Pharmaceuticals and Medical Devices Safety Information

No. 275 December 2010

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

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

Pharmaceuticals and Medical Devices Safety Information

No. 275 December 2010

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

[Outline of Information]

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

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

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

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

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

Abbreviations

ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
ARDS	Acute respiratory distress syndrome
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
Al-P	Alkaline phosphatase
BF	Bronchofiberscopy
BOOP	Bronchiolitis obliterans organizing pneumonia
CD	Cluster of differentiation
CK(CPK)	Creatine kinase (Creatine phosphokinase)
CPR	C-peptide reactivity
CRP	C-reactive protein
CT	Computed tomography
Ch-E	Cholinesterase
DPP-4	Dipeptidyl peptidase-4
DLST	Drug lymphocyte stimulation test
DNA	Deoxyribonucleic acid
EPPV	Early Post-marketing Phase Vigilance
γ-GTP	gamma-glutamyl transpeptidase
GAD	Glutamic acid decarboxylase
GLP-1	Glucagon-like peptide-1
HA	Hepatitis A
HBs	Hepatitis B surface
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HbA1c	Hemoglobin A1c
IP	Interstitial pneumonia
IgM	Immunoglobulin M
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MAT	Microscopic agglutination test
$PaCO_2$	Arterial carbon Carbon dioxide partial pressure
PaO_2	Arterial oxygen Oxygen partial pressure
RA	Rheumatoid arthritis
S.I.	Stimulation index
SMBG	Self-monitoring of blood glucose
SP-D	Surfactant protein D
SS-A/Ro	Sjögren's syndrome A/Ro
SS-B/La	Sjögren's syndrome B/La
SU	Sulfonylurea
SpO_2	Oxygen saturation
TBLB	Transbronchial lung biopsy
WBC	White blood cell count

1

Safety Measures for Use of the Antidiabetic Drugs with New Action Mechanisms (DPP-4 inhibitors and GLP-1 receptor agonists)

	Active ingredient	Brand Name (name of company)
Active ingredient Brand Name (name of company)	[1] Sitagliptin Phosphate Hydrate	[1] GLACTIV Tablets 25 mg, 50 mg, 100 mg (Ono Pharmaceutical Co., Ltd.) JANUVIA Tablets 25mg, 50 mg, 100 mg (MSD K.K.)
	[2] Vildagliptin	[2] Equa Tablets 50 mg (Novartis Pharma K.K.)
	[3] Alogliptin Benzoate	[3] NESINA Tablets 6.25 mg, 12.5 mg, 25 mg (Takeda Pharmaceutical Company Limited)
	[4] Liraglutide (Genetical Recombination)	[4] ViCTOZA Subcutaneous Injection 18mg (Novo Nordisk Pharma Ltd.)
	[5] Exenatide	[5] Byetta Subcutaneous Injection 5 μg Pen 300, 10 μg Pen 300 (Eli Lilly Japan K.K.)
Therapeutic Category	Antidiabetic agents, Hormones-Miscellaneous	
Indications	[1] Sitagliptin Phosphate Hydrate Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies (3) Thiazolidine along with diet and exercise therapies (4) Biguanide along with diet and exercise therapies [2] Vildagliptin Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies [3] Alogliptin Benzoate Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments: (1) Diet and exercise therapies alone (2) α-glucosidase inhibitor along with diet and exercise therapies (3) Thiazolidinedione along with diet and exercise therapies [4] Liraglutide (Genetical Recombination) Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies	

	[5] Exenatide Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to sulfonylurea (including concomitant use with biguanide or thiazolidinedione) along with diet and exercise therapies

1. Introduction

Antidiabetic drugs with new action mechanisms which use incretin for glycaemic control have recently appeared in the market.

Incretin is a gastrointestinal hormone which stimulates the insulin secretion depending on the blood glucose level. Dipeptidyl peptidase-4 (DPP-4) inhibitors, which inhibit DPP-4 inactivating incretin, are intended to treat type 2 diabetes mellitus by increasing the endogenous active incretin level and controlling the blood glucose. As of December 2010, sitagliptin phosphate hydrate, vildagliptin, and alogliptin benzoate have been approved in Japan. These drugs were launched in December 2009, April 2010, and June 2010, respectively.

Glucagon-like peptide-1 (GLP-1) receptor agonists are also intended to treat type 2 diabetes mellitus, by binding to the GLP-1 receptor to promote insulin secretion in response to the increase of blood glucose. As of December 2010, liraglutide (genetical recombination) and exenatide have been approved. The former was launched in June 2010 while the latter was approved in October 2010 and will be on the market shortly.

DPP-4 inhibitors and GLP-1 receptor agonists are antidiabetic drugs with new action mechanisms. Additional safety measures for the use of these drugs have been taken based on the information including adverse reactions reported in the EPPV in Japan. Details of the safety measures are described below.

2. Possible hypoglycaemia associated with concomitant use of DPP-4 inhibitors and sulfonylureas

The MHLW has issued an alert about possible hypoglycaemia associated with antidiabetics on package inserts. These package inserts have included information on careful administration of these drugs to patients with high risk of hypoglycaemia, communication with patients about hypoglycaemia, treatment at the time of onset of hypoglycaemia, and precautions against concomitant use of multiple antidiabetic drugs in the sections of "Careful Administration," "Important Precautions," "Drug Interactions," and "Clinically Significant Adverse Reactions" under Precautions. However, 29 cases of hypoglycaemia following administration of a DPP-4 inhibitor sitagliptin phosphate hydrate had been reported during the approximately 4 months of the EPPV conducted after the initial marketing of the drug on December 11, 2009 until April 19, 2010 (**Table 1**). Among them, causality to the drug could not be denied in 25 cases, including 8 cases in which loss of consciousness occurred after hypoglycaemia. In 21 of the 25 cases, sulfonylureas (SUs) were concomitantly used. In 8 cases, patients received the maximum dose of SU, which exceeded the maintenance dose specified in the Dosage and Administration section of the package insert.

Based on the above information and the experts' review, the MHLW required marketing authorization holders (MAHs) to revise the Precautions section in the package insert of sitagliptin phosphate hydrate in order to further alert against possible hypoglycasemia on April 27, 2010. In the sections "Careful Administration," "Important Precautions" and "Clinically Significant Adverse Reactions" of the updated package inserts, the following information was included: 1) the increased risk of hypoglycaemia especially with concomitant use of SU, 2) serious hypoglycaemia followed by loss of consciousness reported in patients treated with concomitant use of SU, and 3) dose reduction of SU to be considered when used concomitantly with sitagliptin to lower the risk of SU-induced hypoglycaemia.

Table 1 The number of hypoglycaemia cases reported as adverse reactions after administration of sitagliptin phosphate hydrate (December 11, 2009 to April 19, 2010)*

Concomitant use of SU	Number of ADR cases (number of cases for which a causality to the drug could not be denied)	Number of cases of loss of consciousness (number of cases for which a causality to the drug could not be denied)
Used	26 (23)	7 (7)
Not used (including unknown case)	2 (2)	1 (1)

* Estimated 230,000 patients used sitagliptin phosphate hydrate during the surveillance period. See Pharmaceuticals and Medical Devices Safety Information No. 269 (May 2010) for the summaries of the reported adverse reactions.

Post-marketing information on hypoglycaemia associated with other DPP-4 inhibitors was yet to be available as of April 2010: vildagliptin was only recently launched in the market and alogliptin benzoate was not launched then. However, the same alerts against possible hypoglycaemia were considered necessary. In addition, since liraglutide (genetical recombination), the GLP-1 receptor agonist was already approved then, binds to the GLP-1 receptor to promote insulin secretion, the same alerts issued for sitagliptin phosphate hydrate were also considered necessary for the concomitant use of SU. Therefore, the MHLW required MAHs to revise the Precautions of the package inserts of other DPP-4 inhibitors and GLP-1 receptor agonists on the same day. (See Pharmaceuticals and Medical Devices Safety Information No. 269 [May 2010].)

Specific revisions of the Precautions in the package inserts are described below. (The underlined parts are revised.)

Sitagliptin Phosphate Hydrate

[Careful Administration]

Patients on treatment with other agents <u>for</u> diabetes mellitus <u>(especially sulfonylureas)</u>

[Important Precautions]

When administering this drug, patients should be thoroughly informed of possible hypoglycaemia and its treatment in advance. <u>In particular, the risk of hypoglycaemia increases when this drug is used concomitantly with sulfonylureas. Dose reduction of sulfonylureas should be considered when used concomitantly with this drug to reduce the risk of sulfonylurea-induced hypoglycaemia.</u>

[Adverse Reactions (clinically significant adverse reactions)]

Hypoglycaemia: Hypoglycaemia may occur when this drug is administered in concomitant with other drugs <u>for</u> diabetes mellitus (<u>5.3% with glimepiride, 0.8% with pioglitazone, and 0.7% with metformin</u>). <u>Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated concomitantly with sulfonylureas. Dose reduction of sulfonylureas should be considered when used concomitantly with this drug.</u> Hypoglycaemia may also occur (1.0%) even if other agents <u>for</u> diabetes mellitus are not used. If symptoms of hypoglycaemia are observed, appropriate measures such as taking sugar-containing food should be taken.

Vildagliptin

[Careful Administration]

Patients on treatment with sulfonylureas

[Important Precautions]

When administering this drug, patients should be thoroughly informed of possible hypoglycaemia and its treatment in advance. In particular, the risk of hypoglycaemia may increase when this drug is used concomitantly with sulfonylureas. Dose reduction of sulfonylureas should be considered when used concomitantly with this drug to reduce the risk of sulfonylurea-induced hypoglycaemia.

[Adverse Reactions (clinically significant adverse reactions)]

Hypoglycaemia: Hypoglycaemia may occur related to administration of this drug. Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated concomitantly with other DPP-4 inhibitors and sulfonylureas. Dose reduction of sulfonylureas should be considered when used concomitantly with this drug. If symptoms of hypoglycaemia are observed, appropriate measures such as taking sugar-containing food should be taken.

Alogliptin Benzoate

[Important Precautions]

Symptoms of hypoglycaemia may occur when this drug is used concomitantly with other antidiabetics. Patients should be thoroughly informed of possible symptoms of hypoglycaemia and its treatment to raise awareness before starting concomitant use of alogliptin and other antidiabetics. Clinical efficacy and safety of concomitant use of alogliptin and sulfonylureas have not been established; however, risks of hypoglycaemia may increase with concomitant use of DPP-4 inhibitors and sulfonylureas. Dose reduction of sulfonylureas should be considered when used concomitantly with a DPP-4 inhibitor to reduce the potential risks of hypoglycaemia.

[Adverse Reactions (clinically significant adverse reactions)]

Symptoms of hypoglycaemia may occur. This drug should be administered while carefully monitoring the patient's condition. If symptoms of hypoglycaemia occur, this drug or concomitant oral antidiabetics should be temporarily discontinued, or the dose should be reduced and administered carefully. Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated with concomitant use of other DPP-4 inhibitors and sulfonylureas. If symptoms of hypoglycaemia are observed in association with administration of this drug, sucrose should be administered in general. If symptoms of hypoglycaemia are observed in concomitant use of α-glucosidase inhibitors, glucose should be administered.

Liraglutide (Genetical Recombination)

[Careful Administration]

Patients on treatment with sulfonylureas

[Important Precautions]

When administering this drug, patients should be thoroughly informed of possible hypoglycaemia and its treatment in advance. The incidence of hypoglycaemia increases when using this drug concomitantly with oral antidiabetics, compared with liraglutide monotherapy. Periodic blood glucose measurement should be conducted. In particular, the risk of hypoglycaemia may increase when this drug is used concomitantly with sulfonylureas. Dose reduction of sulfonylureas should be considered when used concomitantly with this drug to reduce the risk of sulfonylurea-induced hypoglycaemia.

[Adverse Reactions (clinically significant adverse reactions)]

Hypoglycaemia: Hypoglycaemia and its symptoms (e.g, feelings of weakness, malaise, severe hunger, cold sweat, facial pallor, palpitations, tremor, headache, dizziness, queasy, paraesthesia) may occur. The incidences of these symptoms especially increase when this drug is used concomitantly with oral antidiabetics. If symptoms of hypoglycaemia occur, this drug or concomitant oral antidiabetics

should be temporarily discontinued, or the dose should be reduced and administered carefully.Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated in concomitant use of other DPP-4 inhibitors and sulfonylureas. Dose reduction of sulfonylureas should be considered when used concomitantly with this drug.
If symptoms of hypoglycaemia are observed, sucrose should be administered in general. If symptoms of hypoglycaemia are observed in concomitant use of α-glucosidase inhibitors, glucose should be administered.

3. Possible diabetic ketoacidosis and hyperglycaemia after switching from insulin to GLP-1 receptor agonists

Liraglutide (genetical recombination) is an incretin analogue that binds to the GLP-1 receptor to promote insulin secretion and decrease the blood glucose. The drug is therefore contraindicated for patients with type 1 diabetics lacking insulin secretion and should be carefully administered to patients with type 2 diabetics requiring insulin therapy. Two fatal cases of diabetic ketoacidosis associated with liraglutide (genetical recombination) have been reported during the EPPV conducted during the approximately 3 months after the initial marketing on June 11, 2010 until September 24, 2010. Since insulin had been switched to liraglutide (genetical recombination) in both cases, the MHLW required MAHs to immediately provide medical institutions with information to ensure proper use of the drug, specifically, not to switch insulin to liraglutide (genetical recombination) in patients with type 1 diabetics or type 2 diabetics requiring insulin therapy.

However, similar adverse reactions have been reported after the provision of the information: 4 cases of diabetic ketoacidosis (2 fatal cases) and 16 cases of hyperglycaemia (**Table 2**). In 17 of the 20 cases, the events occurred after insulin was switched to liraglutide (genetical recombination).

Table 2 The number of diabetic ketoacidosis and hyperglycaemia cases reported as adverse reactions after administration of liraglutide (genetical recombination) (June 11 to October 7, 2010)*

Adverse reactions	Number of ADR cases (number of fatal cases)	Number of cases in which insulin was switched to liraglutide (genetical recombination) (number of cases for which a causality to the drug could not be denied**)
Diabetic ketoacidosis	4 (2)	3 (3)
Hyperglycaemia	16 (0)	14 (14)

* Estimated 9,000 patients used liraglutide (genetical recombination) during the surveillance period.
** Causal relationship between "switching from insulin to liraglutide (genetical recombination)" and "occurrence of diabetic ketoacidosis or hyperglycaemia."

Based on the above information and the experts' review, the MHLW required MAHs to revise "Important Precautions" under Precautions in the package insert on October 12, 2010. Specifically, the following descriptions were added.

(1) Liraglutide (genetical recombination) is not an alternative to insulin.
(2) Use of liraglutide (genetical recombination) should be determined based on the patient's insulin dependence.
(3) Sudden hyperglycaemia and diabetic ketoacidosis occurred in insulin-dependent patients after switching from insulin to liraglutide (genetical recombination).

The MHLW required MAHs to immediately inform medical institutions of the package insert revision and provide them with information to ensure proper use of the drug, specifically, not to switch

insulin to liraglutide (genetical recombination) in insulin-dependent patients and, if liraglutide was already switched from insulin, to provide necessary medical care, e.g., glycaemic control monitoring, to patients who may need to go back to insulin.

As for exenatide, a GLP-1 receptor agonist approved on October 27, 2010, the alert against switching from insulin will also be included in the package insert at the time of launch of the product.

Specific revisions of the Precautions in the package inserts are described below. (The underlined parts are revised.)

Liraglutide (Genetical Recombination)

[Important Precautions]

<u>This drug is not an alternative to insulin. Use of this drug should be determined based on the patient's insulin dependence. Sudden hyperglycaemia and diabetic ketoacidosis have been reported in insulin-dependent patients after switching from insulin to this drug.</u>

4. Summary of fatal cases of diabetic ketoacidosis after switching from insulin to liraglutide (genetical recombination)

<Liraglutide (Genetical Recombination)>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Diabetes mellitus (chronic renal failure, diabetic neuropathy in the lower extremities, hypertension)	0.3 mg for 1 day	**Diabetic ketoacidosis** Approximately 18 years before administration: The patient was diagnosed with diabetes mellitus. Approximately 12 years before administration: Treatment with insulin was started. Approximately 2 years before administration: Dialysis was started. Dialysis was performed at 3 times per week. Glycaemic control was poor despite insulin therapy. Insulin aspart (genetical recombination) 18 U/day and insulin glargine (genetical recombination) 8 U/day were administered. 2.5 months before administration: HbA_{1c} 10.3% 1.5 months before administration: HbA_{1c} 8.0% Day 1 of administration: Dialysis was performed. Administration of insulin was discontinued, and treatment with liraglutide 0.3 mg was started after the dialysis session. Day 2 of administration (day of discontinuation): The self-monitoring of blood glucose (SMBG) showed high blood glucose in the morning and the patient repeated vomiting. However, he did not visit the hospital. The patient lost consciousness and was brought to the hospital by ambulance in the evening. Blood pressure was 40 mmHg. Saline 500 mL + sodium bicarbonate 20 mL × 2A was administered followed by saline 500 mL + sodium bicarbonate 20 mL × 2A + adrenaline 1 mg. The patient was endotracheally intubated and taken to the university hospital by helicopter because of blood glucose of 700 mg/dL or more and potassium of 7 mEq/L or more. The patient was diagnosed with diabetic ketoacidosis based on blood glucose 1450 mg/dL and pH 7.092 at the university hospital.

				Transfusion was started followed by bolus injection of rapid-acting human insulin (genetical recombination) 10 U and continuous IV infusion at 5 U/hour. 1 day after discontinuation: The blood test showed blood glucose 200 mg/dL, pH 7.450, and ketone body absent. Ketoacidosis improved. Blood C-peptide reactivity (CPR) 0.1 ng/mL, anti-glutamic acid decarboxylase (anti-GAD) antibody 9.4 U/mL. Dyspnea, cough, and pyrexia of 38.6 °C developed. SpO_2 decreased. The chest CT showed a significant infiltrative shadow in the lower left lung. Pneumonia was suspected. 2 days after discontinuation: SpO_2 decreased. The chest X-ray and laboratory tests showed an aggaravation of the chest shadow. The death of the patient was confirmed.
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Type 2 diabetes mellitus (hypertension, duodenal ulcer, dyslipidaemia, chronic arterial occlusion in the lower extremity, diabetic simple retinopathy)	0.3 mg for 1 day	**Diabetic ketoacidosis** The patient weighed 104 kg 3 months before starting the treatment (had weighed 106 kg at maximum). The patient had once discontinued the treatment at an early stage. HbA_{1c} was 11.0% immediately before the treatment. 1 day before administration: The patient was admitted to a hospital for glycaemic control in type 2 diabetes mellitus. The oral medications included metformin hydrochloride (750 mg/day), pioglitazone (45 mg/day), voglibose (0.6 mg/day), insulin human (genetical recombination) preparation (30R Injection) 48 U/day. Urinary acetone (-), body weight 98.1 kg Day 1 of administration: Administration of metformin hydrochloride, pioglitazone, voglibose and insulin human (genetical recombination) preparation (30R Injection) was all discontinued. Treatment with liraglutide 0.3 mg and glimepiride 4 mg/day were started. Fasting blood CPR was 0.03 ng/mL. Liraglutide was administered after breakfast. Blood glucose was 500 mg/dL or more before lunch and before dinner. Day 2 of administration: The patient vomited around noon. Ketoacidosis was suspected based on blood glucose 992 mg/dL and urinary acetone (3+). Saline transfusion and continuous infusion of insulin were started. 3 days after administration (day of discontinuation): The patient was found in cardio-respiratory arrest late at night. Despite resuscitation, the death of the patient was confirmed in the morning.
	Concomitant medications: glimepiride, amlodipine besilate, valsartan, imidapril hydrochloride, aspirin			

5. Closing comments

An independent expert committee, called the "Committee for Proper Use of Incretins (GLP-1 Receptor Agonists and DPP-4 Inhibitors) (the former Committee of Proper Use of Incretin and Sulfonylureas)," issued a recommendation concerning precautions for possible hypoglycaemia associated with concomitant use of a DPP-4 inhibitors and SU on the websites of the Japan Association for Diabetes Education and Care and the Japan Diabetes Society in April 2010 (http://www.nittokyo.or.jp/kinkyu_incretin100408m.html) (only available in Japanese language). The recommendation was updated in October 2010 to include advice to determine the use of liraglutide (genetical recombination) based on an assessment of the insulin-treated patient to see whether he/she is insulin-dependent or not because liraglutide (genetical recombination) is not an alternative to insulin.

DPP-4 inhibitors and GLP-1 receptor agonists are drug products with new action mechanisms. New evidence will be further collected and evaluated in cooperation with the MAHs and relevant associations. Up-to-date information will be provided to healthcare professionals, patients and family members in an appropriate and effective manner as necessary.

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 package inserts of drugs that have been revised in accordance with the Notification dated October 26, 2010.

[Brand name]: Major product names are showed.

1 Keigairengyoto, Nijutsuto

Brand Name (name of company)	**Keigairengyoto** TSUMURA Keigairengyoto Extract Granules for Ethical Use (Tsumura & Co.) **Nijutsuto** TSUMURA Nijutsuto Extract Granules for Ethical Use (Tsumura & Co.)
Therapeutic Category	Kampo medicines
Indications	**Keigairengyoto** Empyema, chronic rhinitis, chronic tonsillitis, acne **Nijutsuto** Frozen shoulder

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia: If pyrexia, cough, dyspnoea or abnormal chest sound are observed, administration of this drug should be discontinued, examinations including chest X-ray and chest CT scan should be performed, and appropriate measures including administration of corticosteroids should be taken.

<Reference Information>

Keigairengyoto
The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 2007 to September 2010)
- Interstitial pneumonia: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs: approximately 22,000 (for FY 2009)
Marketed in Japan in: October 1986

Nijutsuto
The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 2007 to September 2010)
- Interstitial pneumonia: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs: approximately 8,100 (for FY 2009)
Marketed in Japan in: October 1986

Case Summary
<Keigairengyoto>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Unknown (unknown)	5.0 g for 34 days	**Interstitial pneumonia** Day 34 of administration (day of discontinuation): The patient developed pyrexia and cough. She visited a nearby hospital and received a prescription of acetaminophen, dextromethorphan hydrobromide hydrate and L-carbocisteine. Her condition was followed-up, but her symptoms were aggravated. 5 days after discontinuation: The patient visited the hospital again. Chest X-ray and blood tests were performed. 6 days after discontinuation: The patient visited the emergency outpatient department in the evening. Infiltrative shadows in both lungs, SpO_2 80% (room air); the patient was admitted to the hospital for treatment. The chest CT also showed diffuse ground-glass opacities and interlobular septal thickening. Acute respiratory distress syndrome (ARDS), carinii pneumonia, drug-induced pneumonia, and acute exacerbation of interstitial pneumonia (IP) were suspected. Administration of antibiotics was started. Administration of steroids was withheld because bronchofiberscopy (BF) was scheduled for the next day. 7 days after discontinuation: Before dawn, the respiratory condition worsened. Steroid pulse therapy (methylprednisolone sodium succinate 1 g × 3) was performed. The respiratory condition improved. 14 days after discontinuation: Prednisolone 30 mg was administered for 6 days. 18 days after discontinuation: Oxygen therapy was discontinued. Bronchoscopy showed decreased CD4/CD8 ratio. Transbronchial lung biopsy (TBLB) showed bronchiolitis obliterans organizing pneumonia (BOOP)-like finding. 27 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: acetaminophen, dextromethorphan hydrobromide hydrate, L-carbocisteine			

Laboratory examination

	6 days after discontinuation	7 days after discontinuation	13 days after discontinuation	22 days after discontinuation
WBC (/mm^3)	12600	11600	6600	7100
LDH (IU/L)	577	500	245	210
KL-6 (U/mL)	-	342	-	-
SP-D (ng/mL)	-	110	-	-
CRP (mg/dL)	27.4	-	-	-

Immune serum test

	6 days after discontinuation	7 days after discontinuation
Antinuclear antibody	Negative	-
RA test	Negative	-
Anti-DNA antibody	Negative	-
Anti-SS-A/Ro antibody	-	Negative
Anti-SS-B/La antibody	-	Negative

Blood gas test

	7 days after discontinuation	26 days after discontinuation
$PaCO_2$ (torr)	28	41
PaO_2 (torr)	68	101
HCO_3 (mEq/L)	17	27.4

<Nijutsuto>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Pain in joint involving shoulder region (none)	7.5 g for 178 days	**Drug-induced lung disorders** Day 1 of administration: The patient started receiving nijutsuto for treatment of shoulder muscle stiffness. Approximately 3 months after administration: The patient had a cough and visited a nearby hospital. An abnormal chest shadow was found; his clinical course was followed. Day 178 of administration (day of discontinuation): The patient was referred to this hospital for treatment of exacerbated dyspnoea. He was admitted to the hospital on the same day, and administration of nijutsuto was discontinued. 15 days after discontinuation: The symptoms gradually improved. Oral administration of steroids was started because the recovery was slow. 35 days after discontinuation: The patient was discharged from the hospital. 147 days after discontinuation: No recurrence was confirmed after administration of steroids was discontinued.
	Concomitant medications: none			

Laboratory examination

	Day 178 of administration (Day of discontinuation)	14 days after discontinuation	34 days after discontinuation	49 days after administration	77 days after discontinuation
KL-6 (U/mL)	8502	5254	2333	1205	669

Blood gas test

	Day 178 of administration (Day of discontinuation)	49 days after discontinuation
pH	7.461	7.434
$PaCO_2$ (torr)	29.0	34.6
PaO_2 (torr)	66.1	83.8
HCO_3^- (mEq/L)	20.3	22.7

2 Ryutanshakanto

Brand Name (name of company)	TSUMURA Ryutanshakanto Extract Granules for Ethical Use (Tsumura & Co.) Kotaro Ryutanshakanto Extract Fine Granules (Kotaro Pharmaceutical Co., Ltd.) Sanwa Ryutanshakanto Extract Fine Granules (Sanwa Shoyaku Co., Ltd.) JUNKOU Ryutanshakanto Extract Fine Granules for Ethical Use (Kowa Yakutsu Co., Ltd.)
Therapeutic Category	Traditional Chinese medicinesKampo medicines
Indications	(TSUMURA Ryutanshakanto Extract Granules for Ethical Use, KTS Ryutanshakanto Extract Granules, Following symptoms of those patients with a comparatively strong constitution whose muscles in the lower abdomen are likely to become tense: Micturition pain, and feeling of residual urine, turbid urine, and leukorrhea (Kotaro Ryutanshakanto Extract Fine Granule) Following symptoms of those patients with a comparatively strong constitution: Urethritis, bladder catarrh, vaginitis, genital eczema, leukorrhea, genital itching/pain, endometritis (Sanwa Ryutanshakanto Extract Fine Granule) Following symptoms of those patients with a comparatively strong constitution who have inflammation in the bladder, urethra or uterus and micturition pain or dysuria: Urethritis, bladder catarrh, vaginitis, fluor, genital eczema, bartholinitis, genital pruritus, endometritis, and orchitis (JUNKOU Ryutanshakanto Extract Fine Granules for Ethical Use) Following symptoms of those patients with a comparatively strong constitution whose muscles in the lower abdomen are likely to become tense: Micturition pain, feeling of residual urine, turbid urine, and leukorrhea

≪PRECAUTIONS (underlined parts are revised)≫

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic dysfunction, jaundice: Hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), Al-P and γ-GTP 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.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 2007 to September 2010)

- Hepatic dysfunction, jaundice: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by the MAHs: approximately 9,900 (for FY 2009)
Marketed in Japan in: October 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Feeling of residual urine (hypertension, hyperlipidaemia, cystitis, depression)	7.5 g for 32 days	**Drug-induced hepatitis** 6 years before administration: The patient had been treated for hypertension at another hospital on an outpatient basis. Administration of olmesartan medoxomil, lorazepam, fluvoxamine maleate, and pitavastatin calcium was started. Day 1 of administration: The patient visited the reporting hospital for morning hypertension and malaise. She had cystitis symptoms. Administration of olmesartan medoxomil 20 mg, pitavastatin calcium 1 mg, and ryutanshakanto 7.5 g was started. Fluvoxamine maleate and lorazepam were discontinued. Day 5 of administration: Fluvoxamine maleate 25 mg and lorazepam 0.5 mg × 2 were added due to insomnia. Day 26 of administration: The patient became able to sleep with lorazepam 0.5 mg alone. Saikokaryukotsuboreito 7.5 g was added. Day 31 of administration: The patient visited the hospital for stomach discomfort and red urine. Day 32 of administration (day of discontinuation): The medications were discontinued. Administration of inchingoreisan 7.5 g was started. 1 day after discontinuation: No change was seen in the patient's condition. 3 days after discontinuation: Malaise persisted but the patient was able to eat rice porridge. 4 days after discontinuation: The patient started to have an appetite. Inchingoreisan was switched to shishihakuhito 6.0 g. 6 days after discontinuation: The patient started to feel better. 8 days after discontinuation: The subjective symptoms were improving. The patient was referred to another hospital for inpatient care because her transaminase level had not improved. 14 days after discontinuation: Transaminase level was improving. 22 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: saikokaryukotsuboreito, olmesartan medoxomil, pitavastatin calcium, fluvoxamine maleate, lorazepam			

Laboratory examination

	Day 1 of administration	Day 31 of administration	Day 32 of administration (Day of discontinuation)	3 days after discontinuation	4 days after discontinuation	7 days after discontinuation	9 days after discontinuation	11 days after discontinuation	14 days after discontinuation	20 days after discontinuation
AST (GOT) (IU/L)	22	669	821	944	961	1057	906	692	457	147
ALT (GPT) (IU/L)	23	816	892	1084	1069	1181	1122	969	719	335
Al-P (IU/L)	326	2208	2166	2091	2084	1835	1520	1318	1054	822

γ-GTP (IU/L)	39	359	338	298	282	226	187	-	111	96
Total bilirubin (mg/dL)	0.8	3.7	4.2	4.8	4.5	6.5	6.7	4.9	2.6	1.6
Direct bilirubin (mg/dL)	0.2	2.9	3.3	-	3.5	5.5	5.0	3.7	2.0	1.2
LDH (IU/L)	200	388	431	436	454	451	387	362	253	184
Ch-E (IU/L)	374	296	296	322	326	315	349	336	303	370

Viral markers

	4 days after discontinuation
IgM HA antibody	0.2 (-)
Quantitative HBs antigen-MAT	LT 8
HCV antibody (3rd)	0.053 (-)

Drug lymphocyte situmulation test (DLST)

	24 days after discontinuation
Ryutanshakanto	Positive (S.I.: 15.6)
Saikokaryukotsuboreito	Positive (S.I.: 32.8)

3

Revision of Precautions (No. 221)

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 October 26, 2010 (excluding those presented in "2. Important Safety Information" of this Bulletin).

[Brand name]: Major product names are showed.

1 < Antihypertensives >

Aliskiren Fumarate

[Brand Name]	Rasilez Tablets 150 mg (Novartis Pharma K.K.)
[Contraindications]	Patients on treatment with itraconazole or ciclosporin
[Interactions (contraindications for concomitant use)]	Itraconazole

2 < Digestive organ agents-Miscellaneous >

Ramosetron Hydrochloride (oral dosage form 2.5 μg, 5 μg)

[Brand Name]	Irribow Tablets 2.5 μg, 5 μg (Astellas Pharma Inc.)
[Important Precautions]	Ischaemic colitis or serious constipation may occur. Patients should be instructed to consult physicians if abdominal pain, bloody stool, constipation or hard faeces are observed.
[Adverse Reactions (clinically significant adverse reactions)]	**Ischaemic colitis**: Ischaemic colitis may occur. If any symptoms of suspected ischaemic colitis, e.g., abdominal pain and bloody stool, are observed, appropriate measures such as discontinuing administration of this drug should be taken.

3 < Urogenital and anal organ agents-Miscellaneous >

Imidafenacin

[Brand Name]	URITOS Tablets 0.1 mg (Kyorin Pharmaceutical Co., Ltd.), STAYBLA Tablets 0.1 mg (Ono Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Urinary retention**: Urinary retention may occur. Patients should be carefully monitored, and if any symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

4 **< Antineoplastics-Miscellaneous, Radioactive drugs >**

Yttrium (^{90}Y) Ibritumomab Tiuxetan (Genetical Recombination) Indium (^{111}In) Ibritumomab Tiuxetan (Genetical Recombination)

[Brand Name] Zevalin yttrium injection (Bayer Yakuhin, Ltd.)
Zevalin indium injection (Bayer Yakuhin, Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Infection**: Serious infections including sepsis and pneumonia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

5 **< Antineoplastics-Miscellaneous >**

Sorafenib Tosilate

[Brand Name] Nexavar 200 mg Tablet (Bayer Yakuhin, Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Gastrointestinal perforation, gastrointestinal ulcer**: Gastrointestinal perforation or gastrointestinal ulcer may occur and some cases of gastrointestinal perforation leading to fatal outcome have been reported. If gastrointestinal perforation or gastrointestinal ulcer is suspected, appropriate measures such as discontinuing administration of this drug should be taken.
Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms (e.g., dyspnoea, angioedema, rash, decreased blood pressure) 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.
Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored, and if symptoms including myalgia, feeling of weakness, increased CK (CPK), increased blood myoglobin or urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be taken. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

6 **< Acting mainly on gram-positive bacteria >**

Vancomycin Hydrochloride (ophthalmic agent)

[Brand Name] Vancomycin Ophthalmic Ointment 1% (Toa Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Corneal disorder**: Corneal epithelium disorder including erosion may occur. Patients should be carefully monitored, and if such symptoms are observed, appropriate measures such as discontinuing administration should be taken.

7 **< Chemotherapeutics-Miscellaneous >**

Itraconazole

[Brand Name] ITRIZOLE Capsules 50, ITRIZOLE Oral Solution 1%, ITRIZOLE Injection 1% (Janssen Pharmaceutical K.K.)

[Contraindications] Patients on treatment with pimozide, quinidine, bepridil, triazolam, simvastatin, azelnidipine, nisoldipine, ergotamine, dihydroergotamine, vardenafil, eplerenone, blonanserin, sildenafil (Revatio), tadalafil (Adcirca) or aliskiren.

[Interactions (contraindications for concomitant use)] Aliskiren

8

< Over-the-counter drugs >

Keigairengyoto Nijutsuto

[Brand Name] Tsumura Kampo Keigairengyoto Extract Granule (Tsumura & Co.)
Nijutsuto "Takizawa"(Takizawa Kanpoushou)

[Consultation] If you experience any of the following symptoms after taking the product, immediately discontinue the use of the product, and show this document to your physician or pharmacist for consultation.

If the following symptoms are observed after taking this drug:

The following serious symptoms occur in rare cases. In such cases, immediately seek medical aid.

Interstitial pneumonia: Shortness of breath, dyspnoea, and pyrexia etc. may occur together with cough.

9

< Over-the-counter drugs >

Ryutanshakanto

[Brand Name] JPS Ryutanshakanto Extract Tablet N (JPS Pharmaceutical Co., Ltd.)

[Consultation] If you experience any of the following symptoms after taking the product, immediately discontinue the use of the product, and show this document to your physician or pharmacist for consultation.

If the following symptoms are observed after taking this drug:

The following serious symptoms occur in rare cases. In such cases, immediately seek medical aid.

Hepatic dysfunction: General malaise, jaundice (skin and white of the eyes become yellow) etc. may occur.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its 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 December 1, 2010)

Nonproprietary name Brand name on	Name of the marketing authorization holder	Date of EPPV initiate
Travoprost/Timolol Maleate DuoTrav Combination Ophthalmic Solution	Alcon Japan Ltd.	June 11, 2010
Dorzolamide Hydrochloride/Timolol Maleate COSOPT Ophtalmic Solution	Banyu Pharmaceutical Co., Ltd.	June 11, 2010
Eculizumab (Genetical Recombination) Soliris Intravenous Drip Infusion 300 mg	Alexion Pharmaceuticals, Inc.	June 14, 2010
Alogliptin Benzoate NESINA Tablets 6.25 mg., 12.5 mg., 25 mg.	Takeda Pharmaceutical Company Limited	June 15, 2010
Candesartan Cilexetil/Amlodipine Besilate UNISIA Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 15, 2010
Panitumumab (Genetical Recombination) Vectibix Intravenous Drip Infusion 100 mg	Takeda Pharmaceutical Company Limited	June 15, 2010
Pregabalin Lyrica Capsules 25 mg, 75 mg, 150 mg	Pfizer Japan Inc.	June 22, 2010*1 October 27, 2010*2
Fentanyl Citrate Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	June 24, 2010
Metformin Hydrochloride/Pioglitazone Hydrochloride METACT Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	July 6, 2010
Ramelteon ROZEREM Tablets 8 mg	Takeda Pharmaceutical Company Limited	July 6, 2010
Lenalidomide Hydrate Revlimid Capsules 5 mg	Celgene K.K.	July 20, 2010*3 August 20, 2010*4
Olopatadine Hydrochloride ALLELOCK Tablets 2.5, 5*5	Kyowa Hakko Kirin Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate PASIL INTRAVENOUS DRIP INFUSION 300 mg, 500 mg*6	Toyama Chemical Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate Pazucross INJECTION 300, 500*5	Mitsubishi Tanabe Pharma Corporation	July 23, 2010

Budesonide Pulmicort 100 μg Turbuhaler 112 doses, Pulmicort 200 μg Turbuhaler 56, 112 doses*[7]	AstraZeneca K.K.	July 23, 2010
Lansoprazole Takepron capsules 15, Takepron OD Tablets 15	Takeda Pharmaceutical Company Limited	July 23, 2010*[8] August 20, 2010*[9]
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, NEPS 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
Pazufloxacin Mesilate PASIL INTRAVENOUS DRIP INFUSION 1000 mg	Toyama Chemical Co., Ltd.	October 13, 2010
Pazufloxacin Mesilate Pazucross INJECTION 1000 mg	Mitsubishi Tanabe Pharma Corporation	October 13, 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*[10]	GlaxoSmithKline K.K.	October 27, 2010
Adalimumab (Genetical Recombination) HUMIRA Subcutaneous Injection 40 mg Syringe 0.8 mL*[11]	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*[12]	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*[7]	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*13	Benesis Corporation	October 27, 2010
Drospirenone/Ethinylestradiol YAZ Combination Tablet	Bayer Yakuhin, Ltd.	November 16, 2010

*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 administration for “pediatrics (aged 7 and older)”

*6 An additional indication for “treatment of patients with sepsis, applicable microorganism; *Streptococcus pneumonia*”

*7 An additional administration for “pediatrics”

*8 An additional indication for “treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of low-dose aspirin”

*9 An additional indication for “treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of non-steroidal anti-inflammatory drugs”

*10 An additional indication for "treatment of patients with upper limb spasms or lower limb spasms"

*11 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)"

*12 An additional indication for "treatment of manic symptoms in patients with bipolar disorder"

*13 An additional indication for “improvement of muscular weakness associated with polymyositis or dermatomyositis (limited to patients who are not adequately responsive to steroids)”