Pharmaceuticals and Medical Devices Safety Information

No. 236 May 2007

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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. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

Published by
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This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

Pharmaceuticals and Medical Devices Safety Information

No. 236 May 2007

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

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, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

1

Post-marketing safety measures for ticlopidine hydrochloride products and TAXUS Express2 Stent

MHLW has called for the proper use of ticlopidine hydrochloride in the Pharmaceuticals and Medical Devices Safety Information No. 156 (August 1999) and "Dear Healthcare Professional Letters" (June 30, 1999, July 23, 2002). In light of the approval of TAXUS Express2 Stent (name of marketing authorisation holder: Boston Scientific Japan K.K.), MHLW has called for reminding healthcare providers of the further alert.

As for proper use of ticlopidine hydrochloride products and TAXUS Express2 Stent, MHLW has notified related companies to ensure the proper use, and have asked prefectural and city governments, related academic societies and organizations for cooperation and dissemination of the information as a measure of safety for coronary stent treatment using this stent under PFSB/ELD notification No. 0420003-0420007 and PFSB/SD notification No. 0420001-0420005 dated April 20, 2007. This section presents the contents of the notifications etc.

1. Summary

Drug-eluting coronary stent, "TAXUS Express2 Stent", (approval No. 21900BZX00340000) was approved in March 2007. It is the second drug-eluting coronary stent approved in Japan. Antiplatelet therapy is required for stent treatment.

Aspirin products and ticlopidine hydrochloride products are the drugs used in standard antiplatelet therapy for TAXUS Express2 Stent. For it was recommended that ticlopidine hydrochloride products should be administered based on the results of clinical trials etc. for at least 6 months after the operation.

MHLW has been requested healthcare providers, etc. to ensure the proper use for the prevention of serious adverse reactions including thrombotic thrombocytopenic purpura (TTP) and agranulocytosis that may be caused by ticlopidine hydrochloride products administered in conjunction with drug-eluting coronary stent placement. In response to marketing of the stent, MHLW is also notifying the related companies to ensure the proper use and is asking the prefectural and city governments, related academic societies, and organizations for the cooperation and dissemination of information to promote the proper use.

2. Requests for proper use of ticlopidine hydrochloride products and TAXUS Express2 Stent

For the prevention of clinically significant adverse reactions including thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder associated with ticlopidine hydrochloride products, following language is described in "WARNING" section of the package insert of TAXUS Express2 Stent. MHLW would like to require proper use of ticlopidine hydrochloride products and the stent with regard to the aforementioned points.

<Warning>

1. Measures to reduce the risks

(1) This product should be used by physicians who are well-experienced in coronary angiography (CAG), PTCA, intracoronary stenting, and antiplatelet therapy and have taken the required trainings for the product.

(2) Long-term prognosis for the period exceeding 1 year after the stent placement has not been sufficiently observed in Japanese healthcare environment at this point. Compared to non-drug coated bare metal stents, the TAXUS Express2 Stent requires a longer administration period of ticlopidine hydrochloride products as antiplatelet therapy following the stent placement. Use of this stent with ticlopidine hydrochloride products increases risks of haemorrhage and serious adverse reactions. Therefore, physicians should be encouraged to carefully select appropriate patients before using this stent by balancing risks and benefits for each patient. In the selection of patients, the location of the target lesion (blood vessel), reference vessel diameter, lesion length and its characteristics, and the size of the myocardial area exposed to the risk of acute or subacute thrombosis should be considered.

(3) Before use of the TAXUS Express2 Stent, physicians should adequately advise the patients of the risks associated with the antiplatelet therapy following the stent placement as well as the characteristics of the stent (risks and benefits) and ensure that the patient is fully aware of the information given before using. Physicians should adequately instruct the patients to contact the physician if ischemic symptoms such as chest pain appear after the stent placement. In particular, physicians should inform the patient of the possible occurrence of life-threatening serious adverse reactions associated with the administration of ticlopidine hydrochloride products, and give the following instructions.

① In principle, the patient should consult a physician once every 2 weeks since periodical blood test is required for the first 2 months after the initiation of administration.

② The patient should contact a physician immediately if symptoms that suggest any adverse reactions occur.

(4) In using the TAXUS Express2 Stent, proper antiplatelet and anticoagulant therapy as well as periodical follow-up after the stent placement should be conducted. For antiplatelet therapy, in particular, premedicate the patient adequately beforehand so that full effect will be achieved at the time of stent placement.

① Indefinite aspirin therapy and a postoperative regimen of ticlopidine hydrochloride products for a period of at least 6 months are recommended for the patients with the TAXUS Express2 Stent placement. However, considerations to extend the administration period or to employ other antiplatelet therapy should be made depending on the conditions of the patients. In addition, patients should be continuously monitored even after the treatment duration is completed, and readministration should be considered if necessary.

② Safety of the TAXUS Express2 Stent with antiplatelet therapy less than 6 months has not been established. Moreover, the frequency and time of occurrence of thrombosis has not been determined in large-scale clinical studies in Japanese patients treated concurrently with the TAXUS Express2 Stent and ticlopidine hydrochloride products.

③ Antiplatelet therapy/anticoagulant therapy following the stent placement with the TAXUS Express2 Stent may result in haemorrhage/haematoma.

④ The package insert of antiplatelet drug should surely be referred for each concomitant use.

In addition, clinically significant adverse reactions such as thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder etc. may occur following administration of ticlopidine hydrochloride products. These symptoms have been reported to occur most commonly within 2 months after the initiation of administration, leading to fatal outcome in some cases. Physicians should pay adequate attention to the following points.

① For 2 months after initiating administration, physicians should be particularly alerted to the

emergence of initial symptoms of the above-mentioned adverse reactions. In principle, blood count (including differential leukocyte count) and hepatic function tests should be performed once every 2 weeks. If these adverse reactions are observed, administration should be discontinued and appropriate measures should be taken. Physicians should conduct periodical blood test during the treatment period of the product and be alerted to these adverse reactions.

② If thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and liver disorder etc. are suspected from the conditions of the patient during the administration of the product, physicians should conduct haemogram or liver function tests as necessary and take appropriate measures.

③ Physicians should prescribe the drug for 2 weeks at one time during the first 2 months after the initiation of the administration as a general rule.

(5) Coronary stent placements must only be conducted at medical institutions where emergent coronary-artery bypass can be operated expeditiously, in case life-threatening complications may occur.

2. Applicable patients

Use of TAXUS Express2 Stent (hereafter referred to as "the product") is associated with the risks related to coronary stent placement such as thrombosis (acute, subacute, tardive), vascular complications, haemorrhage etc. Patients indicated for the product should be selected carefully.

3. Outline of the instruction for companies

As a safety measure of the coronary stent treatment using TAXUS Express2 Stent, MHLW has notified the related companies to ensure the proper use.

(1) Proper use of TAXUS Express2 Stent

a) Training sessions and briefings should be held at medical offices etc. for the proper use of the stent, and distribution should be limited to the medical institutions participating in the trainings.

b) Explanatory materials with important instructions to patients, patient handbooks etc. should be prepared, and full information should be provided to the medical institutions so that appropriate explanations can be given to the patients with such materials. Additionally, it should be ensured that blood tests after stent placement is thoroughly conducted and that the medical institutions should be periodically alerted to adverse reactions related to ticlopidine hydrochloride products.

(2) Proper use of ticlopidine hydrochloride products

In collaboration with the marketing authorisation holders of ticlopidine hydrochloride products, the related companies should provide information to the medical institutions regarding the proper use of ticlopidine hydrochloride products after stent placement, including the following points.

① A postoperative regimen of ticlopidine hydrochloride products for a period of at least 6 months are recommended for the patients with the TAXUS Express2 Stent placement.

② For at least 2 months after initiating administration, physicians should be particularly alerted to the emergence of initial symptoms of the clinically significant adverse reactions such as thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder. In principle, blood counts and other clinical examinations should be conducted once every 2 weeks.

③ If the above-mentioned adverse reactions are suspected from the conditions of the patient on medication with the product, physicians should conduct haemogram or liver function tests as necessary and take appropriate measures.

(3) Safety measures at the time of patient transfer

a) When the patient is transferred to another hospital, the cooperation of the medical institution should be required to provide the necessary information to the attending physician of the new hospital.
b) Efforts should be made to obtain patient information, provided that the patient gives the consent. It should be required that the medical institution is periodically asked to cooperate for the acquisition of patient consent. If the patient is transferred to another hospital, patient information should be provided to the marketing authorisation holders of ticlopidine hydrochloride products, and information on the proper use of the drug should be provided to the new hospital.

4. Closing comments

There is a potential increased risk of adverse reactions associated with ticlopidine hydrochloride products, since longer administration of ticlopidine hydrochloride products is recommended for patients with TAXUS Express2 Stent placement. MHLW again calls for reminding all the healthcare providers of the proper use of the product. Also, if information on adverse reactions relating to ticlopidine hydrochloride products or adverse events of TAXUS Express2 Stent is obtained, it is requested to report to Safety Division, the Pharmaceutical and Food Safety Bureau in MHLW under Article 77-4-2, 2 of the Pharmaceutical Affairs Law.

2

Important Safety Information

This section presents 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 March 23, 2007.

1 Edaravone

Brand Name (name of company)	Radicut Inj. 30 mg (Mitsubishi Pharma Corporation)
Therapeutic Category	Central nervous system agents-Miscellaneous
Indications	Improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke

《**PRECAUTIONS** (underlined parts are additions)》

[Important Precautions]

After administration, aggravation of acute renal failure or renal impairment, severe liver disorder, and/or disseminated intravascular coagulation (DIC), which can be fatal, may be observed. Among these patients, serious cases concurrently developing renal impairment, hepatic impairment, and/or hematological disorders, etc., have been reported.

[Adverse Reactions (clinically significant adverse reactions)]

Fulminant hepatitis, hepatic dysfunction, jaundice: Liver function tests should be performed frequently, and patients should be monitored carefully, since severe hepatitis including fulminant hepatitis, hepatic dysfunction or jaundice with significant increase in AST (GOT), ALT (GPT), Al-P, γ-GTP, LDH, blood bilirubin, etc. may occur. This product should be discontinued and appropriate therapeutic measures should be taken when any abnormalities are found.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to February 28, 2007) (events for which a causality to the drug could not be denied)
• Hepatitis fulminant: 6 cases (of which 1 had a fatal case)
The number of patients treated with Edaravone for a year estimated by MAH (Marketing Authorisation Holder): approximately 140000 (March 2006 to February 2007)
Marketed in Japan in: June 2001

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Cerebral infarction (gastritis, dilated cardiomyopathy, ventricular extrasystoles)	30 mg 4 days	**Hepatitis fulminant, acute renal failure** On day 1 of administration: The patient was hospitalized for cerebral infarction (JCSII-10, left paresis), and the treatment with this drug etc. was initiated. On day 4 of administration (day of discontinuation): Mild hepatic function disorder was observed (AST (GOT) 98 IU/L, ALT (GPT) 67 IU/L, LDH 355 IU/L) and the administration of this drug etc. was discontinued. 1 day after discontinuation: Hepatic failure was developed with AST (GOT) 12966 IU/L, ALT (GPT) 5477 IU/L, LDH 16562 IU/L. Furthermore, continuous hemodiafiltration (hereafter referred to as CHDF) and plasma exchange (hereafter referred to as PE) were performed, as BUN and creatinine levels increased to BUN 41.8 mg/dL and Cr 3.05 mg/dL, respectively, urine output could not be maintained and renal failure occurred concurrently. Coma hepatic, blood ammonia 42 μg/dL, hepaplastin test 23%, and prothrombin activity 23% confirmed hepatitis fulminant (HCV (−), HBsAg (−)). 7 days after discontinuation: CHDF and PE have resulted in some improvement in hepatic/renal functions. CHDF was performed for 24 consecutive hours until 7 days after discontinuation. Although the hepatic function improved with AST (GOT) 72 IU/L, ALT (GPT) 174 IU/L, LDH 251 IU/L, BUN 39.4 mg/dL, Cr 5.27 mg/dL, the renal function remained low. The treatment method was changed to hemodialysis (hereafter referred to as HD). HD was performed for 2 days, then terminated. Normal urination became possible. 21 days after discontinuation: Significant improvement was obtained with BUN 11.0 mg/dL, Cr 1.28 mg/dL. 35 days after discontinuation: Improvement was confirmed with BUN 29.6 mg/dL, Cr 1.08 mg/dL, AST (GOT) 33 IU/L, ALT (GPT) 20 IU/L. General condition became also good. 37 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: dextran 40/glucose, lactated Ringer's solution (containing maltose), heparin sodium, ranitidine hydrochloride, furosemide			

Clinical Laboratory Values

	On day 1 of admin.	On day 4 of admin. (Day of discontinuation)	1 day after discontinuation	3 days after discontinuation	7 days after discontinuation	17 days after discontinuation	21 days after discontinuation	35 days after discontinuation
PT (seconds)	--	11.6	35.8	23.2	--	14.3	--	--
Prothrombin activity (%)	--	--	23	--	--	--	--	--
AST (GOT) (IU/L)	19	98	12966	2264	72	23	--	33
ALT (GPT) (IU/L)	14	67	5477	2350	174	24	--	20
γ-GPT (IU/L)	--	51	70	98	--	84	--	--
Al-P (IU/L)	--	229	336	370	--	264	--	--
LDH (IU/L)	207	355	16562	839	251	236	--	--
Total bilirubin (mg/dL)	0.6	2.8	2.8	4.1	--	1.0	--	--

Blood ammonia (μg/dL)	--	--	42	--	--	--	--	--
Hepaplastin test (%)	--	--	23	--	--	--	--	--
BUN (mg/dL)	17.7	18.3	41.8	39.9	39.4	18.2	11.0	29.6
Cr (mg/dL)	0.97	1.20	3.05	4.29	5.27	1.86	1.28	1.08

Pt: Prothrombin Time
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
γ-GPT: γ-Glutamyltranspeptidase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
BUN: Blood Urea Nitrogen
Cr: Creatinine

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Cerebellar infarction [lacunar infarction] (hypertension, diabetes mellitus, mild renal failure and myocardial infarction)	60 mg 6 days	**Hepatitis fulminant** On day 1 of administration: Administration of this drug was initiated for the treatment of cerebral infarction. On day 6 of administration (day of discontinuation): Although no particular symptoms were observed, the administration of the drug was discontinued because of hepatic enzyme increased in blood sample. 1 day after discontinuation: Strong general malaise and further increase in hepatic enzymes were confirmed, and the patient was transferred to the department of surgery due to venous obstruction of lower extremities. In the evening, the patient's state of consciousness worsened. Hepatic enzyme increased to 2000 level, and the patient was re-admitted to this department (the state of consciousness was about JCSII-10 and there were no symptoms suggestive of hepatic encephalopathy. Depressed level of consciousness associated with aggravation of general condition was suspected. Hepatic atrophy etc. was not observed with abdominal CT). The patient was treated conservatively, with rest, discontinuation of medication, and administration of glycyrrhizin/glycine/cysteine. 2 days after discontinuation: The level of consciousness improved, but hepatic enzymes increased further (AST (GOT) 5980 IU/L, ALT (GPT) 3658 IU/L). 3 days after discontinuation: The patient's condition stabilized afterwards, however, the level of hepatic enzymes continued to decrease. 8 days after discontinuation: The patient was recovered. Test date unknown: HBsAg 0.1, HBsAb (–), HCV antibodies (the third generation) 0.1.
	Concomitant medications: benzbromarone, warfarin potassium, mexiletine hydrochloride, alprostadil, urokinase, ticlopidine hydrochloride, spironolactone, aspirin, quinapril hydrochloride, azelastine hydrochloride, glimepiride, furosemide, carvedilol			

Clinical Laboratory Values

	On day 1 of admin.	On day 2 of admin.	On day 6 of admin. (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	7 days after discontinuation
PT (seconds)	--	--	19.3	35.1	35.8	--	35.7	19.5
Prothrombin activity (%)	--	--	54.4	24.5	23.9	--	24.0	53.6
AST (GOT) (IU/L)	16	34	111	2525	5980	1874	762	111
ALT (GPT) (IU/L)	11	13	73	1947	3658	2311	1558	628
γ-GPT (IU/L)	28	27	157	155	163	143	137	106
Al-P (IU/L)	168	274	355	354	378	329	318	277
LDH (IU/L)	182	333	276	3784	5885	710	346	219
Total bilirubin (mg/dL)	0.38	0.24	0.42	0.65	0.56	0.75	0.83	0.74
Hepaplastin test (%)	--	--	--	--	18.0	--	--	--

PT: Prothrombin Time
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
γ-GPT: γ-Glutamyltranspeptidase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase

2 Amiodarone Hydrochloride (oral dosage form)

Brand Name (name of company)	Ancaron Tablets 100 (Sanofi-Aventis K.K.) Amiodarone Hydrochloride Tablets 100 mg "SAWAI" (Medisa Shinyaku Inc.)
Therapeutic Category	Antiarrhythmic agents
Indications	Following life-threatening recurrent arrhythmia in which other antiarrhythmic agents are ineffective or they can not be used: Ventricular fibrillation, ventricular tachycardia, and atrial fibrillation associated with hypertrophic cardiomyopathy

《**PRECAUTIONS** (underlined parts are additions)》 >

[Warning]

WARNING

Restriction of patient
This drug should be used only in patients with life-threatening arrhythmia, and other antiarrhythmic agents are ineffective or not appropriate for usage due to adverse reactions. [The incidence of adverse reaction is high, and the occurrence of life-threatening adverse reactions (interstitial pneumonia, alveolitis, pulmonary fibrosis, liver disorder, hyperthyroidism, thyroiditis) have been reported]

[Contraindications]

Patients with a history of hypersensitivity either to ingredients in this drug or to iodine.
Patients receiving ritonavir, saquinavir, saquinavir mesilate, indinavir sulfate ethanolate, nelfinavir mesilate, sparfloxacin, moxifloxacin hydrochloride, vardenafil hydrochloride hydrate, sildenafil citrate.

[Interactions (precautions for concomitant use)]

Ritonavir, saquinavir, saquinavir mesilate, indinavir sulfate ethanolate, vardenafil hydrochloride hydrate, sildenafil citrate

[Adverse Reactions (clinically significant adverse reactions)]

Hyperthyroidism, thyroiditis, hypothyroidism: Hyperthyroidism, thyroiditis, hypothyroidism may occur. Fatal cases of hyperthyroidism and thyroiditis have been reported in the past. Thyroid function test should be performed. If any abnormalities are observed in the test, appropriate measures, such as discontinuation of administration, should be taken. Since these adverse reactions

may occur not only during the period of administration but also several months after discontinuation, thyroid function test should be performed during administration and several months after discontinuation.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to January 31, 2007) (events for which a causality to the drug could not be denied)
• Hyperthyroidism, thyroiditis: 9 cases (of which 1 had a fatal case)
• Hypothyroidism: 5 cases (no fatal case)
The number of patients treated with Amiodarone for a year estimated by MAH: approximately 28000 (2006)
Marketed in Japan in: October 1992

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 40s	Ventricular tachycardia (dilated cardiomyopathy, congestive cardiac failure, hyperuricaemia, gastric ulcer)	100 mg About 5 years ↓ 200 mg Continuous admin.	**Hyperthyroidism** On day 1 of administration: Administration of 100 mg of this drug was initiated for ventricular tachycardia associated with dilated cardiomyopathy. ICD implantation was performed. Approx. on year 6 of administration: The dose of this drug was increased to 200 mg. Approx. on year 6 and month 9 of administration: (day of hospitalization) The patient was hospitalized by referring from another hospital due to aggravation of cardiac failure congestive. Body weight on the day of hospitalization was 82.0 kg. Thyroid function was within normal range. Intravenous injection of furosemide and carperitide (Genetical recombination) IV drip infusion were started. Blood pressure was low at 80 mmHg range and continuous administration of dopamine hydrochloride was initiated. Symptoms of cardiac failure were rapidly improved. Administration of omeprazole was started at 20 mg/day for gastric ulcer. On day 5 of hospitalization: Administration of warfarin potassium was started at 1.5 mg/day for cardiac failure congestive. On day 6 of hospitalization: Administration of trichlormethiazide was started at 1 mg/day for cardiac failure congestive. On day 14 of hospitalization: Body weight was decreased to 73 kg. On the same day, watery diarrhoea and palpitations on exertion were developed. Body weight continued to gradually decrease despite the reduction of diuretics etc. On day 16 of hospitalization: Administration of carvedilol was started at 5 mg/day for cardiac failure congestive. On day 18 of hospitalization: Palpitations and general malaise was experienced after low-level activity. Body weight was decreased to 69.8 kg. The patient was conscious of tremulousness of hand and night sweats. On day 37 of hospitalization: (day of confirmation of adverse reactions) The patient complained of palpitations during nighttime. Electrocardiogram confirmed atrial fibrillation, which had not been observed thus far.

				Hyperthyroidism was confirmed by blood test. Findings which suggest inflammation, such as electrolyte abnormalities, pyrexia, white blood cell increased, and CRP increased etc. were not confirmed. 1 day after confirmation: Oral administration of thiamazole 30 mg/day was started. ICD was used for atrial fibrillation and sinus rate returned to normal by performing cardio version. No recurrence was observed afterwards. 3 days after confirmation: Aggravation of hyperthyroidism was confirmed by blood tests for monitoring. The dose of thiamazole was increased to 60 mg/day. 12 days after confirmation: Blood test result showed no sign of improvement in hypothyroidism. Thiamazole was considered as being ineffective, and its administration was discontinued. Oral administration of inorganic iodine was started. 14 days after confirmation: Autoantibody tests related to thyroid were both negative. Hyperthyroidism (type II) in relation to this drug was suspected, and oral administration of prednisolone 30 mg/day was initiated. After the initiation of prednisolone administration, symptoms such as palpitations and sweaty were improved. 27 days after confirmation: Reduction in thyroid hormone was confirmed by blood tests. Unknown: Later, the hormone level returned to normal and the dose of prednisolone was reduced to 20 mg/day. Unknown: No recurrence was observed afterwards. 36 days after confirmation: The patient became in remission.
	Concomitant medications: allopurinol, furosemide, omeprazole, warfarin potassium, trichlormethiazide, carvedilol, spironolactone, candesartan cilexetil, carperitide (Genetical recombination), dopamine hydrochloride			

Clinical Laboratory Values

	Approx. on year 6 and month 9 of admin. (day of hospitalization)	On day 37of hospitalization (day of confirmation of adverse drug reaction)	3 days after confirmation	13 days after confirmation	21 days after confirmation	27 days after confirmation
TSH (μIU/mL)	5.49	0.02	0.02	0.01	0.01	0.01
FT_3 (pg/mL)	2.41	12.12	14.71	30.64	21.03	7.15
FT_4 (ng/dL)	1.69	5.00	6.28	≥7.77	≥7.77	5.42

TSH: Thyroid-Stimulating Hormone
FT_3: Free Triiodothyronine
FT_4: Free Thyroxine

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 30s	Non-sustained ventricular tachycardia (dilated cardiomyopathy, chronic cardiac failure)	200 mg Unknown ↓ 100 mg Unknown	**Thyroiditis** On day 1 of administration: Non-sustained ventricular tachycardia of 41 consecutive beats (heart rate of 200) was confirmed. Therefore, oral administration of this drug initiated at 200 mg was changed to maintenance dose of 100 mg. Approx. on month 2 of administration: FT_3, FT_4, and TSH were all normal. Both amiodarone and desethylamiodarone (DEA) presented low blood concentration. Approx. on month 5 of administration: (day of confirmation of adverse reaction) Hyperthyroidism was confirmed with FT_3 11.6 pg/mL, FT_4 7.7 ng/dL, and TSH 0.02 μIU/mL. Thyroiditis in relation with this drug was suspected. 2 days after confirmation: Oral administration of propylthiouracil was initiated for the treatment of thyroiditis. Urine volume was started to decrease from nighttime, and right heart failure worsened rapidly. Cardiac failure and acute prerenal failure due to hyperthyroidism was considered. 3 days after confirmation: Doses of furosemide and dobutamine hydrochloride were increased. Addition of dopamine hydrochloride was resulted in oliguria. Blood pressure and heart rate were gradually decreased. The patient's death was confirmed.
	Concomitant medications: carvedilol, pimobendan, spironolactone, allopurinol, olprinone hydrochloride, alprazolam, flunitrazepam, digoxin, teprenone, trimebutine maleate, lansoprazole, lactomin, sodium ferrous citrate, metoclopramide, milrinone, furosemide, warfarin potassium, dopamine hydrochloride, dobutamine hydrochloride			

Clinical Laboratory Values

	Approx. on month 2 of admin.		Approx. on month 4 of admin.		Approx. on month 5 of admin. (day of confirmation of adverse reaction)	1 day after confirmation	3 days after confirmation
BNP (pg/mL)	178.8	--	513.9	--	2800.6	--	--
Blood amiodarone concentration (μg/mL)	--	0.20	--	0.23	--	--	--
Blood DEA concentration (μg/mL)	--	0.13	--	0.22	--	--	--
TSH (μIU/mL)	2.61	--	4.16	--	0.02		--
FT_3 (pg/mL)	2.3	--	2.5	--	11.6	--	11.2
FT_4 (ng/dL)	1.6	--	1.7	--	7.7	--	--
Thyroglobulin (ng/mL)	--	--	--	--	--	<100	--
Microsome (double)	--	--	--	--	--	<100	--
TSH receptor antibody (%)	--	--	--	--	--	1.8	--
TSH stimulating receptor antibody (%)	--	--	--	--	--	82	--

BNP: Brain Natriuretic Peptide
TSH: Thyroid-Stimulating Hormone
FT_3: Free Triiodothyronine
FT_4: Free Thyroxine

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Ventricular tachycardia (old myocardial infarction, hypothyroidism cerebral infarction, and chronic cardiac failure)	400 mg 3 days ↓ 200 mg Continuation of admin.	**Hypothyroidism** On day 1 of administration: Administration of amiodarone hydrochloride at 400 mg was initiated for ventricular tachycardia associated with old myocardial infarction. On day 4 of administration: The dosage of this drug was adjusted to a maintenance dose of 200 mg On day 15 of administration: Slight increase of TSH level was confirmed by blood tests. But as the patient's TSH level was slightly high from the beginning, administration of the drug was continued. On day 557 of administration: The patient was rehospitalized due to acute exacerbation of chronic cardiac failure and renal failure. A large increase in TSH level was confirmed by blood tests at the time, and the patient was diagnosed with hypothyroidism. Milrinone IV drip infusion was conducted for cardiac failure. On day 559 of administration: Treatment with levothyroxine sodium at 50 μg/day was started. On day 591 of administration: Under the treatment with levothyroxine sodium, test results were improved.
	Concomitant medications: warfarin potassium, famotidine, allopurinol, ticlopidine hydrochloride, carvedilol, candesartan cilexetil, furosemide, spironolactone			

Clinical Laboratory Values

	150 days before admin.	On day 1 of admin.	On day 15 of admin.	On day 557 of admin.	On day 591 of admin.
TSH (μIU/mL)	13.93	14.74	17.84	326.34	122.23
FT_3 (pg/mL)	1.60	1.65	1.10	1.41	1.43
FT_4 (ng/dL)	0.75	0.67	0.65	0.40	0.42

TSH: Thyroid-Stimulating Hormone
FT_3: Free Triiodothyronine
FT_4: Free Thyroxine

3 Cibenzoline Succinate (oral dosage form)

Brand Name (name of company)	Cibenol Tablets 50 mg and 100 mg (Astellas Pharma Inc.) Cinobezile Tablets 50 mg and 100 mg (Towa Pharmaceutical Co., Ltd.)
Therapeutic Category	Antiarrhythmic agents
Indications	The following disease in which other antiarrhythmic agents can not be used or they are ineffective: Tachyarrhythmia

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia: Interstitial pneumonia manifested by fever, cough, dyspnoea or abnormal chest X-ray, etc. may occur. If such reactions are observed during treatment, this product should be discontinued and appropriate measures such as giving adrenocortical hormones should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to February 26, 2007) (events for which a causality to the drug could not be denied)
• Interstitial pneumonia: 3 cases (no fatal case)
The number of patients treated with Cibenzoline Succinate for a year estimated by MAH: approximately 110000 (January to December 2006)
Marketed in Japan in: January 1991

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Atrial fibrillation (hypertension, sick sinus syndrome)	300 mg 36 days ↓ (no treatment for 7 days) ↓ 300 mg 5 days ↓ (no treatment for 13 days) ↓ 200 mg 3 days ↓ 300 mg 1 day	**Drug-induced lung disorder (interstitial pneumonia)** On day 1 of administration: The initial prescription was nifedipine, aspirin/dialuminate, and pilsicainide hydrochloride, but pilsicainide hydrochloride was switched to 300 mg of this drug. The administration of nifedipine and aspirin/dialuminate were continued. On day 32 of administration: Pyrexia, cough, and sputum developed. On day 36 of administration (day of discontinuation): Hyporexia was observed, in addition to pyrexia, cough, and sputum. Infiltrative shadow was observed in chest XP. The patient was hospitalized and a drip infusion of panipenem/betamipron was started. Oral administration of this drug, nifedipine, and aspirin/dialuminate was discontinued. 1 day after discontinuation: Inflammation reaction worsened and bronchoscopy was conducted. Antibiotics were changed from panipenem/betamipron to pazufloxacin mesilate. Pyrexia was gradually abated. Subjective symptoms were also improved. 8 days after discontinuation (on day 1 of readministration): CRP was improved from 20.1 mg/dL to 3.5 mg/dL. Chest XP findings were also improved. Subjective symptoms were almost disappeared. The administration of this drug and nifedipine was resumed in the evening. On day 2 of readministration: In the evening, pyrexia of 38.4°C was developed. On day 5 of readministration (day of discontinuation of readministration): CRP was worsened with 12.6 mg/dL. Chest XP findings were also worsened. Administration of both this drug and nifedipine was discontinued. 3 days after discontinuation of readministration: Pyrexia was abated and subjective symptoms were improved. CRP was improved to 1.9 mg/dL. 7 days after discontinuation of readministration: CRP was 0.4 mg/dL. White blood cell count was 6500/mm^3. PaO_2 81.0 Torr. The findings of chest XP were improved. Nifedipine was readministered. 14 days after discontinuation of readministration (on day 1 of second readministration): CRP was 0.2 mg/dL. White blood cell count was 5800/mm^3. Chest XP was almost clear. Readministration of this drug was restarted in the evening, at a dose of 200 mg.

				On day 4 of second readministration (day of discontinuation of second readministration): The dosage was increased to 300 mg at noon. In the evening, the body temperature was 37.0°C, but decrease in CRP 5.1 mg/dL, white blood cell count 9300/mm^3 and PaO_2 60.8 Torr were observed. The administration of the drug was discontinued at night. Nifedipine administration was continued. 8 days after discontinuation of second readministration: CRP and PaO_2 were improved to 0.2 mg/dL and 92.3 Torr, respectively. Pilsicainide hydrochloride and aspirin/dialuminate were additionally administered. Aggravation of symptoms was not observed. 14 days after discontinuation of second readministration: The patient was recovered. DLST test: this drug (–), nifedipine (–)
	Concomitant medications : nifedipine, aspirin/dialuminate			

Clinical Laboratory Values

	1 day after discontinuation	8 days after discontinuation (on day 1 of readministration)	On day 5 of readministration (day of discontinuation of readministration)	7 days after discontinuation of readministration	14 days after discontinuation of readministration (on day 1 of second readministration)	On day 4 of second readministration (day of discontinuation of second readministration)	8 days after discontinuation of second readminstration
Body temperature (°C)	38.3	--	--	--	--	37.0	--
Pulse rate (/min)	80	--	--	--	--	--	--
Diastolic blood pressure (mmHg)	84	--	--	--	--	--	--
Sistolic blood pressure (mmHg)	146	--	--	--	--	--	--
RBC ($\times10^4/mm^3$)	390	357	375	375	388	395	380
Hb (g/dL)	11.8	10.7	11.1	11.1	11.4	11.6	11.3
HCT (%)	35.2	31.9	33.7	33.5	34.8	35.3	33.4
WBC (/mm^3)	7400	8400	8900	6500	5800	9300	5400
EOS (%)	0.2	0.0	0.1	0.9	0.4	0.6	2.5
Bas (%)	0.1	0.3	0.3	0.7	0.9	0.4	0.6
Neutrophils (%)	75.7	73.5	76.7	56.7	68.6	80.6	59.0
Lymphocytes (%)	15.0	17.0	12.5	31.2	22.6	11.3	29.5
Monocytes (%)	9.0	9.2	10.4	10.5	7.5	7.1	8.4
Platelet count ($\times10^4/mm^3$)	12.3	31.8	33.9	30.3	20.7	14.9	19.4
CRP (mg/dL)	20.1	3.5	12.6	0.4	0.2	5.1	0.2
CK (CPK) (IU/L)	47	31	38	42	55	32	40
PaO_2 (Torr)	--	--	--	81.0	--	60.8	92.3

RBC: Red Blood Cell
Hb: Haemoglobin
HCT: Haematocrit
WBC: White Blood Cell
EOS: Eosinophil
Bas: Basophil
CRP: C-Reactive Protein
CK: Creatine Kinase
PaO_2: Partial Pressure Arterial Oxygen

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Revision of PRECAUTIONS (No. 186)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated March 20, March 23, and April 13, 2007 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 <Antivirals> Oseltamivir Phosphate

[Brand Name]

Tamiflu Capsules 75, Tamiflu Dry Syrup 3% (Chugai Pharmaceutical Co., Ltd.)

[Warning]

WARNING

Abnormal behaviour that have resulted in accidents such as falls have been reported in patients aged 10 to 19 years following administration of this drug, although the causal relationship to this drug is unknown. Generally, this drug should not be used in these patients for the above reason except that the patient may have a high-risk based on complications and medical history, etc.
When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, (1) abnormal behaviour may occur and (2) caregivers should be careful not to let patients alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents including falls due to abnormal behaviour.
Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

[Adverse Reactions (clinically significant adverse reactions)]

Psychoneurological symptoms: Psychoneurological symptoms (e.g. consciousness disturbed, abnormal behaviour, delirium, hallucination, delusion, convulsions) may occur. Patients should be carefully monitored. If any abnormality is observed, administration should be discontinued, and appropriate measures should be taken according to individual symptoms.

[PRECAUTIONS of Indications]

TAMIFLU should only be used for the treatment of patients diagnosed with influenza A or B virus infection. However, considering that the anti-viral agent is not necessarily essential for all patients with influenza A and B viral infections, the need for treatment with TAMIFLU should be carefully examined by thoroughly observing the condition of patient.
The mortality caused by influenza infection is especially lower in the other age groups compared with infants and the elderly.

2 <Antiepileptics> Carbamazepine

[Brand Name] Tegretol Fine Granules 50%, Tegretol Tablets 100 mg and 200 mg (Novartis Pharma K.K.), and others

[Contraindications] Patients with porphyria

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythroderma (dermatitis exfoliative): Serious skin disorders may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

SLE-like symptoms: SLE-like symptoms (skin disorders such as butterfly rash, pyrexia, arthralgia, white blood cell decreased, platelets decreased, antinuclear antibody positive, etc.) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

3 <Psychotropics> Aripiprazole

[Brand Name] Abilify Powder 1%, Abilify Tablets 3 mg and 6 mg (Otsuka Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Convulsion: Convulsion may occur. If any abnormalities are observed, appropriate measures such as discontinuation of the administration should be taken.

4 <Antiarrhythmic agents> Sotalol Hydrochloride

[Brand Name] Sotacor Tablets 40 mg and 80 mg (Bristol-Myers K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Ventricular fibrillation, ventricular tachycardia, Torsades de pointes, sinus arrest, atrioventricular block complete, cardiac failure, cardiomegaly: Arrhythmogenicity of this drug may cause symptoms of ventricular fibrillation, ventricular tachycardia, Torsades de pointes, sinus arrest, atrioventricular block complete, cardiac failure or cardiomegaly. Electrocardiogram, chest X-ray, or echocardiography should be performed periodically. If any abnormalities are observed, appropriate measures such as reducing the dosage or discontinuation of administration should be taken. (Following treatments should be considered in case of ventricular fibrillation, ventricular tachycardia, or Torsades de pointes).

DC defibrillation, intravenous pacing, administration of epinephrine, administration of magnesium sulfate

5 <Cardiovascular agents-Miscellaneous>
Bosentan Hydrate

[Brand Name] Tracleer Tablets 62.5 mg (Actelion Pharmaceuticals Japan Ltd.)

[Important Precautions] The administration of this drug may induce haemoglobin decreased and platelets decreased. Blood tests should be conducted on the 1st day of administration and once a month for 4 months after the start of administration, and thereafter once every 3 months.

[Adverse Reactions (clinically significant adverse reactions)] **Platelets decreased:** Platelets decreased may occur. Periodical examinations should be conducted, and patients should be carefully monitored. If any abnormalities are observed, appropriate measures, such as reduction of dosage or discontinuation of the drug, should be taken.

6 <Pituitary hormone preparations>
Oxytocin

[Brand Name] Atonin-O Injection 1 u and 5 u (Aska Pharmaceutical Co., Ltd.), and others

[Precautions of Dosage and Administration] Increase of infusion rate should be done gradually, with 1 to 2 mU/min, and by monitoring the patients for 30 minutes and more. If labor pains are not achieved even when the infusion rate is raised to 20 mU/min, stop increasing as further increase will not be effective.

7 <Hormones-Miscellaneous>
Dinoprost

[Brand Name] Prostarmon F Injection 1000 and 2000 (Ono Pharmaceutical Co., Ltd.), and others

[Contraindications] Patients with asthma bronchial or a history of asthma bronchial

8 <Urogenital and anal organ agents-Miscellaneous>
Naftopidil

[Brand Name] Flivas Tablets 25 mg, 50 mg, and 75 mg, Flivas OD Tablets 50 mg (Asahi Kasei Pharma Corporation), and others

[Adverse Reactions (clinically significant adverse reactions)] **Syncope, loss of consciousness:** Temporary loss of consciousness associated with blood pressure decreased may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

9 <Protein and amino acid preparations>
Enterued

[Brand Name] Enterued (Terumo Corporation)

[Careful Administration] Patients with ovalbumin allergy

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored. If blood pressure decreased, consciousness disturbed, dyspnoea, cyanosis, nausea, chest distressed feeling of, flushed face, itching, and sweaty etc. occur, administration should be immediately discontinued and appropriate measures should be taken.

10 <Antineoplastics-Miscellaneous>
Anastrozole, Exemestane

[Brand Name] Arimidex Tablets 1 mg (AstraZeneca K.K.)
Aromasin Tablets 25 mg (Pfizer Japan Inc.)

[Important Precautions] Osteoporosis and fracture are more likely to occur in patients treated with this drug. It is recommended to conduct periodical check-up of bone conditions, such as bone density.

11 <Synthetic antibacterials>
Ciprofloxacin, Ciprofloxacin Hydrochloride

[Brand Name] Ciproxan-I.V. 200 mg and 300 mg (Bayer Yakuhin, Ltd.)
Ciproxan Tablets 100 mg and 200 mg (Bayer Yakuhin, Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Bone marrow depression, pancytopenia, agranulocytosis, platelets decreased:** Bone marrow depression, pancytopenia, agranulocytosis, and platelets decreased etc. may occur. Patients should be carefully monitored. If an abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

12 <Antivirals>
Indinavir Sulfate Ethanolate

[Brand Name] Crixivan Capsules (Banyu Pharmaceutical Co., Ltd.)

[Contraindications] Patients receiving amiodarone hydrochloride, cisapride, triazolam, midazolam, alprazolam, pimozide, ergotamine tartrate/anhydrous caffeine, dihydroergotamine mesilate, methylergometrine maleate, or ergometrine maleate

[Interactions (contraindications for concomitant use)] Amiodarone hydrochloride, cisapride, triazolam, midazolam, alprazolam, pimozide, ergotamine tartrate/anhydrous caffeine, dihydroergotamine mesilate, methylergometrine maleate, ergometrine maleate

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List of products subject to Early Post-marketing Phase Vigilance

(As of May 1, 2007)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Interferon Beta-1a (Genetical recombination) Avonex IM Injection Syringe 30 μg	Biogen Idec Japan Ltd.	November 6, 2006
Moxifloxacin Hydrochloride Vegamox Ophthalmic Solution 0.5%	Alcon Japan Ltd.	November 6, 2006
Pneumococcal Vaccine Pneumovax NP	Banyu Pharmaceutical Co., Ltd.	November 29, 2006
Bortezomib Velcade Injection 3 mg	Janssen Pharmaceutical K.K.	December 1, 2006
Itraconazole Itrizole Injection 1%	Janssen Pharmaceutical K.K.	December 6, 2006
Ropinirole Hydrochloride ReQuip Tablets 0.25 mg, 1 mg, and 2 mg	GlaxoSmithKline K.K.	December 6, 2006
Lansoprazole Takepron Intravenous 30 mg	Takeda Pharmaceutical Company Limited	December 7, 2006
Losartan Potassium/Hydrochlorothiazide Preminent Tablets	Banyu Pharmaceutical Co., Ltd.	December 8, 2006
Polidocanol Polidocasklerol 0.5% Inj. 2 mL, 1% Inj. 2 mL, and 3% Inj. 2 mL	Sakai Chemical Industry Co., Ltd.	December 14, 2006
Fexofenadine Hydrochloride Allegra Tablets 30 mg	Sanofi-Aventis K.K.	January 9, 2007
Perflubutane Sonazoid for Injection	Daiichi-Sankyo Co., Ltd.	January 10, 2007
Pemetrexed Sodium Hydrate Alimta Injection 500 mg	Eli Lilly Japan K.K.	January 22, 2007
Remifentanil Hydrochloride Ultiva Intravenous 2 mg and 5 mg	Janssen Pharmaceutical K.K.	January 22, 2007
Infliximab (Genetical recombination) Remicade for I.V. Infusion 100[*1]	Tanabe Seiyaku Co., Ltd.	January 26, 2007
Zanamivir Hydrate Relenza[*2]	GlaxoSmithKline K.K.	January 26, 2007
Tacrolimus Hydrate Prograf Capsules 0.5 mg and 1 mg[*3]	Astellas Pharma Inc.	January 26, 2007
Baclofen Intrathecal Gabalon 0.005%, 0.05%, and 0.2%[*4]	Daiichi-Sankyo Co., Ltd.	January 26, 2007
Micafungin Sodium Funguard 25 mg, 50 mg, and 75 mg for Infusion[*5]	Astellas Pharma Inc.	January 26, 2007

Rurioctocog Alfa (Genetical recombination) Advate Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method 250, 500, and 1000	Baxter Limited	February 22, 2007
Follitropin Beta (Genetical recombination) Follistim Inj. 50 and 75[*6]	Nippon Organon K.K.	March 16, 2007
Peginterferon Alpha-2a (Genetical recombination) Pegasys s.c. 90 μg and 180 μg[*7]	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Ribavirin Copegus Tablet 200 mg	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Modafinil Modiodal Tablets 100 mg	Alfresa Parma Corporation	March 28, 2007
Valaciclovir Hydrochloride Valtrex Granules 50%[*8]	GlaxoSmithKline K.K.	April 18, 2007
Entacapone Comtan Tablets 100 mg	Novartis Pharma K.K.	April 19, 2007

*1: An additional indication for "the treatment of refractory uveitis in patients with Behcet's disease (only in cases which are not adequately responsive to conventional therapies)"
*2: An additional indication for "prophylaxis of influenza A or B virus infection"
*3: An additional indication for "Lupus nephritis (in a case where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions)"
*4: Additional administration for "pediatrics"
*5: An additional indication for "Prophylaxis of Aspergillus and Candida infections in patients undergoing hematopoietic stem cell transplantation"
*6: An additional indication for "the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamic-pituitary dysfunction"
*7: An additional indication for "the use in combination with ribavirin, for the improvement of viraemia in one of the following chronic hepatitis C: (1) serogroup 1 (genotype I (1a) or II (1b)) with high serum HCV-RNA loads, or (2) patients who failed interferon monotherapy or who developed reactivation (of chronic hepatitis C) following interferon monotherapy"
*8: An additional indication for "varicella"