operating status should be monitored, and appropriate emergency measures should be prepared for malfunctions, etc.	Radiation (electromagnetic wave or particle beam) may affect the circuits of medical electronic devices.

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 March 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Levobupivacaine Hydrochloride POPSCAINE 0.5% inj. 50 mg/10 mL, POPSCAINE 0.5% inj. syringe 50 mg/10 mL	Maruishi Pharmaceutical Co., Ltd.	September 7, 2011
Vorinostat ZOLINZA Capsules 100 mg	MSD K.K.	September 14, 2011
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg	AstraZeneca K.K.	September 15, 2011
Landiolol Hydrochloride COREBETA for Intravenous 12.5 mg	Ono Pharmaceutical Co., Ltd.	September 15, 2011
Linagliptin Trazenta Tablets 5 mg	Nippon Boehringer Ingelheim Co., Ltd.	September 15, 2011
Golimumab (Genetical Recombination) Simponi Subcutaneous Injection Syringe 50 mg	Janssen Pharmaceutical K.K.	September 16, 2011
Minodronic Acid Hydrate Bonoteo Tablets 50 mg	Astellas Pharma Inc.	September 16, 2011
Minodronic Acid Hydrate RECALBON Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	September 16, 2011
Mirabegron Betanis Tablets 25 mg, 50 mg	Astellas Pharma Inc.	September 16, 2011
Alogliptin Benzoate/Pioglitazone Hydrochloride LIOVEL Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	September 20, 2011
Indacaterol Maleate onbrez inhalation capsules 150 µg	Novartis Pharma K.K.	September 20, 2011
Daptomycin CUBICIN IV 350 mg	MSD K.K.	September 22, 2011
Itraconazole ITRIZOLE Oral Solution 1%*[1]	Janssen Pharmaceutical K.K.	September 26, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 µg, 180 µg*[2]	Chugai Pharmaceutical Co., Ltd.	September 26, 2011

Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*[3]	Chugai Pharmaceutical Co., Ltd.	September 26, 2011
Olopatadine Hydrochloride ALLELOCK Granules 0.5%*[4]	Kyowa Hakko Kirin Co., Ltd.	November 15, 2011
Live Attenuated Human Rotavirus Vaccine, Oral Rotarix Oral Solution	GlaxoSmithKline K.K.	November 21, 2011
Imiquimod BESELNA CREAM 5%*[5]	Mochida Pharmaceutical Co., Ltd.	November 25, 2011
Teriparatide Acetate Teribone Inj. 56.5 μg	Asahi Kasei Pharma Corporation	November 25, 2011
Fulvestrant FASLODEX intramuscular injection 250 mg	AstraZeneca K.K.	November 25, 2011
Modafinil MODIODAL Tablets 100 mg*[6]	Alfresa Pharma Corporation	November 25, 2011
Telaprevir TELAVIC Tablets 250 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride IMUSERA Capsules 0.5 mg	Mitsubishi Tanabe Pharma Corporation	November 28, 2011
Fingolimod Hydrochloride GILENYA Capsules 0.5 mg	Novartis Pharma K.K.	November 28, 2011
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg	Pfizer Japan Inc.	December 7, 2011
Canakinumab (Genetical Recombination) ILARIS for s.c. injection 150 mg	Novartis Pharma K.K.	December 7, 2011
Fosaprepitant Meglumine PROEMEND for Intravenous Infusion 150 mg	Ono Pharmaceutical Co., Ltd.	December 9, 2011
Everolimus AFINITOR tablets 5 mg*[7]	Novartis Pharma K.K.	December 22, 2011
Everolimus Certican Tablets 0.25 mg, 0.5 mg, 0.75 mg*[8]	Novartis Pharma K.K.	December 22, 2011
Pranlukast Hydrate ONON drysyrup 10%*[9]	Ono Pharmaceutical Co., Ltd.	December 22, 2011
Peginterferon Alfa-2b (Genetical Recombination) PEGINTRON Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL*[10]	MSD K.K.	December 22, 2011
Ribavirin REBETOL Capsules 200 mg*[11]	MSD K.K.	December 22, 2011
Rebamipide Mucosta ophthalmic suspension UD 2%	Otsuka Pharmaceutical Co., Ltd.	January 5, 2012
Human Fibrinogen/Thrombin Fraction TachoSil Tissue Sealing sheet	CSL Behring K.K.	January 17, 2012
Fosphenytoin Sodium Hydrate Fostoin 750 mg for Injection	Nobelpharma Co., Ltd.	January 17, 2012
Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, 24 mg*[12]	Otsuka Pharmaceutical Co., Ltd.	January 18, 2012

Duloxetine Hydrochloride Cymbalta Capsules 20 mg, 30 mg*[13]	Shionogi & Co., Ltd.	February 22, 2012

*1 Additional indications for “treatment of patients with fungal infection caused by *Aspergillus*, *Cryptococcus*, *Blastomyces*, or *Histoplasma* (fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, blastomycosis, histoplasmosis)”, “treatment of patients with febrile neutropenia of suspected fungal infection”, and “prophylaxis of deep mycosis in patients with haematological malignancy possibly associated with neutropenia or patients who underwent hematopoietic stem cell transplantation”

*2 An additional indication for “improvement of viraemia in chronic active hepatitis B

*3 An additional indication for “treatment of patients with inoperable or recurrent breast cancer”

*4 An additional administration for “pediatrics (aged 2 to under age of 7)”

*5 An additional indication for “treatment of patients with actinic keratosis (limited to face or baldness)”

*6 An additional indication for “treatment of excessive daytime sleepiness in patients with obstructive sleep apnoea syndrome who receive treatment for airway obstruction with continuous positive airway pressure (CPAP) therapy, etc.”

*7 An additional indication for “treatment of patients with pancreatic neuroendocrine tumour”

*8 An additional indication for “prophylaxis rejection in renal transplantation”

*9 An additional indication for “treatment of patients with allergic rhinitis”

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

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

*12 An additional indication for “improvement of manic symptoms in patients with bipolar disorder”

*13 An additional indication for “treatment of pain in patients with diabetic neuropathy”